PROPHYLACTIC CYCLO-OXYGENASE INHIBITOR DRUGS FOR THE PREVENTION OF MORBIDITY AND MORTALITY IN EXTREMELY PRETERM INFANTS: A CLINICAL PRACTICE GUIDELINE INCORPORATING FAMILY VALUES AND PREFERENCES

By

Souvik Mitra

Submitted in partial fulfilment of the requirements
for the degree of Doctor of Philosophy

at

Dalhousie University
Halifax, Nova Scotia
July 2022

TABLE OF CONTENTS

LIST OF TABLES

CHAPTER 2

CHAPTER 3

CHAPTER 4

LIST OF FIGURES

CHAPTER 1

CHAPTER 2

CHAPTER 5

ABSTRACT

Prophylactic cyclooxygenase inhibitor (COX-I) drugs such as indomethacin, ibuprofen and acetaminophen may prevent morbidity and mortality in extremely preterm infants (born ≤28 weeks gestational age). Extensive variability in clinical practice exists based on controversy around which COX-I drug is the most effective and has the best safety profile.

This project was designed to develop rigorous clinical practice guideline recommendations for the prophylactic use of COX-Is in extremely preterm infants through a de novo synthesis of evidence from RCTs using a network meta-analysis (NMA), and a cross-sectional mixed-methods study exploring family values and preferences conducted in parallel.

The Bayesian random-effects NMA of 28 RCTs (3999 infants) demonstrated that prophylactic indomethacin probably resulted in a small reduction in severe intraventricular hemorrhage (IVH) and a moderate reduction in death. Prophylactic ibuprofen probably resulted in a small reduction in severe IVH and may result in a moderate reduction in death. The evidence was very uncertain about the effect of acetaminophen on any of the clinically relevant outcomes.

The two-phase cross-sectional mixed methods study conducted using results from the above-mentioned NMA included 44 participants (34 parents of preterm infants; 10 adults born preterm). The study showed that there was minimal variability in how participants valued the main outcomes, with death and severe IVH being rated as the two most important undesirable outcomes. While indomethacin was the most preferred form of prophylaxis, variability was noted in the choice of COX-I interventions when participants were presented with the benefits and harms of each drug.

Finally, the 12-member guideline panel, that included five experienced neonatal care providers, two methods experts, one pharmacist, two parents of former extremely preterm infants and two adults born extremely preterm, was presented with the results from the above-mentioned NMA and the cross-sectional mixed methods study. Using the GRADE Evidence-to-Decision framework for multiple comparisons, the panel provided a conditional recommendation in favor of indomethacin prophylaxis, a conditional recommendation against ibuprofen prophylaxis and a strong recommendation against acetaminophen prophylaxis in extremely preterm infants. The panel strongly encouraged shared decision making with parents to evaluate their values and preferences prior to prescribing either indomethacin or ibuprofen.

LIST OF ABBREVIATIONS AND SYMBOLS USED

AAP	American Academy of Pediatrics
ACP	American College of Physicians
AGREE	Appraisal of Guidelines for Research & Evaluation
aOR	Adjusted Odds Ratio
ARD	Absolute risk difference
ASD	Autism spectrum disorder
BSID-MDI	Bayley Scales of Infant Development - Mental Development Index
BSITD	Bayley Scales of Infant and Toddler Development
BUN	Blood urea nitrogen
BW	Birth weight
CAD	Canadian dollars
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
cFTOE	Cerebral fractional tissue oxygen extraction
CGC	Clinical guidelines committee
CI	Confidence interval
CIHR	Canadian Institutes of Health Research
CLD	Chronic lung disease
COI	Conflict of interest
COIN	Core outcome sets in neonatology
COVID	Coronavirus disease
COX-I	Cyclo-oxygenase inhibitor
CP	Cerebral palsy
CPS	Canadian pediatric society
CrI	Credible interval
CRSU	Cochrane complex review support unit
DARE	Database of Abstracts of Reviews of Effectiveness
ELBW	Extremely low birth weight
ELGAN	Extremely low gestational age neonates
EtD	Evidence-to-Decision
GA	Gestational age
GCI	General cognitive index
GI	Gastrointestinal
GIN	Guideline international network
GMH	Germinal matrix hemorrhage
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
ICU	Intensive care unit
IHDCYH	Institute of Human Development, Child and Youth Health

IPD	Individual patient data
IQ	Intelligence quotient
IQR	Interquartile range
iSOF	Interactive summary of findings
IV	Intravenous
IVH	Intraventricular hemorrhage
IWK	Izaak Walton Killam
MD	Mean difference
NaCl	Sodium chloride
NEC	Necrotizing enterocolitis
NICHD	National Institute of Child Health and Human Development
NICU	Neonatal intensive care units
NMA	Network meta-analysis
NSAIDs	Non-steroidal anti- inflammatory drugs
OR	Odds ratio
PDA	Patent ductus arteriosus
PVH	Periventricular- intraventricular hemorrhage
PVL	Periventricular leukomalacia
QALY	Quality-adjusted life years
$RcSO_2$	Regional cerebral oxygen saturation
RCT	Randomized controlled trial
RDS	Respiratory distress syndrome
REB	Research ethics board
RoB	Risk of Bias
ROP	Retinopathy of prematurity
RR	Relative risk
SD	Standard deviation
SIP	Spontaneous intestinal perforation
sIVH	Severe intraventricular hemorrhage
SpO2	Peripheral oxygen saturation
SRNMA	Systematic review network meta-analysis
SUCRA	Surface under the cumulative ranking
THAM	Tromethamine
TIPP	Trial of Indomethacin Prophylaxis in Preterms
USA	United States of America

CHAPTER 1: INTRODUCTION

BACKGROUND

The patent ductus arteriosus as a cause of morbidity and mortality in preterm infants

About 25,000-30,000 infants are born preterm [<37 weeks gestational age (GA)] every year in Canada. Prematurity is the leading cause of infant death, cerebral palsy, and disability, resulting in Canadian healthcare costs of >$8 billion/year[1,2]. Infants born extremely preterm (≤28 weeks' GA) are considered the most vulnerable of the preterm population and are 7.5 times more likely to need income support later in life than term neonates[3]. There is also growing evidence that extreme preterm birth can have significant cardiovascular and renal consequences lasting into adulthood[4,5].

Important contributors to morbidity and mortality in extremely preterm infants include intraventricular hemorrhage (IVH), prolonged duration of endotracheal mechanical ventilation with consequent lung injury, and hemodynamic disturbance leading to compromised end organ perfusion. A common contributor in all three of these pathophysiological mechanisms is postulated to be the patent ductus arteriosus (PDA)[6]. The ductus arteriosus is a blood vessel that connects the two major arteries coming out of the heart, i.e., the aorta from the left ventricle and the pulmonary artery from the right ventricle *(Figure 1)*[7].

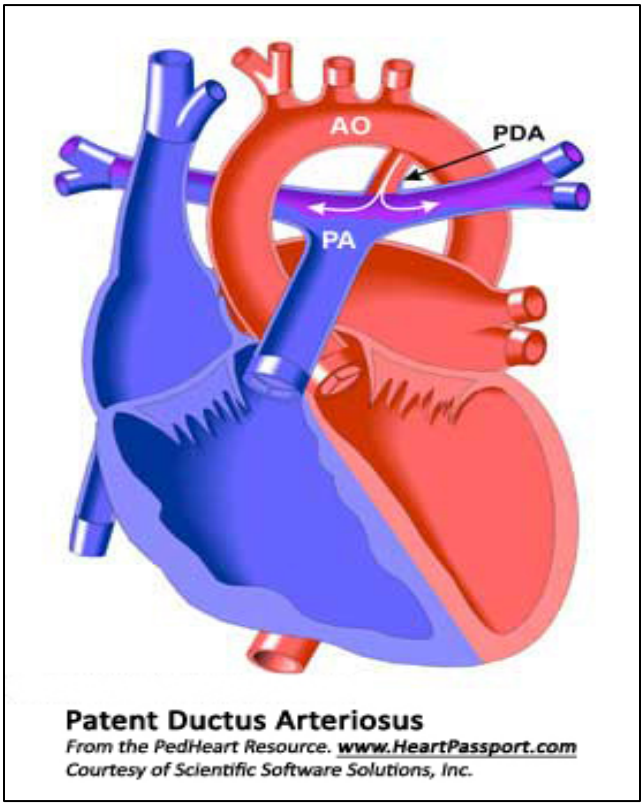


Figure 1. Shows a PDA connecting the aorta (AO) and the pulmonary artery (PA) *[Image courtesy of: http://www.secondscount.org/]*

Closure of the ductus arteriosus begins shortly after birth and functional closure occurs over the next 24-72 hours[7]. In preterm infants the closure is usually delayed leading to the ductus arteriosus remaining patent (open) beyond the first few days after birth. One physiologic consequence is excessive blood flow through the lungs, predisposing to development of pulmonary congestion, surfactant inactivation, and worsening respiratory failure leading to increased oxygen exposure and higher ventilator support[8]. At the same time, diversion of blood flow away from the systemic circulation leads to systemic hypoperfusion, resulting in compromised perfusion to the bowel, kidney, and brain[6]. Persistence of a PDA along with clinical signs of pulmonary congestion and/or systemic hypoperfusion is defined as a symptomatic or hemodynamically significant PDA[7]. A persistent, symptomatic ductus arteriosus in extremely preterm infants is associated with harmful sequelae including IVH and cerebral palsy, prolonged duration of endotracheal mechanical ventilation and chronic lung disease (CLD), necrotizing enterocolitis (NEC), renal failure, and higher rates of death[9–14].

According to the Canadian Neonatal Network 2020 Annual report, out of 1556 extremely preterm infants born in tertiary care neonatal intensive care units (NICUs) across Canada in 2020, 57% developed a symptomatic PDA, 26% developed IVH, and 61% died or developed CLD[15]. While prematurity itself remains the most important factor contributing to morbidity and mortality, a number of perinatal and postnatal interventions have been shown to reduce the incidence of IVH, CLD, and death in preterm infants. These include antenatal corticosteroids, delayed cord clamping, early surfactant administration for respiratory distress syndrome, volume guarantee ventilation, and prevention of symptomatic PDA using cyclo-oxygenase inhibitor (COX-I) drugs such as indomethacin[16].

Pharmacologic prevention of PDA to reduce morbidity and mortality in preterm infants

Currently available pharmacotherapeutic options to prevent a persistent PDA include cyclo-oxygenase inhibitor (COX-I) drugs such as indomethacin, ibuprofen, and acetaminophen. COX-Is such as indomethacin and ibuprofen act by inhibition of the cyclo-oxygenase enzyme thereby leading to down-regulation of prostaglandin E2, a potent relaxant of the PDA[17]. Indomethacin has been the most widely used medication for PDA

prophylaxis, followed by ibuprofen[18,19]. Recently, acetaminophen, a selective inhibitor of the COX-2 enzyme, has emerged as another treatment option for PDA closure. Acetaminophen is postulated to inhibit the peroxidase enzyme resulting in downregulation of prostaglandin E2 production[19,20]. The mechanism of action of COX-I drugs in the downregulation of prostaglandin E2 on the arachidonic acid metabolism pathway is depicted in figure 2[19,21].

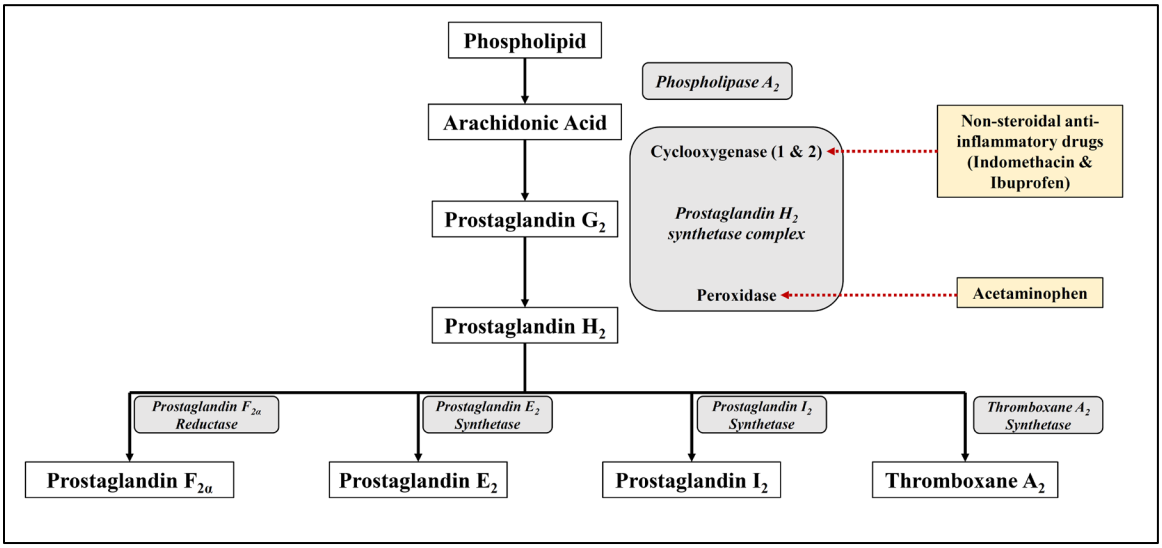


Figure 2. Arachidonic acid metabolism pathway depicting inhibitory effects of COX-I drugs

The primary mechanism through which these drugs are postulated to prevent morbidities such as IVH and CLD is through modulation of the ductal shunt. In addition, animal studies have shown that indomethacin stimulates basement membrane deposition in the germinal matrix microvessels, which in turn may prevent IVH[22]. While acetaminophen may reduce harmful mitochondrial superoxide production and intracellular oxidant stress, thereby preventing IVH[23].

Although the majority of extremely preterm infants develop a persistent PDA, decision on pharmacoprophylaxis has always been a contentious issue. It is known that the peak incidence of IVH in preterm infants is within the first three days after birth[24]. Therefore, previous randomized controlled trials (RCTs) have examined whether prophylactic indomethacin reduces the incidence of symptomatic PDA and IVH. A Cochrane systematic review of 19 RCTs (2872 infants) showed that prophylactic indomethacin significantly reduced the incidence of symptomatic PDA [relative risk (RR) 0.44, 95% confidence interval (CI): 0.38-0.50], PDA ligation (RR 0.51, 95% CI: 0.37-0.71) and severe IVH (RR

0.66, 95% CI: 0.53-0.82) [25]. It has also been shown that the risk of death or CLD increases with longer exposure to the PDA. In a prospective observational study of 397 extremely preterm infants born ≤28 weeks' gestation, Liebowitz et al showed that infants receiving prophylactic indomethacin had a significantly lower incidence of CLD (RR 0.68; 95% CI: 0.46-0.89) and CLD or death (RR 0.78; 95% CI: 0.62-0.95) than infants in whom no treatment was provided in the first 8 days of life[26]. The authors further suggested that the increased incidence of CLD and CLD/death in the conservative management group was primarily contributed by the presence of a moderate-large PDA at day 7 of life[26]. Given that the highest period of vulnerability is in the first few days of life, clinicians may choose to prophylactically use interventions within the first 24 hours after birth to prevent a symptomatic PDA, especially in extremely preterm infants born ≤28 weeks of gestation who are at the highest risk of IVH, CLD, and death.

The decision on pharmacoprophylaxis, however, has primarily been driven by the perceived benefits versus potential risks as determined by the treating physician. Use of indomethacin in preterm infants has been associated with spontaneous intestinal perforation (SIP) and NEC, derangement of renal function, alteration of platelet function, and impairment of cerebral blood flow[27–31]. Ibuprofen use is also associated with renal injury and NEC, along with increased risk of hyperbilirubinemia[32,33]. Compared to indomethacin, ibuprofen appears to be associated with a lower risk of NEC and acute kidney injury and does not seem to increase the risk of hyperbilirubinemia[33]. No short term adverse effects have been noted with acetaminophen[34]. However, recent observational studies have linked maternal acetaminophen exposure with later development of autism and attention deficit/hyperactivity disorder[35,36]. There have been a number of placebo-controlled randomized trials that have examined the effectiveness and safety of these medications that have been summarized in systematic reviews. However, no systematic review has compared all the three medications simultaneously, thereby adding to the dilemma of clinicians as to which drug, if any at all, is the safest and most effective pharmacoprophylactic option among preterm infants at risk of PDA.

CONCEPTUAL FRAMEWORK OF THE PROJECT

Variation in clinical practice and need for a clinical practice guideline

Given the uncertainties outlined above, it is not surprising that there is wide variation in clinical practice regarding the prophylactic use of COX-Is in extremely preterm infants. A retrospective cohort study of 4268 extremely preterm infants admitted to Canadian neonatal units between 2010 and 2014 demonstrated marked variation (0-78%) in the use of prophylactic COX-Is across Canadian NICUs[37]. Similarly, a survey of 35 Neonatal Research Network hospitals across the United States showed that while one-third of NICUs never used COX-I prophylaxis, a third of the centers used pharmacoprophylaxis in 45%–98% of their extremely preterm neonates[38]. Interestingly, in the United States, the odds of CLD (OR 0.31; 95% CI 0.14–0.69) as well as CLD or death (OR 0.35; 95% CI 0.18–0.71) were significantly lower in hospitals with a high use of COX-I prophylaxis compared with hospitals that did not use prophylaxis[38]. Therefore, prophylactic COX-Is might be beneficial in preterm infants but its use is restricted in a substantial proportion of NICUs due to the concomitant harms as perceived by the care-provider. The potential harms include SIP and NEC, two surgical emergencies with high death rates. Stavel et al. showed that the odds for SIP in infants born <30 weeks of gestation was significantly higher with prophylactic indomethacin (adjusted OR 2.43; 95% CI 1.41-4.19)[37]. Similarly, a recent individual patient data meta-analysis has shown that concomitant use of prophylactic indomethacin to prevent IVH and hydrocortisone to improve survival without CLD also increases the risk of SIP (OR 2.50; 95% CI 1.33-4.69)[39].

Therefore, successful prevention of a symptomatic PDA may reduce the risk of severe IVH and CLD but at the same time increase the risk of SIP and NEC (as illustrated in Figure 3). As a result, for some care-providers the desirable consequences of COX-I prophylaxis may not clearly outweigh its undesirable consequences, and hence there is often a reluctance among neonatal practitioners to consider pharmacoprophylaxis for PDA in preterm infants. This suggests that there is a need for a systematic analysis of the available data and a comprehensive high-quality clinical practice guideline on the prophylactic use of COX-Is for the prevention of morbidity and mortality in preterm infants.

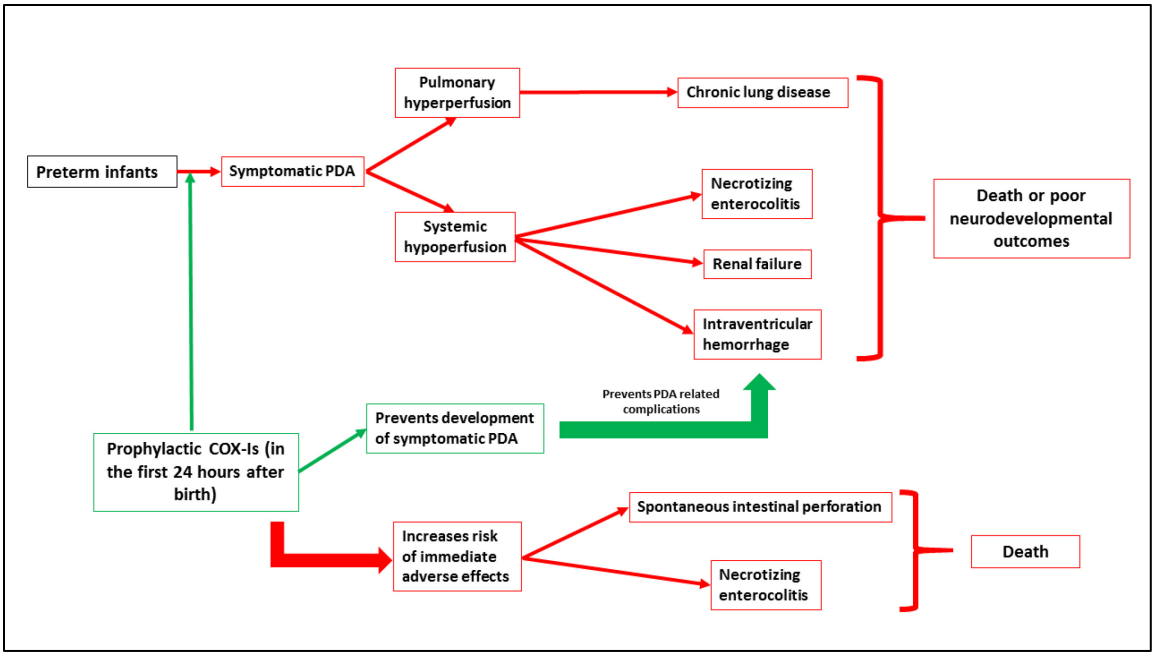


Figure 3. Concept map illustrating potential PDA-related complications in preterm infants as well as potential benefits and risks associated with prophylactic COX-Is

The missing link: patient and family values and preferences

Patient and family preferences, as defined by Montori et al, specifically refer to the "perspectives, beliefs, expectations, and goals for health and life" of the parents/guardians for their infants, and to the processes that families use in "considering the potential benefits, harms, costs, and inconveniences of the management options in relation to one another"[40,41]. Consequently, it is plausible that the preference for or against an intervention is determined by the relative importance of the health outcomes that the family attaches to the intervention[41]. With regards to use of COX-Is, the choice of COX-I prophylaxis is largely driven by clinician preferences with little or no input from families regarding their values and preferences. This is primarily due to the fact that there is limited research on how to incorporate family values and preferences into clinical decision making in neonatology. Neonatal care is largely guided by practice guidelines and position statements developed locally by the respective institutions as well as by national and international organizations such as the Fetus and Newborn Committees of the American Academy of Pediatrics and the Canadian Pediatric Society. These guidelines are often developed almost exclusively by health care professionals with little or no input from families of the infants being cared for[42]. In a recent qualitative study, Weiss et al explored how characteristics of

medical decisions influence parents' preferences for control over decisions for their seriously ill infants. Parents identified two main factors that were associated with a preference to delegate decisions to the medical team: a high degree of urgency and a high level of required medical expertise[43]. These two factors apply to most clinical decisions in preterm infants in the first few hours after birth. Therefore, it is not surprising that clinical decisions such as whether to use COX-I prophylaxis, and if so, in which gestational age group and with what medication are primarily directed by the neonatal care provider. An exploration and optimization of shared family and neonatal care provider decision-making is needed to facilitate clinical practice guideline development, alongside high-quality systematic review and meta-analysis of the absolute estimates, including the certainty of these estimates for both benefits and harms associated with prophylactic COX-Is.

Available evidence on family values related to COX-I prophylaxis

In consultation with a research librarian, I conducted a comprehensive electronic search of MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) for clinical practice guidelines on COX-I pharmacoprophylaxis in preterm infants as well as for studies exploring family values and preferences related to COX-I prophylaxis. Review of literature showed that there is only one study that explored maternal values and preferences for decision on PDA pharmacoprophylaxis[44]. This 2015 study was limited by the fact that it only considered indomethacin prophylaxis as a management option. Furthermore, while presenting outcome probabilities, only absolute estimates were presented without an accompanying certainty of evidence for each estimate across the entire spectrum of prematurity. It has been shown that families better understand absolute risk reduction and visual aids (such as icon arrays and bar graphs) for risk communication, and decision making is likely to be improved when decision makers have knowledge of the certainty of evidence[45,46]. To our knowledge, there are no clinical practice guidelines on PDA pharmacoprophylaxis that explicitly incorporate family values and preferences. With the availability of potentially safer medications such as ibuprofen and acetaminophen, parental thresholds for providing pharmacoprophylaxis may be different for different medications at different gestations. Therefore, to provide clinicians with trustworthy practice recommendations, a comprehensive synthesis of available evidence is required;

the evidence then needs to be summarized for parents and families and used to explore their preferences for choice of pharmacotherapy.

Incorporating patient and family values and preferences using the GRADE approach

GRADE (Grading of Recommendations, Assessment, Development and Evaluations) methodology as applied to practice guidelines involves two key steps[47]. First, the GRADE approach is a system for rating the certainty of a body of evidence on an outcome-by-outcome basis, based on a systematic literature review and meta-analysis. Second, in moving from evidence to guideline recommendations, the GRADE approach offers a transparent and structured process for developing clinical practice guideline recommendations, either strong or conditional (previously referred to as weak), and either for or against an intervention[48]. Emerging GRADE methodology provides guidance for the systematic consideration of family values and preferences to make guideline recommendations that involve trading off the benefits with the potential harms, and inconveniences of treatment[48,49].

THESIS PROJECT AIMS & OBJECTIVES

The overarching aim of this project was to develop a rigorous and transparent clinical practice guideline for the prophylactic use of COX-Is for prevention of morbidity and mortality in extremely preterm infants incorporating family values and preferences.

The guidelines were developed in accordance with the Guideline International Network (GIN)-McMaster Guideline Development Checklist and the AGREE II instrument[50,51]. The AGREE II (Appraisal of Guidelines for Research & Evaluation II) instrument was developed to address the issue of variability in quality of guidelines. The instrument systematically assesses the methodological rigor and transparency with which guideline recommendations are formulated[51]. The guideline development process involved three distinct projects which comprised the three specific objectives of this thesis:

Specific Objectives:

The specific objectives of the project were to:

1. Compare the available pharmacoprophylactic COX-I drugs to prevent morbidity and mortality in preterm infants through a systematic review and network meta-analysis of the available evidence
2. Evaluate family values and preferences for COX-I prophylaxis in preterm infants
3. Formulate guideline recommendations using the GRADE evidence-to-decision framework

THESIS OVERVIEW

The thesis has been developed in a publication thesis format comprising three papers, each corresponding to one of the specific objectives outlined above, in addition to this introductory chapter and a final concluding chapter.

In the first paper (chapter two), I present the results of a comprehensive systematic review and network meta-analysis of RCTs that compared the prophylactic use of indomethacin, ibuprofen or acetaminophen compared against each other or placebo. This review identified 28 RCTs that enrolled a total of 3999 preterm infants. Bayesian random-effects network meta-analysis demonstrated that prophylactic indomethacin (19 RCTs, 2877 infants) probably results in a small reduction in severe IVH, a moderate reduction in mortality and need for PDA ligation and may result in a small increase in CLD. Prophylactic indomethacin likely results in trivial differences in NEC, gastrointestinal perforation and cerebral palsy. Prophylactic ibuprofen (7 RCTs, 914 infants) probably results in a small reduction in severe IVH and a moderate reduction in need for PDA ligation. Prophylactic ibuprofen may result in a moderate reduction in death and trivial differences in CLD and NEC. The evidence was very uncertain about the effect of acetaminophen (2 RCTs, 208 infants) on any of the clinically relevant outcomes. This study was recently published in the Cochrane Database of Systematic Reviews and the search is updated until December 9, 2021[52].

The second paper (chapter three) explores the health-related values and preferences of former preterm infants and families of preterm infants on the use of COX-I prophylaxis for the prevention of PDA related morbidity and mortality. A cross-sectional semi-structured

mixed-methods study involving adults born very preterm (born <32 weeks of gestation) or families of very preterm infants currently in the NICU or having graduated from the NICU in the last 5 years was conducted in two phases*: (a) a pilot feasibility study (phase I)* involving 7 participants (5 parents; 2 adults born preterm) with the objective of learning from and modifying any logistic or methodological issues that could arise during the formal values and preferences study and *(b) a formal values and preferences study (phase II)* with a pre-defined convenience sample of 40 participants that was decided by the research team based on the recruitment rate and feedback from the pilot phase. This study showed that there was minimal variability in how participants valued the main outcomes, with death and severe IVH rated as the two most serious outcomes. Variability was noted in the choice of pharmacoprophylaxis when participants were presented with the benefits and harms of each drug. The manuscript of this paper is ready for submission to a peer-reviewed journal.

The final paper (chapter four) outlines the guideline development process and the final practice recommendations as per the AGREE II instrument. The GRADE Evidence-to-Decision (EtD) framework for multiple comparisons was used to develop the guideline recommendations. A 12-member expert panel, including five experienced neonatal care providers, two methods experts, one pharmacist, two parents of former extremely preterm infants and two adults born extremely preterm, was convened. Patient-important clinical outcomes were defined a priori. The panel recommended that prophylaxis with intravenous indomethacin may be considered in extremely preterm infants *[conditional recommendation, moderate certainty in estimate of effects]*, with due emphasis on shared decision making with parents to evaluate their values and preferences. The panel recommended against routine use of ibuprofen prophylaxis in this gestational age group *[conditional recommendation, low certainty in estimate of effects]*. However, the panel did encourage shared decision making with parents in centers that lack access to indomethacin and have high rates of severe IVH and death in extremely preterm infants. The panel strongly recommended against use of prophylactic acetaminophen until further research evidence becomes available *[strong recommendation, very low certainty in estimate of effects]*. The manuscript of this paper is also ready for submission to a peer-reviewed journal.

The concluding chapter (chapter five) summarizes the results of the network meta-analysis (chapter two), the cross-sectional semi-structured mixed-methods study on health-related values and preferences (chapter three), and the final practice recommendations on prophylactic COX-I drug use in extremely preterm infants (chapter four). The chapter then discusses the relative merits and limitations of this project and concludes by outlining the possible future directions that may help enhance evidence-based family centered clinical decision-making.

References

1. Government of Canada, Canadian Institutes of Health Research, and Institute of Human Development, Child and Youth Health. “New Pan-Canadian Network Aims to Boost Health Outcomes for Preterm Infants." [Internet]. CIHR; Available from: http://www.cihr-irsc.gc.ca/e/50654.html.

2. Lim G, Tracey J, Boom N, Karmakar S, Wang J, Berthelot JM, et al. CIHI survey: Hospital costs for preterm and small-for-gestational age babies in Canada. Healthc Q. 2009;12(4):20–4.

3. Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm birth. N Engl J Med. 2008 Jul 17;359(3):262–73.

4. Lewandowski AJ. The preterm heart: a unique cardiomyopathy? Pediatr Res. 2019;85(6):738–9.

5. Crump C, Sundquist J, Winkleby MA, Sundquist K. Preterm birth and risk of chronic kidney disease from childhood into mid-adulthood: national cohort study. BMJ. 2019 01;365:l1346.

6. Gournay V. The ductus arteriosus: physiology, regulation, and functional and congenital anomalies. Arch Cardiovasc Dis. 2011 Nov;104(11):578–85.

7. Benitz WE, Committee on Fetus and Newborn, American Academy of Pediatrics. Patent Ductus Arteriosus in Preterm Infants. Pediatrics. 2016 Jan;137(1). doi: 10.1542/peds.2015-3730. Epub 2015 Dec 15

8. Clyman RI. The role of patent ductus arteriosus and its treatments in the development of bronchopulmonary dysplasia. Semin Perinatol. 2013 Apr;37(2):102–7.

9. Ballabh P. Intraventricular hemorrhage in premature infants: mechanism of disease. Pediatr Res. 2010 Jan;67(1):1–8.

10. Drougia A, Giapros V, Krallis N, Theocharis P, Nikaki A, Tzoufi M, et al. Incidence and risk factors for cerebral palsy in infants with perinatal problems: a 15-year review. Early Hum Dev. 2007 Aug;83(8):541–7.

11. Chung MY, Fang PC, Chung CH, Huang CB, Ou Yang MH, Chen CC. Risk factors for hemodynamically-unrelated cystic periventricular leukomalacia in very low birth weight premature infants. J Formos Med Assoc. 2005 Aug;104(8):571–7.

12. Dollberg S, Lusky A, Reichman B. Patent ductus arteriosus, indomethacin and necrotizing enterocolitis in very low birth weight infants: a population-based study. J Pediatr Gastroenterol Nutr. 2005 Feb;40(2):184–8.

13. Brown ER. Increased risk of bronchopulmonary dysplasia in infants with patent ductus arteriosus. J Pediatr. 1979 Nov;95(5 Pt 2):865–6.

14. Dice JE, Bhatia J. Patent Ductus Arteriosus: An Overview. J Pediatr Pharmacol Ther. 2007;12(3):138–46.

15. The Canadian Neonatal Network™ [Internet]. [cited 2019 Dec 4]. Available from: http://www.canadianneonatalnetwork.org/portal/CNNHome.aspx

16. Howes A, Hilditch C, Keir A. What clinical practice strategies have been shown to decrease incidence rates of intraventricular haemorrhage in preterm infants? Journal of Paediatrics and Child Health. 2019;55(10):1269–78.

17. Jain A, Shah PS. Diagnosis, Evaluation, and Management of Patent Ductus Arteriosus in Preterm Neonates. JAMA Pediatr. 2015 Sep;169(9):863–72.

18. Ohlsson A, Shah SS. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev. 2019 21;6:CD004213.

19. Allegaert K, Anderson B, Simons S, van Overmeire B. Paracetamol to induce ductus arteriosus closure: is it valid? Arch Dis Child. 2013 Jun;98(6):462–6.

20. Gillam-Krakauer M, Reese J. Diagnosis and Management of Patent Ductus Arteriosus. NeoReviews. 2018 Jul 1;19(7):e394–402.

21. Ferguson JM. Pharmacotherapy for patent ductus arteriosus closure. Congenit Heart Dis. 2019 Jan;14(1):52–6.

22. Ment LR, Stewart WB, Ardito TA, Huang E, Madri JA. Indomethacin promotes germinal matrix microvessel maturation in the newborn beagle pup. Stroke. 1992 Aug;23(8):1132–7.

23. Härmä A, Aikio O, Härkin P, Leskinen M, Valkama M, Saarela T, et al. Subgroup analysis of the early paracetamol trial to preterm infants found haemodynamic changes and improved oxygenation. Early Hum Dev. 2020 Jun;145:105042.

24. Enzmann D, Murphy-Irwin K, Stevenson D, Ariagno R, Barton J, Sunshine P. The natural history of subependymal germinal matrix hemorrhage. Am J Perinatol. 1985 Apr;2(2):123–33.

25. Fowlie PW, Davis PG, McGuire W. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. Cochrane Database Syst Rev. 2010 Jul 7;(7):CD000174.

26. Liebowitz M, Clyman RI. Prophylactic Indomethacin Compared with Delayed Conservative Management of the Patent Ductus Arteriosus in Extremely Preterm Infants: Effects on Neonatal Outcomes. J Pediatr. 2017;187:119-126.e1.

27. Seyberth HW, Rascher W, Hackenthal R, Wille L. Effect of prolonged indomethacin therapy on renal function and selected vasoactive hormones in very-low-birth-weight infants with symptomatic patent ductus arteriosus. J Pediatr. 1983 Dec;103(6):979–84.

28. Coombs RC, Morgan ME, Durbin GM, Booth IW, McNeish AS. Gut blood flow velocities in the newborn: effects of patent ductus arteriosus and parenteral indomethacin. Arch Dis Child. 1991 Oct;66(10):1261.

29. Wolf WM, Snover DC, Leonard AS. Localized intestinal perforation following intravenous indomethacin in premature infants. J Pediatr Surg. 1989 Apr;24(4):409–10.

30. Friedman WF, Hirschklau MJ, Printz MP, Pitlick PT, Kirkpatrick SE. Pharmacologic closure of patent ductus arteriosus in the premature infant. N Engl J Med. 1976 Sep 2;295(10):526–9.

31. Ohlsson A, Bottu J, Govan J, Ryan ML, Fong K, Myhr T. Effect of indomethacin on cerebral blood flow velocities in very low birth weight neonates with a patent ductus arteriosus. Dev Pharmacol Ther. 1993;20(1–2):100–6.

32. Mitra S, Rønnestad A, Holmstrøm H. Management of patent ductus arteriosus in preterm infants--where do we stand? Congenit Heart Dis. 2013 Dec;8(6):500–12.

33. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. Cochrane Database Syst Rev. 2018 28;9:CD003481.

34. Ohlsson A, Shah PS. Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants. Cochrane Database Syst Rev. 2018 06;4:CD010061.

35. Ji Y, Azuine RE, Zhang Y, Hou W, Hong X, Wang G, et al. Association of Cord Plasma Biomarkers of In Utero Acetaminophen Exposure With Risk of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in Childhood. JAMA Psychiatry. 2019 Oct 30;1–11.

36. Ystrom E, Gustavson K, Brandlistuen RE, Knudsen GP, Magnus P, Susser E, et al. Prenatal Exposure to Acetaminophen and Risk of ADHD. Pediatrics. 2017 Nov;140(5):e20163840.

37. Stavel M, Wong J, Cieslak Z, Sherlock R, Claveau M, Shah PS. Effect of prophylactic indomethacin administration and early feeding on spontaneous intestinal perforation in extremely low-birth-weight infants. J Perinatol. 2017;37(2):188–93.

38. Reese J, Shelton EL, Slaughter JC, McNamara PJ. Prophylactic Indomethacin Revisited. J Pediatr. 2017 Jul;186:11-14.e1.

39. Shaffer ML, Baud O, Lacaze-Masmonteil T, Peltoniemi OM, Bonsante F, Watterberg KL. Effect of Prophylaxis for Early Adrenal Insufficiency Using Low-Dose Hydrocortisone in Very Preterm Infants: An Individual Patient Data Meta-Analysis. J Pediatr. 2019 Apr;207:136-142.e5.

40. Montori VM, Elwyn G, Devereaux P, Straus SE, Haynes RB, Guyatt G. Decision Making and the Patient. In: Guyatt G, Rennie D, Meade MO, Cook DJ, editors. Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice, 3rd ed [Internet]. New York, NY: McGraw-Hill Education; 2015 [cited 2022 Apr 17]. Available from: jamaevidence.mhmedical.com/content.aspx?aid=1183878213

41. Zhang Y, Coello PA, Brożek J, Wiercioch W, Etxeandia-Ikobaltzeta I, Akl EA, et al. Using patient values and preferences to inform the importance of health outcomes in practice guideline development following the GRADE approach. Health Qual Life Outcomes. 2017 May 2;15(1):52.

42. Mitra S, Reid M, McDougall B, Johnston BC. Are neonatal clinical practice guidelines truly evidence-based? A case for incorporating family values and preferences. Acta Paediatr. 2019 Sep;108(9):1564–6.

43. Weiss EM, Barg FK, Cook N, Black E, Joffe S. Parental Decision-Making Preferences in Neonatal Intensive Care. J Pediatr. 2016;179:36-41.e3.

44. AlFaleh K, Alluwaimi E, AlOsaimi A, Alrajebah S, AlOtaibi B, AlRasheed F, et al. A prospective study of maternal preference for indomethacin prophylaxis versus symptomatic treatment of a patent ductus arteriosus in preterm infants. BMC Pediatr. 2015 Apr 22;15:47.

45. Zipkin DA, Umscheid CA, Keating NL, Allen E, Aung K, Beyth R, et al. Evidence-based risk communication: a systematic review. Ann Intern Med. 2014 Aug 19;161(4):270–80.

46. Hultcrantz M, Rind D, Akl EA, Treweek S, Mustafa RA, Iorio A, et al. The GRADE Working Group clarifies the construct of certainty of evidence. J Clin Epidemiol. 2017 Jul;87:4–13.

47. Schünemann HJ, Wiercioch W, Brozek J, Etxeandia-Ikobaltzeta I, Mustafa RA, Manja V, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. Journal of Clinical Epidemiology. 2017 Jan 1;81:101–10.

48. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008 Apr 26;336(7650):924–6.

49. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol. 2013 Jul;66(7):719–25.

50. McMaster University > CE&B Grade > Guideline Development Checklist [Internet]. [cited 2019 Dec 4]. Available from: https://cebgrade.mcmaster.ca/guidecheck.html

51. Brouwers MC, Kerkvliet K, Spithoff K, AGREE Next Steps Consortium. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. BMJ. 2016 Mar 8;i1152.

52. Mitra S, Gardner CE, MacLellan A, Disher T, Styranko DM, Campbell-Yeo M, et al. Prophylactic cyclo-oxygenase inhibitor drugs for the prevention of morbidity and mortality in preterm infants: a network meta-analysis. Cochrane Database Syst Rev. 2022 Apr 1;4:CD013846.

CHAPTER 2: SYSTEMATIC REVIEW & NETWORK META-ANALYSIS

Prophylactic cyclo-oxygenase inhibitor drugs for the prevention of morbidity and mortality in preterm infants: a network meta-analysis

Authors

Souvik Mitra[1]; Courtney E Gardner[2]; Abigale MacLellan[3]; Tim Disher[4]; Danielle M Styranko[2]; Marsha Campbell-Yeo[5]; Stefan Kuhle[6]; Bradley C Johnston[7]; Jon Dorling[8]

Affiliations

[1]Departments of Pediatrics, Community Health & Epidemiology, Dalhousie University & IWK Health Centre, Halifax, Canada; [2]Division of Neonatal-Perinatal Medicine, IWK Health Centre, Halifax, Canada; [3]Faculty of Medicine, Dalhousie University, Halifax, Canada; [4]Evidence Synthesis and Data Analytics, EVERSANA Inc, Sydney, Canada; [5]Neonatal Intensive Care Unit, IWK Health Centre, Halifax, Canada; [6]Departments of Pediatrics and Obstetrics & Gynecology, Dalhousie University, Halifax, Canada; [7]Department of Nutrition, Texas A&M University, College Station, Texas, USA; [8]Division of Neonatal-Perinatal Medicine, Department of Pediatrics, Faculty of Medicine, Dalhousie University, Halifax, Canada

Citation: Mitra S , Gardner CE, MacLellan A, Disher T, Styranko DM, Campbell-Yeo M, Kuhle S, Johnston BC, Dorling J. Prophylactic cyclo-oxygenase inhibitor drugs for the prevention of morbidity and mortality in preterm infants: a network meta- analysis. Cochrane Database of Systematic Reviews 2022, Issue 4. Art. No.: CD013846. DOI: 10.1002/14651858.CD013846.pub2.

STATUS: PUBLISHED

Contributions of authors

SM conceived the project, under the mentorship of BCJ and JD. SM analyzed the data and drafted the review. SM, DS, AM, CEG, MCY, SK, BCJ and JD reviewed all drafts, and approved the final version of the review.

Abstract

Background

Patent ductus arteriosus (PDA) is associated with significant morbidity and mortality in preterm infants. Cyclooxygenase inhibitors (COX-I) may prevent PDA-related complications. Controversy exists on which COX-I drug is the most effective and has the best safety profile in preterm infants.

Objectives

To compare the effectiveness and safety of prophylactic COX-I drugs and 'no COXI prophylaxis' in preterm infants using a Bayesian network meta-analysis (NMA).

Search methods

Searches of Cochrane CENTRAL via Wiley, OVID MEDLINE and Embase via Elsevier were conducted on 9 December 2021. We conducted independent searches of clinical trial registries and conference abstracts; and scanned the reference lists of included trials and related systematic reviews.

Selection criteria

We included randomized controlled trials (RCTs) that enrolled preterm or low birth weight infants within the first 72 hours of birth without a prior clinical or echocardiographic diagnosis of PDA and compared prophylactic administration of indomethacin or ibuprofen or acetaminophen versus each other, placebo or no treatment.

Data collection and analysis

We used the standard methods of Cochrane Neonatal. We used the GRADE NMA approach to assess the certainty of evidence derived from the NMA for the following

outcomes: severe intraventricular haemorrhage (IVH), mortality, surgical or interventional PDA closure, necrotizing enterocolitis (NEC), gastrointestinal perforation, chronic lung disease (CLD) and cerebral palsy (CP).

Main results

We included 28 RCTs (3999 preterm infants). Nineteen RCTs (n = 2877) compared prophylactic indomethacin versus placebo/no treatment, 7 RCTs (n = 914) compared prophylactic ibuprofen versus placebo/no treatment and 2 RCTs (n = 208) compared prophylactic acetaminophen versus placebo/no treatment. Nine RCTs were judged to have high risk of bias in one or more domains. We identified two ongoing trials on prophylactic acetaminophen.

Bayesian random-effects NMA demonstrated that prophylactic indomethacin probably led to a small reduction in severe IVH (network RR 0.66, 95% Credible Intervals [CrI] 0.49 to 0.87; absolute risk difference [ARD] 43 fewer [95% CrI, 65 fewer to 16 fewer] per 1000; median rank 2, 95% CrI 1-3; moderate-certainty), a moderate reduction in mortality (network RR 0.85, 95% CrI 0.64 to 1.1; ARD 24 fewer [95% CrI, 58 fewer to 16 more] per 1000; median rank 2, 95% CrI 1-4; moderate-certainty) and surgical PDA closure (network RR 0.40, 95% CrI 0.14 to 0.66; ARD 52 fewer [95% CrI, 75 fewer to 30 fewer] per 1000; median rank 2, 95% CrI 1-2; moderate-certainty) compared to placebo. Prophylactic indomethacin resulted in trivial difference in NEC (network RR 0.76, 95% CrI 0.35 to 1.2; ARD 16 fewer [95% CrI, 42 fewer to 13 more] per 1000; median rank 2, 95% CrI 1-3; high-certainty), gastrointestinal perforation (network RR 0.92, 95% CrI 0.11 to 3.9; ARD 4 fewer [95% CrI, 42 fewer to 137 more] per 1000; median rank 1, 95% CrI 1-3; moderate-certainty) or CP (network RR 0.97, 95% CrI 0.44 to 2.1; ARD 3 fewer [95% CrI, 62 fewer to 121 more] per 1000; median rank 2, 95% CrI 1-3; low-certainty) and may result in a small increase in CLD (network RR 1.10, 95% CrI 0.93 to 1.3; ARD 36 more [95% CrI, 25 fewer to 108 more] per 1000; median rank 3, 95% CrI 1-3; low-certainty).

Prophylactic ibuprofen probably led to a small reduction in severe IVH (network RR 0.69, 95% CrI 0.41 to 1.14; ARD 39 fewer [95% CrI, 75 fewer to 18 more] per 1000; median rank 2, 95% CrI 1-4; moderate-certainty) and moderate reduction in surgical PDA closure (network RR 0.24, 95% CrI 0.06 to 0.64; ARD 66 fewer [95% CrI, from 82 fewer to 31

fewer] per 1000; median rank 1, 95% CrI 1-2; moderate-certainty) compared to placebo. Prophylactic ibuprofen may result in moderate reduction in mortality (network RR 0.83, 95% CrI 0.57 to 1.2; ARD 27 fewer [95% CrI, from 69 fewer to 32 more] per 1000; median rank 2, 95% CrI 1-4; low-certainty) and leads to trivial difference in NEC (network RR 0.73, 95% CrI 0.31 to 1.4; ARD 18 fewer [95% CrI, from 45 fewer to 26 more] per 1000; median rank 1, 95% CrI 1-3; high-certainty), or CLD (network RR 1.00, 95% CrI 0.83 to 1.3; ARD 0 fewer [95% CrI, from 61 fewer to 108 more] per 1000; median rank 2, 95% CrI 1-3; low-certainty). The evidence is very uncertain on effect of ibuprofen on gastrointestinal perforation (network RR 2.6, 95% CrI 0.42 to 20.0; ARD 76 more [95% CrI, from 27 fewer to 897 more] per 1000; median rank 3, 95% CrI 1-3; very low-certainty).

The evidence is very uncertain on the effect of prophylactic acetaminophen on severe IVH (network RR 1.17, 95% CrI 0.04 to 55.2; ARD 22 more [95% CrI, from 122 fewer to 1000 more] per 1000; median rank 4, 95% CrI 1-4; very low-certainty), mortality (network RR 0.49, 95% CrI 0.16 to 1.4; ARD 82 fewer [95% CrI, from 135 fewer to 64 more] per 1000; median rank 1, 95% CrI 1-4; very low-certainty), or CP (network RR 0.36, 95% CrI 0.01 to 6.3; ARD 70 fewer [95% CrI, from 109 fewer to 583 more] per 1000; median rank 1, 95% CrI 1-3; very low-certainty).

In summary, based on ranking statistics, both indomethacin and ibuprofen were equally effective (median ranks 2 respectively) in reducing severe IVH and mortality. Ibuprofen (median rank 1) was more effective than indomethacin in reducing surgical PDA ligation (median rank 2). However, no statistically-significant differences were observed between the COX-I drugs for any of the relevant outcomes.

Authors' conclusions

Prophylactic indomethacin probably results in a small reduction in severe IVH and moderate reduction in mortality and surgical PDA closure (moderate-certainty), may result in a small increase in CLD (low-certainty) and results in trivial differences in NEC (high-certainty), gastrointestinal perforation (moderate-certainty) and cerebral palsy (low-certainty). Prophylactic ibuprofen probably results in a small reduction in severe

IVH and moderate reduction in surgical PDA closure (moderate-certainty), may result in a moderate reduction in mortality (low-certainty) and trivial differences in CLD (low-certainty) and NEC (high-certainty). The evidence is very uncertain about the effect of acetaminophen on any of the clinically-relevant outcomes.

Plain language summary

Prophylactic cyclo-oxygenase inhibitor drugs to prevent morbidity and mortality in preterm infants

Review question

Among the available cyclo-oxygenase inhibitor (COX-I) drugs (indomethacin, ibuprofen, acetaminophen), which one is the safest and most effective in preventing death and poor outcomes in preterm infants when given prophylactically without the prior knowledge of the presence of a patent ductus arteriosus (PDA) within the first 72 hours after birth?

Background

A PDA is a common complication in preterm or low-birth weight infants. PDA is an open vascular channel between the lungs and the heart which usually closes shortly after birth. In preterm infants, the PDA frequently remains open and may contribute to life- threatening complications. COX-I drugs such as indomethacin, ibuprofen and acetaminophen may prevent a PDA and related poor outcomes. Controversy exists on which of the three COX-I drugs, if any, improves clinical outcomes in preterm infants.

Study characteristics

We searched scientific databases for randomized controlled trials (clinical studies where people are randomly put into one of two or more treatment groups) in preterm babies (born at less than 37 weeks into pregnancy) or low-birthweight (weighing less than 2500 grams) infants where COX-I drugs were given without the prior knowledge of the presence of a PDA, within the first 72 hours after birth. The included studies compared administration of indomethacin or ibuprofen or acetaminophen versus each other, placebo or no treatment.

Key results

This review of 28 clinical trials (3999 preterm infants) found that prophylactic indomethacin probably results in a small reduction in severe brain bleeding, a moderate reduction in death and need for PDA surgery, and may result in a small increase in chronic lung disease. Prophylactic indomethacin likely results in trivial differences in necrotizing enterocolitis, gastrointestinal perforation and cerebral palsy. Prophylactic ibuprofen

probably results in a small reduction in severe brain bleeding and a moderate reduction in need for PDA surgery. Prophylactic ibuprofen may result in a moderate reduction in death and trivial differences in chronic lung disease and necrotizing enterocolitis. The evidence is very uncertain about the effect of acetaminophen on any of the clinically relevant outcomes. There are currently two ongoing trials on prophylactic use of acetaminophen.

Certainty of the evidence

According to GRADE (a method to score the certainty of the trials supporting each outcome), the certainty of the evidence varied from very low to high but was moderate for the most important outcomes of severe brain bleeding and death.

How up to date is the search evidence

The search is up to date as of 9 December 2021

Background

Description of the condition

The most important contributors to morbidity and mortality in preterm infants are intraventricular haemorrhage (IVH), prolonged duration of endotracheal mechanical ventilation with consequent lung injury, and hemodynamic disturbance leading to compromised end-organ perfusion (Clyman 2012[2]; The Canadian Neonatal Network 2019[3]). A common factor potentially responsible for these three pathophysiological mechanisms is patent ductus arteriosus (PDA) (Gournay 2011[4]). The ductus arteriosus is a blood vessel that connects the aorta with the pulmonary artery to bypass the lungs during fetal life. Following birth, closure of the ductus arteriosus begins and functional closure occurs over the next 24 to 72 hours (Benitz 2016[5]). In preterm infants, this process is usually delayed, leading to the ductus arteriosus remaining open beyond the first few days after birth. As a consequence, blood flow through the lungs increases and predisposes the infant to pulmonary congestion, surfactant inactivation, and respiratory failure, leading to increased oxygen requirement and need for ventilator support. At the same time, diversion of blood flow from the systemic circulation leads to systemic hypoperfusion of the bowel, kidney, and brain. Persistence of a PDA along with clinical signs of pulmonary congestion or systemic hypoperfusion (or both) is defined as a symptomatic or hemodynamically significant PDA. A persistent, symptomatic PDA in extremely preterm infants (infants born less than 28 weeks of gestational age) is associated with IVH and cerebral palsy, chronic lung disease, necrotizing enterocolitis (NEC), renal failure, and consequently higher rates of death (Ballabh 2010; Brown 1979; Chung 2005; Dice 2007; Dollberg 2005; Drougia 2007)[6–11]. According to The Canadian Neonatal Network 2019 report, 28% of preterm infants born at less than 33 weeks of gestation in Canada developed a PDA, and 48% of infants with a PDA received treatment with pharmacotherapy or surgical ligation.

Description of the intervention

Currently available pharmacotherapeutic options to prevent or treat a symptomatic PDA include cyclo-oxygenase inhibitor (COX-I) drugs such as indomethacin, ibuprofen, and acetaminophen (Mitra 2018[12]). Indomethacin and ibuprofen are non-steroidal anti-inflammatory drugs (NSAIDs) that act by inhibition of the cyclo-oxygenase enzyme,

thereby leading to downregulation of prostaglandin E2, a potent relaxant of the PDA (Clyman 2012; Jain 2015)[2,13]. Recently, acetaminophen, a selective inhibitor of the cyclo-oxygenase-2 enzyme, has emerged as another treatment option for PDA closure (Le 2015)[14]. Acetaminophen is postulated to inhibit the peroxidase enzyme, resulting in downregulation of prostaglandin E2 production (Grèen 1989)[15].

Use of indomethacin in preterm infants is associated with derangement of renal function (Seyberth 1983)[16], NEC (Coombs 1991)[17], gastrointestinal haemorrhage or perforation (Wolf 1989)[18], alteration of platelet function (Friedman 1976)[19], and impairment of cerebral oxygenation and blood flow (Ohlsson 1993)[20]. Ibuprofen appears to be associated with a lower risk of NEC and only transient renal insufficiency compared to indomethacin (Ohlsson 2020a)[21]. Acetaminophen has no documented short-term adverse effects. However, recent observational studies have indicated a possible association of maternal acetaminophen exposure with later development of autism and attention deficit/hyperactivity disorder (Bauer 2013; Ji 2020; Ystrom 2017)[22–24]. This review focuses on the prophylactic use of COX-I drugs (indomethacin, ibuprofen, or acetaminophen) to prevent death and PDA-related morbidities in preterm infants.

How the intervention might work

The aim of prophylactic COX-I drugs is to close a PDA before the development of any adverse hemodynamic consequences but without the need for echocardiographic screening or surveillance. In addition to PDA closure, prophylactic COX-I drugs may also directly affect the cerebral vasculature to prevent occurrence of IVH.

All available COX-I drugs (indomethacin, ibuprofen, and acetaminophen) have been shown to be significantly more effective in closing a PDA compared to no treatment (Mitra 2018)[12]. Ibuprofen appears as effective as indomethacin in closing a PDA (Ohlsson 2020a)[21]. There is moderate-certainty evidence to suggest that acetaminophen is as effective as ibuprofen and low-certainty evidence to suggest that acetaminophen is as effective as indomethacin in closing a PDA (Ohlsson 2020b)[25].

With regards to effect on the cerebral vasculature, Ment 1992[26] demonstrated in animal models that indomethacin stimulates basement membrane deposition in the germinal

matrix microvessels that may prevent germinal matrix haemorrhage and IVH. This postulated reduction in IVH has subsequently been demonstrated through randomized controlled trials (RCTs) of prophylactic indomethacin in preterm infants (Fowlie 2010)[27]. Prophylactic ibuprofen has also been shown to marginally reduce the incidence of severe IVH (Ohlsson 2020c)[28]. The role of acetaminophen in reduction of IVH in preterm infants has not yet been clearly established. Acetaminophen may help to prevent IVH by decreasing harmful mitochondrial superoxide production and intracellular oxidant stress, in addition to its direct effect on ductal constriction (Härmä 2020)[29]. In the post- hoc analysis of a recent RCT of prophylactic acetaminophen in very preterm infants (Härkin 2016)[30], it was shown that infants in the acetaminophen group had a significantly higher ductal closure, significantly higher peripheral oxygen saturation (SpO_2), significantly higher regional cerebral oxygen saturation ($RcSO_2$), and significantly lower cerebral fractional tissue oxygen extraction (cFTOE) during the treatment period compared to the control group (Härmä 2020)[29]. This effect might be a direct effect of ductal constriction and improved cerebral blood flow, or an effect at the cellular level whereby acetaminophen reduced cFTOE by reducing mitochondrial respiration (Bisaglia 2002; Vergeade 2016)[31,32]. Several previous studies have shown that occurrence of IVH in preterm infants is preceded by reduction in $RcSO_2$ and increase in cFTOE (Baik 2015; Cimatti 2020)[33,34]. Therefore, by improving $RcSO_2$ and reducing cFTOE, acetaminophen may help to prevent IVH in preterm infants.

Although PDA and IVH are common morbidities in preterm infants, the clinical use of pharmacoprophylaxis has been a contentious issue. As discussed above, evidence from RCTs suggests that prophylactic use of indomethacin or ibuprofen could reduce severe IVH in preterm infants (Fowlie 2010; Ohlsson 2020c)[27,28], but may unnecessarily expose a large number of preterm infants to the harmful effects of COX-I drugs (Fowlie 2010; Reese 2017; Stavel 2017)[27,35,36].

Why it is important to do this review

The clinical use of pharmacoprophylaxis has primarily been driven by the perceived benefits versus potential risks, as determined by the treating physician. Successful prevention of a symptomatic PDA may reduce the risk of severe IVH, chronic lung disease,

and death, but at the same time may increase the risk of adverse outcomes. As a result, for some care providers the desirable consequences of COX-I prophylaxis may not sufficiently outweigh its undesirable consequences, and hence there is often a reluctance among neonatal practitioners to consider pharmacoprophylaxis for PDA in preterm infants (Reese 2017; Stavel 2017)[35,36]. The thresholds for using COX-I prophylaxis may also vary based on the balance of desirable and undesirable effects of each COX-I drug.

Previous Cochrane Reviews have separately compared placebo/no treatment against prophylactic indomethacin, ibuprofen, or acetaminophen (Fowlie 2010; Ohlsson 2020b; Ohlsson 2020c)[25,27,28]. There are currently no Cochrane Reviews that provide head- to-head comparisons between the three available pharmacoprophylactic agents. With increased emphasis on non-pharmacological conservative management, no prophylactic treatment has also become an increasingly adopted management approach. Given that there are currently four different management options (indomethacin, ibuprofen, acetaminophen, and no prophylaxis) available systematic reviews and meta-analyses using paired comparisons provide care providers with

limited evidence for informed decision-making, which likely leads to substantial practice variation. For example, the Cochrane Review by Fowlie and colleagues demonstrated that prophylactic indomethacin reduces severe IVH with a risk ratio (RR) of 0.66 (95% confidence interval [CI] 0.53 to 0.82) compared to placebo (Fowlie 2010)[27]. Similarly, the review by Ohlsson and colleagues demonstrated that ibuprofen may marginally reduce severe IVH (RR 0.67 [95% CI 0.45 to 1.00]) (Ohlsson 2020c)[28]. However, it is difficult to conclude which drug is better in preventing severe IVH from these two separate analyses. Using network meta-analysis to directly and indirectly compare available pharmacoprophylactic options may provide care providers with more reliable comparative effectiveness evidence with increased precision to help them choose the best available management option. Therefore, a systematic review and network meta- analysis according to Cochrane methodology is justified.

Objectives

To determine the comparative effectiveness and safety of prophylactic cyclo-oxygenase inhibitor (COX-I) drugs (indomethacin, ibuprofen, or acetaminophen) and 'no COX-I prophylaxis' in preterm infants using a Bayesian network meta-analysis.

Methods

Criteria for considering studies for this review

Types of studies

We included all published and unpublished randomized controlled trials (RCTs), irrespective of language and year of publication. Both superiority trials and non- inferiority trials were eligible for inclusion. Unpublished RCTs were only included if the study authors agreed to provide details of the trial methodology so that the internal validity of the study could be adequately ascertained.

Types of participants

We included neonates that are preterm (born at less than 37 weeks' completed gestation) or of low birth weight (less than 2500 grams). Given that we intended to perform a network meta-analysis in this review, the transitivity assumption was strictly considered in the eligibility criteria. Only preterm or low birth weight infants, within the first 72 hours of birth and without a prior clinical or echocardiographic diagnosis of patent ductus arteriosus (PDA), were eligible for inclusion in the network meta-analysis (for details, see Assessment of heterogeneity).

Types of interventions

Interventions included prophylactic administration of indomethacin, ibuprofen, or acetaminophen, compared with active medication, placebo, or no prophylaxis. The intervention must be delivered within the first 72 hours after birth, and there must be no documented clinical or echocardiographic evidence of PDA. In the network meta- analysis, each node was defined by the type of COX-I (indomethacin, ibuprofen, or acetaminophen), or no prophylaxis.

A standard course of prophylactic indomethacin constituted a cumulative dosage of up to 0.6 mg/kg (Fowlie 2010)[27]. A standard course of prophylactic ibuprofen constituted a

cumulative dosage of up to 20 mg/kg (Ohlsson 2020c)[28]. A standard course of prophylactic acetaminophen constituted a cumulative dosage of up to 420 mg/kg (15 mg/kg at six-hour intervals for three to seven days) (Ohlsson 2020b)[25]. The nodes representing each medication in the network corresponded to these standard doses unless otherwise specified. If one or more of the included studies reported that cumulative doses for any of these medications were higher than the standard cumulative doses as mentioned above, separate nodes denoting higher cumulative doses of the medications were planned to be added to the network.

Types of outcome measures

Primary outcomes

1. Severe intraventricular haemorrhage (IVH) (grade 3 or 4) (Papile 1978)[37]

2. Mortality (at discharge or at last reported follow-up, whichever is later)

Secondary outcomes

1. Receipt of pharmacotherapy for symptomatic PDA

2. Surgical or interventional PDA closure

3. Necrotizing enterocolitis (NEC) (stage 2 or greater) (Bell 1978)[38]

4. Gastrointestinal perforation (defined clinically by the presence of pneumoperitoneum in the absence of pneumatosis intestinalis and portal venous air on abdominal radiograph, and postoperatively by presence of isolated bowel perforation in the setting of an otherwise normal bowel, which is confirmed by histopathologic examination) (Meyer 1991; Pumberger 2002)[39,40]

5. Chronic lung disease (CLD) (defined as use of oxygen or respiratory support at 36 weeks' postmenstrual age) (Ehrenkranz 2005)[41]

6. Oliguria (defined as urine output of less than 1 mL/kg/hour)

7. IVH of any grade (Papile 1978)[37]

8. Periventricular leukomalacia (PVL; any grade) (de Vries 1992)[42]

9. Neurodevelopmental outcome (at 18 to 24 months of age)

10. Cerebral palsy

11. Major neurodevelopmental disability, defined as the presence of any of the following: cerebral palsy, developmental delay (an assessment greater than two standard deviations [SDs] below the mean on the following scales: Bayley Scales of Infant Development - Mental Development Index Edition II [BSID-MDI-II; Bayley 1993[43]], Bayley Scales of Infant and Toddler Development - Edition III Cognitive Scale [BSITD-III; Bayley 2005[44]] or Griffiths Mental Development Scale - General Cognitive Index [GCI; Griffiths 1954; Griffiths 1970][45,46]), intellectual impairment (intelligence quotient [IQ] greater than two SDs below the mean), blindness (vision less than 6/60 in both eyes), or sensorineural deafness requiring amplification (Jacobs 2013)[47].

Search methods for identification of studies

An Information Specialist (RP) developed search strategies in consultation with the authors. Leah Boulos peer-reviewed the MEDLINE search. Methodological filters were used to limit retrieval to randomized controlled trials. Searches for trials were conducted without language, publication year, publication type, or publication status restrictions. Methodological filters were sourced from the Cochrane Handbook of Systematic Reviews and the ISSG Search Filters Resource (https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home). Trial registries and conference abstracts were searched. Authors checked the reference lists of related systematic reviews and studies.

Electronic searches

The following databases were searched in December 2021.

- Cochrane Central Register of Controlled Trials (CENTRAL), 9 December 2021(via Wiley, 2021, Issue 12,)
- Ovid MEDLINE(R) ALL <1946 to 8 December 2021>
- Embase 1974 to 9 December2021 (Elsevier)
- Epistemonikos (https://www.epistemonikos.org)

MEDLINE, Embase and CENTRAL search strategies are available in Appendix 1.

Searching other resources

Trial registration records were identified using Cochrane CENTRAL and by independent searching of the following:

- U.S. National Library of Medicine registry (clinicaltrials.gov);
- World Health Organization's International Trial Registry and Platform (https://www.who.int/clinical-trials-registry-platform);
- The ISRCTN Registry (https://www.isrctn.com/).

Trial registry search strategies are available in Appendix 1.

Conference abstracts were identified using CENTRAL, Embase and via the following websites:

- The European Society for Pediatric Research: https://www.espr.eu/
- Pediatric Academic Societies: https://www.pas-meeting.org/past-abstracts/

We checked the reference lists of included studies and the reference lists of related systematic reviews to identify studies not captured in database searches. We searched for errata or retractions for included studies published on PubMed (www.ncbi.nlm.nih.gov/pubmed).

Data collection and analysis

Selection of studies

Pairs of review authors (SM, AM, DS, CEG) independently screened the search results by title and abstract for studies that potentially met the inclusion criteria. We obtained the full text of any articles that were potentially eligible, and two review authors independently performed full-text assessments (SM, AM, CEG). We resolved any disagreements through discussion and consensus. In the absence of consensus, a third person adjudicated on the decision for inclusion or exclusion of studies. We identified and excluded duplicates and collated multiple reports of the same study, so that each study rather than each report was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2009)[48] and to complete 'Characteristics of included studies' and 'Characteristics of excluded studies' tables. We carried out the study selection process on the Covidence platform.

Data extraction and management

Three review authors (SM, AM, CEG) independently extracted, assessed, and coded all data for each study using a standardized, piloted form developed in Microsoft Excel. We resolved any disagreements through consensus. For each study, one review author (SM) entered the extracted data into the GEMTC GUI application (van Valkenhoef 2012)[49], and a second review author (CEG) checked data entry. We collected information regarding the following.

1. General information: name of review author carrying out data extraction; study ID (and any other unique trial identifiers); name and contact address of first/corresponding author of included trial; citation of included trial; language of trial and details of any duplicate publications.
2. Trial information: trial design (type of RCT); location of trial; setting; sample size; study duration; treatment arms; method of randomization; inclusion and exclusion criteria; length of follow-up; trial registration data.
3. Characteristics of participants: gestational age; birth weight; baseline characteristics (sex; mode of delivery; receipt of antenatal steroids; deferred cord clamping); age (in hours) at initiation of treatment.
4. Characteristics of interventions: number of treatment arms; description of experimental and control arm(s); timing, dose and route of administration of intervention; other differences between intervention arms.
5. Outcomes: all relevant arm-level data on primary and secondary outcomes as outlined in Types of outcome measures. We will also collect data on stated outcome measures that have been defined in a manner different from our stated definitions in Types of outcome measures.
6. Risk of bias: sequence generation; allocation concealment; blinding (participants, personnel, outcome assessors); incomplete outcome data; selective outcome reporting; other sources of bias.

We also intended to collect data on any cost or resource information reported in the included studies. Although this does not constitute a formal economic evaluation, it may

provide useful additional information that may be of value in development of a clinical practice guideline. If information was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors (SM, AM, CEG) independently assessed the risk of bias (low, high, or unclear) of all included trials using the Cochrane risk of bias tool for the following domains (Higgins 2019)[50].

1. Sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Any other bias

We resolved any disagreements by consensus. See Appendix 2 for a more detailed description of risk of bias for each domain.

Measures of treatment effect

Relative treatment effects

We used risk ratios (RRs) and absolute risk differences (ARDs) for categorical variables, and mean differences (MDs) for continuous variables. We used Bayesian random-effects models with a binomial likelihood and log link for both initial pairwise meta-analyses as well as subsequent network meta-analyses (see Data synthesis for details). Therefore, we reported the 95% credible intervals (CrIs) for all estimates.

These were summarized in forest plots displaying the results from pairwise, indirect and network (combining direct and indirect) analyses for the comparisons of treatment with one COX-I medication (indomethacin, ibuprofen, acetaminophen) versus another or

control (placebo or no treatment). A network ARD was calculated from the network RR estimates using an assumed control risk that was derived by dividing the total event number by the total infant number in the control groups in the network.

Relative treatment ranking

An overall ranking for each intervention was built from these RRs and was presented as median ranks (with 95% CrIs) for each outcome. We further calculated the surface under the cumulative ranking curve (SUCRA) to explore the potential order of treatment hierarchy (Salanti 2011)[51]. SUCRA is an index reflecting the degree to which an intervention is superior or inferior to the others. Calculation of SUCRA is based on the cumulative probabilities of the treatments being ranked in each position, and the SUCRA is the final area under the curve of the graph for these probabilities. SUCRA would be one when a treatment is certain to be the best and zero when a treatment is certain to be the worst with values ranging from one (the best intervention) to zero (the worst intervention).

Unit of analysis issues

The unit of analysis was the participating infant in individually randomized trials. We included multi-arm trials and accounted for the correlation between the effect estimates in the network meta-analysis (NMA). We treated multi-arm studies as multiple independent comparisons in pairwise meta-analyses, and these were not combined in any analysis.

For cluster-RCTs, if studies had not taken clustering into account, methods in the *Cochrane Handbook of Systematic Reviews of Interventions* were used to perform approximately correct analyses (Higgins 2019)[50]. Data from cluster-randomized trials were only included in meta-analyses if clustering had been quantified and reported using an intra-cluster correlation coefficient (ICC), or if other approximately correct analyses could be performed (Costantini 2020)[52]. For cross-over RCTs, data from only the first period prior to cross-over were used, due to potential carry-over effects.

'No prophylaxis' was included as a node in the NMA to help with indirect analyses and formation of a hierarchy of interventions. In the NMA, we included all comparisons where there are sufficient data to do so.

Dealing with missing data

We handled missing data according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019)[50]. For included studies, we recorded the number of participants lost to follow-up. We contacted corresponding authors to obtain any missing participant outcome data that were not reported. We attempted to contact the authors up to a maximum of three times to obtain missing information. If we were still unable to obtain the missing outcome information, and where missing data were thought to introduce serious bias (defined as 20% or greater missing data), we performed sensitivity analysis to evaluate the impact of missing outcome data. For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis (i.e., all participants will be analyzed in the group to which they are allocated, regardless of whether or not they receive the allocated intervention).

Assessment of heterogeneity

Assessment of clinical and methodological heterogeneity within treatment comparisons

Prior to synthesis, we assessed all studies for clinical and methodological differences that may give rise to heterogeneity. We only pooled data if the studies were judged to be sufficiently similar from a clinical and methodological perspective.

Assessment of transitivity across treatment comparisons

We defined transitivity as the assumption that the studies were sufficiently similar in their distribution of effect modifiers on average so that indirect comparisons could be used as a valid method to compare two treatment options (Baker 2002; Cipriani 2013; Donegan 2010)[53–55].

Transitivity was established if the included infants met the following criteria with respect to potential effect modifiers.

1. Gestational age and birth weight: all infants included in the NMA had a gestational age at birth of less than 37 weeks, or a birth weight of less than 2500 g (or both)

2. PDA status: all included infants were randomized to receive the intervention(s) prophylactically, and not based on prior clinical/echocardiographic knowledge of their PDA

3. Timing of intervention: all included infants received the interventions within the first 72 hours after birth

Investigation of heterogeneity

We explored statistical heterogeneity in both pairwise and network comparisons. In case of pairwise comparisons, we assessed the heterogeneity by visual inspection of the forest plots and by using the I2 statistic, with the following thresholds for interpretation (Higgins 2019)[50].

1. Less than 25%: no heterogeneity

2. 25% to 49%: low heterogeneity

3. 50% to 74%: moderate heterogeneity

4. Greater than 75%: substantial heterogeneity

Assessment of statistical inconsistency

Evidence from an NMA may be inconsistent if the direct and indirect evidence is incompatible (loop inconsistency) or the studies involving one of the treatments are fundamentally different from the studies involving another treatment (design inconsistency) (White 2012)[56]. The consistency assumption among the combined sources of evidence in the network was first evaluated globally for the entire network using the design × treatment interaction model (Dias 2010; White 2012)[56,57]. We then applied the node-splitting model to assess local inconsistency for each comparison. In the node-splitting analysis a treatment comparison was split into a parameter for direct evidence and a parameter for indirect evidence in order to assess whether there was a significant disagreement between the two parameters. A P value of less than 0.05 indicated significant incoherence between the direct and indirect comparisons (Dias 2010; van Valkenhoef 2012; Veroniki 2013; White 2012)[49,56–58]. A common within-network heterogeneity was

assumed as the treatments were of similar nature, belonging to the same class of drugs (COX-I drugs) (Mitra 2018)[12].

Assessment of reporting biases

If there were 10 or more studies in a pairwise meta-analysis, we explored the existence of small-study effects (publication bias) through visual inspection of comparison- adjusted funnel plots (Dias 2013; van Valkenhoef 2012)[49,59]. In addition, we evaluated whether results of published posters and available dissertations were subsequently published as full-length manuscripts. We identified records in trial registries that have been terminated, listed as complete, or should feasibly be complete given last updated status with regard to availability of results or subsequent publication. For preregistered trials or those with published protocols, we assessed for the presence of reporting bias through comparison of their preplanned primary and secondary outcomes and analysis methods against those reported and used in the published report.

Data synthesis

We performed the network meta-analysis (NMA) following the methods stated in the *Cochrane Handbook for Systematic Reviews of Interventions* for all outcome measures (if data were available) (Higgins 2019)[50].

For each outcome, we performed initial pairwise meta-analysis using a Bayesian random-effects model for every direct pairwise comparison, where applicable. We then performed a Bayesian random-effects NMA to compare all interventions simultaneously using the Markov chain Monte Carlo method conducted under the assumption of transitivity (see Assessment of heterogeneity) (Lambert 2005; Lu 2004)[60,61]. We further assessed the inconsistency between the direct and indirect estimates, first globally for the entire network using the design × treatment interaction model, and then locally for each comparison using the node-splitting model (see Assessment of heterogeneity) (Dias 2010; van Valkenhoef 2012; Veroniki 2013; White 2012)[49,56–58].

For both pairwise meta-analysis and the NMA, we used Bayesian hierarchical models with non-informative priors assigned to all model parameters. Prior distributions for the relative effects were determined heuristically based on the following: N(0, (15 · S)2), where N

denotes normal distribution and S denotes the outcome scale. The value of S corresponded to an implausibly large variation on the scale of analysis which was determined heuristically based on available data (van Valkenhoef 2012)[49]. We used a series of 100,000 simulations to allow convergence and, after thinning of 10 and discarding the first 20,000 simulations, produced the outputs. We assessed model convergence on the basis of Gelman and Rubin diagnostic tests (Gelman 1992; Mitra 2018)[12,62]. We planned to conduct all analyses (both pairwise meta-analyses and NMA) using the R (R Core Team 2020)[63] package gemtc on the MetaInsight application (Owen 2019)[64], developed by the Cochrane Complex Review Support Unit (CRSU). We planned to conduct the design × treatment model to assess global network inconsistency using Stata version 15 (StataCorp) using the network command or similar software (Palmer 2016)[65].

Subgroup analysis and investigation of heterogeneity

If the information was available, we planned to conduct subgroup analyses for the following factors, to explore potential effect modification.

1. Gestational age (less than 28 weeks versus 28 weeks or greater)
2. Birth weight (less than 1000 g versus 1000 g or more)
3. Initiation of prophylaxis (24 hours of age or less versus over 24 hours of age)

Based on available information, we planned subgroup analyses for the following outcomes.

1. Severe IVH (grade 3 or 4) (Papile 1978)[37]
2. Mortality (at discharge or last reported follow-up, whichever is later)
3. Surgical or interventional PDA closure
4. NEC (stage 2 or greater) (Bell 1978)[38]
5. Gastrointestinal perforation (Meyer 1991; Pumberger 2002)[39,40]
6. Chronic lung disease (CLD) (defined as use of oxygen or respiratory support at 36 weeks' postmenstrual age) (Ehrenkranz 2005)[41]
7. Major neurodevelopmental disability

We planned to assess subgroup differences by comparing the network diagram for each subgroup. We then planned to perform a pairwise and NMA for each subgroup, and compare their relative treatment effects and their relative treatment ranking.

Sensitivity analysis

We planned to conduct sensitivity analyses to determine whether the findings were affected by including only studies of adequate methodology (low risk of bias), defined as those studies with adequate randomization and allocation concealment, blinding of intervention and measurement, and up to and including a 20% loss to follow-up.

Based on available information, sensitivity analyses were planned for the following outcomes.

1. Severe IVH (grade 3 or 4) (Papile 1978)[37]
2. Mortality (at discharge or last reported follow-up, whichever is later)
3. Surgical or interventional PDA closure
4. NEC (stage 2 or greater) (Bell 1978)[38]
5. Gastrointestinal perforation (Meyer 1991; Pumberger 2002)[39,40]
6. CLD (defined as use of oxygen or respiratory support at 36 weeks' postmenstrual age) (Ehrenkranz 2005)[41]
7. Major neurodevelopmental disability

Network meta-regression

We anticipated that RCTs on prophylactic use of COX-I drugs would have been conducted over the last 40 years, and would encompass wide variation in neonatal intensive care practices which was otherwise difficult to document as co-interventions or possible effect modifiers. Therefore, for each network, if at least 10 studies were available, we conducted a network meta-regression, assuming a common fixed coefficient across comparisons to explore the effect of year of publication on the most important clinical outcomes, i.e. mortality, severe IVH, gastrointestinal perforation, NEC, and CLD (Mitra 2018)[12]. We assumed year of publication as a proxy for contemporary neonatal care practices.

Summary of findings and assessment of the certainty of the evidence

We made an assessment of our confidence in the estimates (certainty of evidence) according to the GRADE criteria for NMA, as outlined by the GRADE working group (Brignardello-Petersen 2018; Puhan 2014)[66,67], for the following outcomes.

1. Severe IVH (grade 3 or 4) (Papile 1978)[37]
2. Mortality (at discharge or last reported follow-up, whichever is later)
3. Surgical or interventional PDA closure
4. NEC (stage 2 or greater) (Bell 1978)[38]
5. Gastrointestinal perforation (Meyer 1991; Pumberger 2002)[39,40]
6. CLD (defined as use of oxygen or respiratory support at 36 weeks' postmenstrual age) (Ehrenkranz 2005)[41]
7. Major neurodevelopmental disability, defined as the presence of any of the following: cerebral palsy, developmental delay (Bayley Scales of Infant Development - Mental Development Index Edition II [BSID-MDI-II; Bayley 1993[43]], Bayley Scales of Infant and Toddler Development - Edition III Cognitive Scale [BSITD-III; Bayley 2005[44]] or Griffiths Mental Development Scale - General Cognitive Index [GCI; Griffiths 1954; Griffiths 1970][45,46] assessment greater than two standard deviations [SDs] below the mean), intellectual impairment (intelligence quotient [IQ] greater than two SDs below the mean), blindness (vision less than 6/60 in both eyes), or sensorineural deafness requiring amplification (Jacobs 2013)[47].

To assess the certainty of evidence in a network meta-analysis, we took both direct and indirect comparisons into account (Brignardello-Petersen 2018; Puhan 2014)[66,67]. We assessed the certainty of evidence for each pairwise comparison using the following steps.

1. Certainty of evidence from the direct comparison, if available (step 1): We assessed and rated the direct comparison between two interventions (if head-to- head RCT data are available) based on the following categories, as outlined in the GRADE Handbook (Guyatt 2008; Schünemann 2013)[68,69]: risk of bias; indirectness; inconsistency (which is determined based on the heterogeneity assessment for pairwise comparisons); imprecision; and publication bias.

2. Certainty of evidence from the indirect comparisons (step 2): We followed step 1 for assessment of confidence from indirect estimates. For rating confidence in the indirect comparisons, we used the information obtained from the first- and second-order loops in the network. We preferentially derived the certainty of evidence of indirect comparisons from the certainty of evidence of the first-order loops. We derived the certainty of evidence of a first-order loop from the lowest certainty of evidence among direct comparisons within the first-order loop. When an indirect comparison has two or more first-order loops, we used the highest certainty of evidence among its first-order loops for the certainty of evidence of the indirect comparison. When no first-order loop was available, we derived the certainty of evidence for an indirect comparison from the second-order loops (Puhan 2014)[67].

3. Overall certainty of evidence for the comparison from the NMA (step 3): We rated the overall certainty in the NMA estimates for any paired comparison using the higher of the certainty rating amongst the contributing direct and indirect comparisons, if no statistically significant incoherence was observed. The specific reason for taking the higher certainty of evidence between the two comparisons was that if the direct and indirect estimates were coherent, the estimate with the lower certainty was not likely to introduce bias relative to the estimate with the higher certainty. If statistically significant incoherence was observed between the direct and indirect estimates, then the certainty of evidence for the comparison that made a dominant contribution to the network estimate was taken as the overall certainty of evidence. We determined the dominant contribution from the 95% CrI of the forest plots for the direct and indirect comparisons. The comparison that had the narrower 95% CrI between the two would have had the dominant contribution to the network (Brignardello-Petersen 2018)[66].

4. Assessment of inconsistency (step 4)*:* If inconsistency was noted either for the entire network using the design × treatment interaction model, or locally for each comparison using the node-splitting model (or both), we rated the certainty in the NMA estimate down by one level. When assessment of statistical inconsistency was not possible due to absence of head-to-head comparisons between interventions, we did not rate down the certainty of evidence any further due to presumed inconsistency, as the NMA would

have been conducted under the strict assumption of transitivity thereby ensuring clinical and methodological homogeneity between the indirect comparisons.

5. Assessment of imprecision (step 5): If the overall certainty in step 3 was rated down due to imprecision in either the certainty of the direct (step 1) or the indirect (step 2) estimate, and the network estimates were no longer imprecise, then we rated the certainty of evidence up by one level.

We mapped the results of the assessments for each of the above steps to a final rating, following the usual GRADE scale of: “high”, “moderate”, “low”, and “very low”. At each stage, two review authors (SM, AM) independently evaluated the certainty rating for the evidence (direct and indirect). We resolved disagreements through discussion and, where necessary, through consultation with a third review author.

When interpreting the relative effects of all COX-I drugs, the summary of findings tables included the network effect estimates and certainty judgments for the comparisons between each of the COX-I drugs versus placebo as the comparator. Given the potential complexity of the summary of findings tables with multiple comparisons, we created a single summary of findings table for each of the outcomes listed above, which was structured based on recent recommendations from the GRADE working group (Yepes-Nuñez 2019)[70]. Any differences between the protocol and the final review was outlined in the “Differences between protocol and review" section.

Results

Description of studies

Results of the search

Database searches identified 7155 records; trial register searches 646; and conference websites 35. After removing 2158 duplicates, 5678 records were available for screening. We excluded 5614 records based on title/abstract; assessed 64 full-text articles, of which 31 were excluded with reasons. We further identified three studies that are awaiting classification (Seok 1998, Akbari Asbagh 2015, Kalani 2016)[71–73] and two ongoing trials on prophylactic use of acetaminophen (NCT03641209;NCT04459117)[74,75], leaving 28

studies which were included in this review. The results of the search conducted in December 2021 are shown in Figure 1.

Included studies

We included a total of 28 studies with 3999 participants. Individual study characteristics, inclusion criteria, treatment details, and outcomes can be found in the Characteristics of included studies table.

Studies using prophylactic indomethacin

Nineteen studies that enrolled 2877 infants used prophylactic indomethacin as the active intervention. The following section provides a brief description of the included studies.

Bada 1989[76] conducted a single-center randomized controlled trial to examine the efficacy of indomethacin in preventing intraventricular haemorrhage (IVH). Infants with a birth weight less than 1500 g were randomized to receive either prophylactic indomethacin (initial dose 0.2 mg/kg intravenously at six hours of age, followed by two doses of 0.1 mg/kg at 18 hours and 30 hours of age; recruited n = 70) or placebo (recruited n = 71). Cranial ultrasounds were performed at 6, 12 and 24 hours of age, and daily thereafter until seven days of age. Perinatal characteristics were similar between the two groups, with the exception of maternal primigravida status and use of oxytocin, both of which more often observed in the placebo group. Compared to placebo, prophylactic indomethacin was associated with a decreased incidence of IVH (grades 2 to 4; 23% of infants in the indomethacin group versus 39% of infants in the control group, P = 0.03) and severe IVH with periventricular echo densities (3% in the indomethacin group versus 14% in the control group, P = 0.02).

Couser 1996[77] conducted a single-center randomized controlled trial to examine the effect of low-dose indomethacin on the development of hemodynamically significant patent ductus arteriosus (PDA) following prophylactic surfactant administration. Preterm infants (birth weight 600 g to 1250 g) who received prophylactic surfactant in the delivery room were randomized to receive either prophylactic indomethacin (0.1 mg/kg dose every 24 hours for a total of six doses; recruited n = 43) or placebo (0.9% sodium chloride (NaCl); recruited n = 47). Perinatal characteristics were similar between the two groups.

Echocardiography was performed prior to treatment, and on postnatal day seven. Presence of a moderate to large PDA was similar between the two groups at the start of treatment, and prophylactic indomethacin was associated with a significantly decreased incidence of hemodynamically significant PDA on day seven when compared to placebo (21% of infants in the indomethacin group versus 47% of infants in the placebo group, P = 0.018). Those with a residual hemodynamically significant PDA were treated with either indomethacin or surgical ligation. No other significant differences in outcomes (including bronchopulmonary dysplasia, IVH, and mortality) were observed between the two groups, nor were any adverse events observed. Couser 2000[78] subsequently published a 36-month follow-up of this study in 2000 which examined long-term neurodevelopmental outcomes. No significant differences in mortality or neurodevelopmental outcomes were observed between the prophylactic indomethacin and placebo groups.

Hanigan 1988[79] conducted a single-center randomized controlled trial to examine the efficacy of prophylactic low-dose indomethacin for the prevention of IVH. Preterm infants (< 34 weeks) with a birth weight < 1500 g were randomized to receive either prophylactic indomethacin (0.1 mg/kg intravenously at 12, 24, 48 and 72 hours of age; recruited n = 56) or placebo (saline; n = 55). Perinatal characteristics were similar between the two groups. Prophylactic indomethacin was associated with lower incidence of IVH (6/56 infants in the indomethacin group versus 11/55 infants in the placebo group, P = 0.174), although the incidence of severe IVH (grade 3 to 4) was not significantly different between the two groups.

Jannatdoust 2014[80] conducted a single-center randomized controlled trial to examine the effect of prophylactic indomethacin on the development of PDA and the duration of mechanical ventilation. Preterm infants (< 32 weeks gestational age) with a birth weight 800 g to 1500 g were randomized to receive either prophylactic indomethacin (initial dose 0.2mg/kg intravenously within 12 hours after birth, followed by two doses of 0.1 mg/kg at 24 and 48 hours; recruited n = 35) or no intervention (recruited n = 35). An echocardiogram was performed on day four, cranial ultrasound was performed at two weeks of age, and the type and duration of respiratory support was recorded. Perinatal characteristics were similar between the two groups. Prophylactic indomethacin was associated with a

decreased incidence of large PDA (none in the indomethacin group versus 25.7% in the control group) and duration of mechanical ventilation (both invasive and non-invasive). Prophylactic indomethacin was also associated with a decreased incidence of grade 1 IVH (22.9% indomethacin versus 8.8% control), grade 2 IVH (25.7% indomethacin versus 5.7% control), and grade 3 IVH (5.7% indomethacin versus 2.9% control), although the incidence of grade 4 IVH was similarly low between the two groups. No adverse events were reported.

Krueger 1987[81] conducted a single-center randomized controlled trial to examine the efficacy of prophylactic indomethacin in the prevention of symptomatic PDA. Preterm infants (birth weight 750 g to 1500 g) with hyaline membrane disease received either a single dose of prophylactic indomethacin (0.2 mg/kg intravenous; recruited n = 15) at 24 hours of age, or no intervention (recruited n = 17). Baseline echocardiography was performed prior to randomization and repeated on postnatal days 3, 5, and 7. Symptomatic PDA was observed less frequently in the treatment group (1/14 surviving infants in the indomethacin group versus 9/16 surviving infants in the control group, P = 0.007). Nine infants in the control group who were diagnosed with a symptomatic PDA after randomization and were subsequently treated with indomethacin, with successful closure of the ductus observed in eight infants. Perinatal characteristics were similar between the two groups. No significant differences were observed between the two groups with regards to major neonatal morbidities, including bronchopulmonary dysplasia, necrotizing enterocolitis (NEC), and IVH, nor was there a significant difference in mortality. No adverse events were observed.

Kumar Nair 2004[82] conducted a single-center randomized controlled trial to examine the efficacy of low dose indomethacin on the development of severe IVH (grade 3 to 4). Infants greater than 26 weeks gestation with a birth weight 750 g to 1250 g were randomized to receive either prophylactic indomethacin (0.1 mg/kg/dose intravenously; recruited n = 56) or no intervention (recruited n = 59). Cranial ultrasound was performed prior to randomization and repeated on days 1, 3, and 7. When stratified by birth weight (750 g to 999 g versus 1000 g to 1250 g), prophylactic indomethacin was associated with a significantly increased incidence of severe IVH only for infants in the lower birth weight

group (RR 2.05, 95% CI 1.29-3.26, P = 0.03). In addition, for the study population as a whole, prophylactic indomethacin was also associated with a significantly increased incidence of chronic lung disease (risk ratio (RR) 1.79, 95% confidence interval (CI) 1.28 to 2.5, P = 0.005). Prophylactic indomethacin was also associated with a significantly lower incidence of PDA, but only in the higher birth weight group (P = 0.02). No significant differences in incidence of renal failure or any other neonatal outcomes were observed, including NEC, bronchopulmonary dysplasia, and mortality.

Mahony 1985[83] conducted a single-center randomized controlled trial to examine the effect of indomethacin on the development of large left-to-right shunting PDA. Preterm infants (birth weight 700 g to 1300 g) were randomized to receive either indomethacin (first dose 0.2 mg/kg within the first 12 to 18 hours after birth followed by two doses of 0.1 mg.kg at 12 hours and 36 hours after the first; recruited n = 51) or placebo (saline; recruited n = 53). Any infant, regardless of study arm, who developed a large left-to- right shunting PDA was treated with indomethacin, surgical ligation or both. Perinatal characteristics, cardiac parameters, and initial ventilator settings were similar between the two groups, with the exception of the presence of hyaline membrane disease which was observed less frequently in those treated with indomethacin (42/53 infants in the placebo group versus 36/51 infants in the indomethacin group). No significant differences were noted between the groups with regards to the primary outcomes of duration of oxygen therapy or intubation, nor was there any significant difference in days to regain birth weight or incidence of surgical ligation of the PDA. Prophylactic indomethacin was associated with a reduced incidence of large left-to-right shunting PDA (2/51 infants in the indomethacin group versus 11/53 infants in the placebo group, P = 0.025). No significant effect on mortality was observed, nor were any complications observed. This study was stopped early due to recruitment challenges.

Maruyama 2012[84] assessed intestinal and renal blood flow in a single-center subset of infants participating in a multi-center randomized controlled trial of prophylactic indomethacin for the reduction of IVH and PDA. Preterm infants participating in the larger study who had been randomized to receive either prophylactic indomethacin (0.1 mg/kg/dose intravenously for a total of three doses; n = 10) or placebo (n = 9) were examined. Baseline perinatal characteristics were similar between the two groups, with the

exception of birthweight which was lower in the indomethacin group (median 677 g, range 528 g to 936 g) compared to the placebo group (median 800 g, range 692 g to 946 g) despite similar gestational ages. Flow velocity in the right renal artery and superior mesenteric artery was measured by Doppler ultrasound before and after the initial dose of indomethacin or placebo. Compared to placebo, prophylactic indomethacin was associated with significantly increased post-dose end-diastolic flow velocity in both the renal artery (P = 0.04) and the superior mesenteric artery (P = 0.02), but not an increase in regional vascular resistance.

Ment 1985[85] conducted a single-center randomized controlled trial to examine the efficacy of indomethacin in the prevention of IVH. Preterm infants (birth weight 600 g to1250 g) without ultrasound evidence of IVH at six hours after birth were randomized to receive either prophylactic intravenous indomethacin (recruited n = 24) or placebo (saline; recruited n = 24). The indomethacin dosing regimen was reduced after the first 10 patients due to observed oliguria (initial dose 0.2 mg/kg followed by four doses of 0.1 mg/kg every 12 hours, reduced to 0.1 mg/kg every 12 hours for a total of five doses). Cranial ultrasounds were performed at 6, 18, 30, 42, and 54 hours after birth, and on postnatal days 4, 5, 7, 14, and 20. Perinatal characteristics and the presence of PDA on day one were similar between the two groups. Indomethacin was associated with a significant reduction in the incidence of IVH (6/24 infants in the indomethacin group versus 14/24 infants in the placebo group, P = 0.02). Treatment with indomethacin was also associated with a significant decrease in serum prostaglandin levels and an increased rate of PDA closure (84% in the indomethacin group versus 60% in the placebo group) independent of the presence of IVH.

Ment 1988[86] conducted a single-center randomized controlled trial to examine the efficacy of prophylactic low-dose indomethacin in the prevention of IVH, and the effect on urine output. Preterm infants with a birth weight of 600 g to 1250 g were randomized to receive either prophylactic indomethacin (0.1mg/kg intravenous, first dose at 6-12 hours of age followed by two additional doses at 24 hour intervals; recruited n = 19) or placebo (saline; recruited n = 17). Perinatal characteristics were similar between the two groups. Prophylactic indomethacin was associated with a decrease in the incidence of IVH compared to placebo (2/19 infants in the indomethacin group versus 8/17 infants in the

placebo group, P = 0.02). In addition, among infants with a PDA shunting left-to- right prior to treatment, indomethacin was associated with higher rates of ductal closure on postnatal day five compared to placebo (64% versus 33%, respectively). In this study, indomethacin was not associated with significant oliguria, electrolyte abnormalities, laboratory evidence of renal dysfunction, or platelet abnormalities.

Ment 1994a[87] conducted a prospective multi-center randomized controlled trial to examine the efficacy of low-dose indomethacin to prevent progression of IVH in infants with early low-grade IVH. The study was conducted in three neonatal intensive care units (NICUs) in the USA. Infants with birth weights of 600 g to 1250 g with ultrasound evidence of grade 1 IVH at 6 to 11 hours of age were randomized to receive either prophylactic indomethacin (0.1 mg/kg intravenously every 24 hours for a total of three doses; recruited n = 27) or placebo (saline; recruited n = 34). No differences in baseline perinatal characteristics were observed between the two groups. There was no significant difference in extension of the IVH with prophylactic indomethacin compared to placebo; however, indomethacin was associated with an increased incidence of PDA closure by postnatal day five when compared to control (P = 0.003). No adverse events were reported.

Ment 1994b[88] conducted a multi-center prospective randomized control trial to examine the effect of low-dose indomethacin on prevention of IVH (both incidence and severity). The study was conducted in three NICUs in the USA. Infants with birth weights 600 g to 1250 g and no ultrasound evidence of IVH at 6 to 11 hours of age were randomized to receive either prophylactic indomethacin (0.1 mg/kg intravenously every 24 hours for a total of three doses; recruited n = 209) or placebo (saline; recruited n = 222). Serial cranial ultrasounds were performed at 24 and 48 hours of age, and then on postnatal days 4, 7, 14, and 21. Echocardiography was performed on postnatal days 1, 2, 3, and 5. Baseline perinatal characteristics were similar between the two groups. Compared to placebo, prophylactic indomethacin was associated with significantly decreased incidence of IVH (12% of infants in the indomethacin group versus 18% of infants in the placebo group, P = 0.03), as well as decreased incidence of grade 4 IVH (4% of infants with IVH in the indomethacin group versus 25% of infants with IVH in the placebo group, P = 0.01). Prophylactic indomethacin was also associated with a significantly increased rate of PDA

closure when compared with control (10% of infants in the indomethacin group versus 34% of infants in the placebo group, $P < 0.001$). No adverse events were reported. Ment 1996[89] subsequently conducted a 36-month follow-up of this study population to examine neurodevelopmental outcomes. No significant differences were observed between the two groups with regards to cerebral palsy, blindness or deafness. Stanford-Binet IQ scores were available for 126 infants and were also similar between the two groups (89.6 [standard deviation (SD) 19.92] in the indomethacin group versus 85.0 [SD 20.79] in the placebo group). Ment 2000[90] conducted another follow-up of this study that examined neurodevelopmental outcomes at 4.5 years of age. The incidence of cerebral palsy was similar to that observed at 36 months.

Compared to placebo, the incidence of intellectual disability was lower among children who had received prophylactic indomethacin (IQ < 70: 9% indomethacin versus 17% placebo; IQ 70 to 80: 12% indomethacin versus 18% placebo; and IQ > 80: 79% indomethacin versus 65% placebo). Vocabulary skills were also stronger among children who had received indomethacin compared to placebo. Vohr 2003[91] also conducted a neurodevelopmental follow-up of this study at school age (eight years).

Children with a history of IVH were more likely to have neurodevelopmental challenges (cerebral palsy, hearing impairment, lower IQ) as well as lower daily living skills scores and greater need of educational supports. Severe IVH (grade 3 to 4), periventricular leukomalacia (PVL), and male gender were all associated with higher incidence of neurodevelopmental challenges. No effect of prophylactic indomethacin on outcomes was demonstrated. Ment 2004[92] conducted a further follow-up study of this population to examine the sex-specific effect of indomethacin on neurodevelopmental outcomes at three to eight years of age. Prophylactic indomethacin in boys was associated with a significant decrease in the incidence of both IVH and PVL, and was associated with higher verbal scores, when compared to the effects of prophylactic indomethacin in girls. Finally, Luu 2009[93] examined neurodevelopmental outcomes at 12 years of age in this population and found no association between prophylactic indomethacin and IQ scores.

Morales-Suarez 1994[94] conducted a single-center randomized controlled trial to examine the effect of prophylactic low-dose indomethacin on IVH in preterm infants on mechanical

ventilation. Infants born between 28 to 36 weeks gestational age (GA) and requiring mechanical ventilation were randomized to intravenous indomethacin (three doses of 0.1 mg/kg/dose every 12 hours) (n = 40) versus placebo (n = 40). Parenteral fluids were given at rates of 70, 80 and 90 mL/kg/day on days 1, 2, and 3, respectively, to maintain a minimum urine output >1.5 mL/kg/24 hours, and urinary density between 1.005 and 1.010. Each participant was mechanically ventilated. Baseline perinatal characteristics were similar between the two groups. Compared to placebo, prophylactic indomethacin was associated with significantly decreased incidence of both grade 3 IVH (4/40 in indomethacin group versus 8/40 in the placebo group; $P < 0.005$) and grade 4 IVH (2/40 in indomethacin group versus 5/40 in the placebo group; $P < 0.005$).

Rennie 1986[95] conducted a single-center randomized controlled trial to examine the effects of indomethacin in preterm infants. Preterm infants (birth weight <1750g) less than 24 hours of age and without ultrasound evidence of IVH at the time of enrolment were randomized to receive either indomethacin (three doses of 0.2mg/kg at 24-hour intervals; recruited n = 24) or placebo (saline; recruited n = 26). Cranial ultrasounds were performed daily for the first four days, followed by weekly scans thereafter. Infants in the placebo group were more likely to be male and had lower 1-minute Apgar scores. The incidence of left-to-right shunting PDA requiring treatment was significantly lower in those who received prophylactic indomethacin (1/24 infants in the indomethacin group versus 8/26 infants in the placebo group, $P = 0.03$). The incidence of gastrointestinal bleeding was significantly higher in those who received prophylactic indomethacin (7/24 infants in the indomethacin group versus 0/26 infants in the placebo group, $P = 0.01$). No significant differences were observed between the two groups with regard to the duration of mechanical ventilation or oxygen requirement, nor were any significant differences observed in the incidence of renal impairment, IVH, or mortality.

Schmidt 2001[96] conducted a multi-center randomized controlled trial to examine the effect of prophylactic low-dose indomethacin on survival without neurosensory impairment. The study was conducted at 32 neonatal intensive care units in Canada, Australia, New Zealand, Hong Kong, and the USA. Preterm infants with a birth weight 500 g to 999 g were randomized to receive either prophylactic indomethacin (0.1 mg/kg intravenously once

daily for three days; recruited n = 574) or placebo (saline; recruited n = 569). Baseline perinatal characteristics were similar between the two groups. The incidence of the composite outcome of death or significant neurosensory impairment (including cerebral palsy, cognitive delay, deafness or blindness) at 18 months of age was not significantly different between the two groups (P = 0.61). However, prophylactic indomethacin was associated with a decreased incidence of PDA (P < 0.001) and severe IVH (P = 0.02). No differences were observed between the two groups with regards to other major neonatal morbidities (including chronic lung disease, NEC, and retinopathy of prematurity) or other neurologic morbidities (including seizures, severe hydrocephalus, and microcephaly). Ohlsson 2005[97] subsequently conducted a secondary analysis of this study which examined whether prophylactic indomethacin had a sex- mediated effect on short- and long-term neurodevelopmental outcomes. Compared to placebo, prophylactic indomethacin reduced the incidence of the composite outcome (as described above) more for girls compared to boys (P = 0.048). No significant sex- mediated effect on any of the other short- or long-term neurodevelopmental outcomes were observed. Schmidt 2006[98] also conducted an additional analysis of this study to examine the effect of prophylactic indomethacin on the development of bronchopulmonary dysplasia among infants with and without PDA. Among infants with PDA, prophylactic indomethacin was not associated with bronchopulmonary dysplasia. In contrast, among infants without PDA, prophylactic indomethacin was associated with a significantly increased incidence of bronchopulmonary dysplasia (43% of infants in the indomethacin group versus 30% of infants in the placebo group, P = 0.015). In addition, Zupancic 2006[99] conducted an economic analysis of this study to examine the cost-effectiveness of indomethacin prophylaxis for PDA prevention, which was not able to demonstrate an economic benefit.

Setzer Bandstra 1988[100] conducted a single-center randomized controlled trial to examine the efficacy of prophylactic indomethacin compared to placebo for the prevention of both IVH and PDA. Preterm infants (birth weight< 1300 g) requiring oxygen who did not have an IVH grade 2 or higher (assessed by pre-study cranial ultrasound) were randomized to receive either prophylactic intravenous indomethacin (initial dose 0.2 mg/kg within 12 hours of birth, followed by two doses of 0.1 mg/kg at intervals of 12 hours; recruited n = 99) or placebo (0.45% NaCl; recruited n = 100). Perinatal characteristics were similar

between the two groups, although there was a greater number of female infants in the placebo group compared to the indomethacin group (57% versus 48%, respectively). Prophylactic indomethacin was associated with a significant decrease in the incidence of IVH grades 2 to 4 compared to placebo (23% versus 46%, $P < 0.002$). Prophylactic indomethacin was also associated with a significant decrease in the incidence of clinically significant PDA compared to placebo (11% versus 42%, $P < 0.001$). Compared to the placebo group, prophylactic indomethacin was associated with oliguria ($P < 0.001$), but no significant differences were noted between the two groups with regard to duration of oxygen therapy or mechanical ventilation, duration of hospitalization, or any of the major neonatal outcomes including NEC, chronic lung disease, sepsis, retinopathy of prematurity, and mortality. The study abstract was published in 1984 as a conference proceeding that showed preliminary results identical to those described above (Setzer 1984a[101]). A second conference abstract was also published in 1984 which demonstrated that prophylactic indomethacin was associated with decreased platelet count and prolonged bleeding time in the first postnatal week, although no data on adverse outcomes related to these laboratory abnormalities were presented (Setzer 1984b[102]).

Supapannachart 1999[103] conducted a single-center randomized controlled trial to examine the efficacy of prophylactic indomethacin to prevent the development of symptomatic PDA. Preterm infants with a birth weight less than 1250 g were randomized to receive either prophylactic indomethacin (initial dose 0.2 mg/kg intravenous within the first 24 hours after birth, followed by two doses of 0.1 mg/kg at 12 hours intervals; recruited n = 15) or placebo (recruited n = 15). Perinatal characteristics were similar between the two groups, with the exception of surfactant administration which occurred more frequently in the indomethacin group. Prophylactic indomethacin was associated with a significantly decreased incidence of symptomatic PDA compared to placebo (4/15 infants in the indomethacin group versus 12/15 infants in the placebo group, $P < 0.005$). No significant differences in major neonatal morbidities were observed, nor was there any significant difference in mortality. No adverse respiratory, renal or haematologcal effects were observed.

Vincer 1987[104] conducted a single-center randomized controlled trial to examine the effect of prophylactic indomethacin on the development of chronic pulmonary insufficiency of prematurity. Infants with a birth weight less than 1500 g who required respiratory support (invasive or non-invasive positive pressure ventilation) at 12 hours of age were randomized to receive either indomethacin (three doses of 0.2 mg/kg intravenously at 12, 24, and 36 hours of age; recruited n = 15) or placebo (saline; recruited n = 15). Perinatal characteristics and baseline respiratory support parameters were similar between the two groups. Among infants who required invasive positive pressure ventilation, placebo was associated with earlier successful weaning of respiratory support compared to indomethacin ($P < 0.05$), although oxygen requirement was not significantly different. Infants who received indomethacin were less likely to have symptomatic PDA (1/15 infants in the indomethacin group versus 5/15 infants in the placebo group, $P < 0.10$). Indomethacin was also associated with hyponatremia and less weight loss in the first 7 postnatal days compared to placebo. No significant differences were observed between the two groups with regards to the incidence of IVH, NEC, or mortality, and no adverse events were observed. Vincer 1998[105] subsequently conducted a 2-year follow-up of this study which examined the incidence of cerebral palsy in those treated with prophylactic indomethacin. Of those infants assessed at two years, prophylactic indomethacin was associated with an increased incidence of cerebral palsy (5/12 in the indomethacin group versus 1/12 in the control group, $P = 0.15$), although it was not associated with an increase in the incidence of severe IVH or cystic periventricular leukomalacia.

Vogtmann 1988[106] conducted a single-center randomized controlled trial to examine the effect of prophylactic oral indomethacin in preterm infants. Infants with a birthweight of ≤ 1500 g and GA ≤ 30 weeks were randomized to oral indomethacin at a dose 0.2 mg/kg/day from days three to five (n = 19) or standard of care (n = 22). There was no statistically significant difference in any clinically relevant outcomes such as mortality or NEC between the two groups.

Studies using prophylactic ibuprofen

Seven studies that enrolled 914 infants used prophylactic ibuprofen as the active intervention. The following section provides a brief description of the included studies.

Dani 2000[107] conducted a two-center randomized controlled trial to assess the efficacy of prophylactic ibuprofen for reducing the occurrence of PDA. Preterm infants (< 34 weeks' gestational age) with respiratory distress syndrome were randomly assigned to receive intravenous ibuprofen (initial dose 10 mg/kg, followed by 5 mg/kg doses at 24 and 48 hours) either prophylactically within the first 24 hours of life (n = 40), or after diagnosis of a PDA by echocardiography (n = 40). Oxygenation Index and Ventilatory Index (initial and highest) were used to measure severity of respiratory distress syndrome (RDS). which were similar between the two groups. Both modes of treatment were found to be effective in closing the PDA. However, early prophylactic treatment significantly reduced the occurrence of PDA on day three of life (prophylaxis 3/40 infants versus post-echocardiography 21/40 infants, $P < 0.0001$). There were no significant differences between the two groups in the frequency of bronchopulmonary dysplasia, IVH, NEC, or retinopathy of prematurity.

Dani 2005[108] conducted a multi-center randomized controlled trial to compare the efficacy of prophylactic ibuprofen versus placebo to reduce the occurrence of IVH, as well as the progression of low-grade (none or grade 1) IVH to higher grade (grades 2 to 4) IVH. The study was conducted at seven Italian NICUs. Preterm infants (< 28 weeks' gestational age) were randomly assigned within the first six hours of life to receive either intravenous ibuprofen (initial dose 10 mg/kg, followed by 5 mg/kg doses at 24 and 48 hours; n = 77) or placebo (n = 78). Serial cranial ultrasounds and echocardiography were subsequently performed. Perinatal characteristics were similar between the two groups with the exception of gestational age at birth (ibuprofen 25.3 + 1.2 days versus placebo 25.9 + 1.1 days). The prevalence of grade 1 IVH on initial cranial ultrasound was also similar between the groups. Prophylactic ibuprofen administration did not significantly decrease the occurrence of IVH (all grades), nor was it effective in preventing progression from low- to higher-grade IVH. Prophylactic administration of ibuprofen was associated with a decreased occurrence of PDA on day three of life (ibuprofen 7/77 infants versus placebo 23/78 infants, $P < 0.002$) No significant differences were observed between the two groups with regards to the frequency of bronchopulmonary dysplasia, NEC, retinopathy of prematurity, sepsis, or mortality.

De Carolis 2000[109] conducted a single-center randomized controlled trial to compare the efficacy of prophylactic ibuprofen versus no intervention to reduce the occurrence of PDA. Preterm infants (<31 weeks' gestational age) were randomized at two hours of life to receive either intravenous ibuprofen (initial dose 10 mg/kg, followed by 5 mg/kg doses at 24 and 48 hours; n = 23) or no treatment (n = 23). Perinatal characteristics and initial respiratory status were similar between the two groups. The rate of PDA closure at three days of age was significantly higher in the group that received prophylactic ibuprofen compared to the control group ($P < 0.01$). There were no differences between the groups with regard to mortality, IVH, NEC, and renal or hematological complications.

Gournay 2004[110] conducted a multi-center randomized controlled trial to compare the efficacy of prophylactic ibuprofen versus placebo to reduce the occurrence of PDA requiring surgical intervention. The study was conducted at 11 NICUs in France. Preterm infants (< 28 weeks' gestational age) were randomized within the first six hours of life to receive either intravenous ibuprofen (initial dose 10 mg/kg, followed by 5 mg/kg doses at 24 and 48 hours; n = 65) or placebo (saline; n = 66). Recruitment stopped early (135/250 patients recruited) due to concerns regarding development of severe pulmonary hypertension in three infants in the prophylactic ibuprofen group. No difference in mortality was noted between the two groups; however, compared to placebo, ibuprofen prophylaxis did reduce the need for surgical ligation of the PDA ($P = 0.03$).

Kanmaz 2013[111] conducted a single-center randomized controlled trial to compare the efficacy of prophylactic oral ibuprofen versus no intervention for the prevention of a hemodynamically significant PDA. Preterm infants (< 28 weeks' gestational age) weighing < 1000 g were randomly assigned to either oral ibuprofen (initial dose 10 mg/kg, followed by 5 mg/kg doses at 24 and 48 hours; recruited n = 23) or no intervention (recruited n = 23). The study was terminated early due to adverse events in the prophylactic ibuprofen group, which included two infants with gastrointestinal bleeding, two infants with spontaneous intestinal perforation, and two infants with renal failure. Of those infants who completed the study, the rate of hemodynamically significant PDA was reduced by was not significantly different between the two groups.

Sangtawesin 2006[112] conducted a single-center randomized controlled trial to compare efficacy of prophylactic oral ibuprofen versus placebo for the prevention of symptomatic PDA. Preterm infants (28 to 32 weeks' gestational age) with birth weight < 1500 g were randomly assigned to either oral ibuprofen (three doses of 10 mg/kg, first dose administered within the first 24 hours of life and then at 24 and 48 hours thereafter; n = 22) or placebo (oral starch suspension; n = 20). Perinatal characteristics and the presence of asymptomatic PDA at the time of first dose administration were similar between the two groups. Compared to placebo, prophylactic treatment with ibuprofen was associated with reduced presence of symptomatic PDA on postnatal day three (ibuprofen 0/22 infants versus placebo 5/20 infants, P = 0.015) and postnatal day 7 (ibuprofen 0/22 infants versus placebo 6/20 infants, P = 0.006), respectively. No significant differences were noted between the groups for the rate of pulmonary hypertension, bronchopulmonary dysplasia, IVH, NEC, or retinopathy of prematurity. A slightly higher, non-significant risk of gastrointestinal bleeding was noted in the prophylactic ibuprofen group compared to the control.

Van Overmeire 2004[113] conducted a multi-center randomized controlled trial to compare the efficacy of prophylactic ibuprofen versus placebo to reduce the occurrence of PDA and IVH. The study was conducted at seven NICUs in Belgium. Preterm infants (< 31 weeks' gestational age) were randomized within the first six hours of birth to receive either intravenous ibuprofen (initial dose 10 mg/kg, followed by 5 mg/kg doses at 24 and 48 hours; n = 205) or placebo (saline; n = 210). No statistically significant difference was observed for rates of IVH between the two groups (RR 0.97 [95% CI 0.51,1,82]). However, rates of PDA closure on day three were higher in the prophylactic ibuprofen group compared to the control group (RR 1.40 [1.23 to 1.59]). No significant differences in other clinical outcomes, including NEC, bronchopulmonary dysplasia, and mortality, or serious adverse events were observed. The study abstract was published in 2002 as a conference proceeding that showed results identical to those described above (Van Overmeire 2002[114]).

Studies using prophylactic acetaminophen

Two studies that enrolled 208 infants used prophylactic acetaminophen as the active intervention. The following section provides a brief description of the included studies.

Bagheri 2018[115] conducted a single-center randomized controlled trial to compare the efficacy of prophylactic acetaminophen versus non-intervention in the prevention of PDA. Preterm infants (< 34 weeks' gestational age) were randomly assigned to receive either intravenous acetaminophen (initial dose 20 mg/kg followed by 7.5 mg/kg doses every six hours for the first three postnatal days; recruited n = 80) or no intervention (recruited n = 80). An echocardiogram was performed on postnatal day four. Perinatal characteristics were similar between the two groups. Compared to no intervention, prophylactic acetaminophen was associated with a significantly lower incidence of PDA (12/80 in the treatment group compared to 57/80 in the control group, $P < 0.001$). Mean ventilator time, mean cardiac shortening fraction, and mortality were not significantly different between the two groups. No adverse events were observed.

Harkin 2016[30] conducted a randomized controlled trial to compare the effect of prophylactic acetaminophen versus placebo on the closure of the ductus arteriosus. Preterm infants (< 32 weeks gestational age) were randomly assigned to receive either intravenous acetaminophen (initial dose 20 mg/kg, given within 24 hours of birth, followed by 7.5 mg/kg every six hours for a total of four days; recruited n = 23) or placebo (0.45% NaCl; recruited n = 25). An echocardiogram was performed prior to the first dose and repeated daily until day five. Perinatal characteristics were similar between the two groups, as were echocardiographic measurements of the ductus arteriosus prior to the first dose. Prophylactic acetaminophen was associated with earlier closure of the ductus arteriosus ($P = 0.045$). Serum acetaminophen levels were noted to be within the therapeutic range, and no short-term adverse effects were observed. Juujärvi 2019[116] subsequently conducted a two-year follow-up of this study which examined the long-term safety and outcomes associated with prophylactic acetaminophen. Forty-four of the 48 infants originally recruited (92%) were assessed using a parental questionnaire in conjunction with clinical and neurodevelopmental assessments. No long-term adverse cardiac outcomes were observed, and neurodevelopmental outcomes were similar between the two groups.

Excluded studies

We excluded 31 publications for the following reasons.

1. Two publications (Liebowitz 2017, Varvarigou 1996)[117,118] were excluded as they were not randomized controlled trials.

2. Four publications (Cotts 2009, Hammerman 1986, Kääpä 1985, Mahony 1982)[83,119–121] were excluded because the study population did not match our inclusion criteria, which stipulated that intervention must be delivered within the first 72 hours after birth and there must be no documented clinical or echocardiographic evidence of PDA.

3. Three publications (Rubaltelli 1998, Schmidt 2011; Valls-i-Soler 1999)[122–124] were excluded as the one of the trial interventions in each of these studies did not include any of the four interventions defined in our review (prophylactic indomethacin, prophylactic ibuprofen, prophylactic acetaminophen, placebo/no treatment).

4. Seven publications were excluded (Alfaleh 2008, Gregoire 2004, Harma 2018, Ment 1999, Naulaers 2005, Pleacher 2004, Vohr 1999)[125–131] as they did not include any of our pre- defined clinical outcomes.

5. Four publications (Domanico 1994, Gutierrez 1987, Puckett 1985, Zarkesh 2013)[132–135] were excluded as they were available as conference abstracts only, and hence, we were unable to assess the quality of the study methodology.

6. Five publications (Meau-Petit 2005, Ment 1987, Morales-Suarez 1992, Roze

2003, van Overmeire 2002)[114,136–139] were excluded as they are conference abstracts of studies already included in our review.

7. Six publications (Barrington 1986, Hammerman 2005, McGuire 2002, Ment 1998, Schmidt 2002, Tyson 2002)[140–145] were excluded as they were either expert reviews or commentaries.

For further details see ***Characteristics of excluded studies***

Risk of bias in included studies

For the summary of the authors' judgements on the risk of bias in individual studies, please see Figure 2 and Figure 3.

Allocation

Both randomization and allocation procedures were clearly described in seven studies (Harkin 2016; Jannatdoust 2014; Kumar Nair 2004; Ment 1994b; Schmidt 2001; Setzer Bandstra 1988; Van Overmeire 2004)[30,80,82,88,96,100,113]. One or both of randomization procedure and allocation concealment was judged to have unclear risk of bias in the remaining 21 studies. No study was judged to have a high risk of selection bias.

Blinding

Blinding processes were clearly described in 18 studies (Bada 1989; Setzer Bandstra 1988; Couser 1996; Dani 2005; Gournay 2004; Hanigan 1988; Harkin 2016; Mahony 1985; Ment 1985; Ment 1988; Ment 1994a; Ment 1994b; Rennie 1986; Sangtawesin 2006; Schmidt 2001; Supapannachart 1999; Van Overmeire 2004; Vincer 1987)[30,76,77,79,83,85–88,95,96,100,103,104,108,110,112,113], while eight studies (Bagheri 2018; Dani 2000; De Carolis 2000; Jannatdoust 2014; Kanmaz 2013; Krueger 1987; Kumar Nair 2004; Vogtmann 1988)[80–82,106,107,109,111,115] were judged to be at a high risk of bias for either performance or detection bias.

Incomplete outcome data

Only one study was judged to be at a high risk for attrition bias as infants who died prior to day eight were removed from the study (Vogtmann 1988)[106]. We judged all the remaining studies to be at low risk for attrition bias.

Selective reporting

Only three studies had a study protocol registered a priori for us to be able to judge the domain of selective outcome reporting. Out of these three studies, two (Harkin 2016; Kanmaz 2013)[30,111] were at low risk for selective outcome reporting while one (Maruyama 2012)[84] was judged to be at a high risk for selective outcome reporting. We were unable to judge the reporting bias for the remaining studies due to lack of an a priori published protocol available for comparison.

Other potential sources of bias

No studies were judged to be at a high risk for other potential sources of bias.

Effects of interventions

Out of the 13 a priori defined outcome measures, outcome data on more than one COX-I drug were available for 11 outcomes. Therefore, effects of interventions have been summarized for 11 out of the 13 listed outcomes where a network meta-analysis was possible. Further, none of the pre-defined subgroup analyses (based on gestational age, birth weight or timing of initiation of prophylaxis) were possible due to lack of complete data in either subgroup in each category. Instead, we performed a post-hoc sensitivity analysis of studies that specifically reported on infants born extremely preterm (less than 28 weeks of gestational age) and/or extremely low birth weight (less 1000 g of birth weight). We reported the sensitivity analysis results for those clinically relevant outcomes where subgroup analyses were planned a priori. The effects of the interventions as obtained on statistical analysis using Bayesian random- effects model were as follows (see Summary of findings table 1).

Primary outcomes

Severe intraventricular haemorrhage (IVH) (grade 3 or 4)

Twenty-three studies (n = 3540) reported on this outcome [Indomethacin versus placebo (16 studies, 2629 infants); ibuprofen versus placebo (6 studies, 863 infants) and acetaminophen versus placebo (1 study, 48 infants)]. The network diagram is presented in Figure 4. Each node in the network diagram indicates a treatment modality and is sized proportionally to the number of participants who received the treatment modality. Each line connecting two nodes indicates a direct comparison between two modalities, and the thickness of each is proportional to the number of studies directly comparing the two modalities.

Initial pairwise meta-analysis using Bayesian random-effects model showed a statistically significant reduction in severe IVH with indomethacin compared to placebo (16 studies, 2629 infants; risk ratio (RR) 0.60, 95% credible interval (CrI) 0.45 to 0.80) (Figure 5). No statistically significant difference was observed with ibuprofen versus placebo (6 studies, 863 infants; RR 0.57, 95% CrI 0.26 to 1.3) (Figure 6) or with acetaminophen versus placebo (1 study, 48 infants; RR 1.09, 95% CrIs 0.07 to 17.64).

Bayesian random-effects network meta-analysis showed that indomethacin significantly reduced severe IVH compared to placebo (Network RR 0.66, 95% CrIs 0.49, 0.87; moderate certainty). No such effects were observed with ibuprofen (Network RR 0.69, 95% CrIs 0.41, 1.1; moderate certainty) or acetaminophen (Network RR 1.2, 95% CrIs 0.04, 55.0; very low certainty) compared to placebo. The relative treatment effects for all possible comparisons obtained from the network meta-analysis are shown in Figure 7; Table 1. Comparison-adjusted funnel plots were not suggestive of any small-study effects (Figure 8). We were unable to run any inconsistency models as there were no head-to-head trials between any of the three COX-I drugs. Both indomethacin (median rank 2, 95% CrI 1 to 3) and ibuprofen (median rank 2, 95% CrI 1 to 4) ranked similarly for reduction of severe IVH (Figure 9). Based on the mean surface under the cumulative ranking curve (SUCRA) values, indomethacin had the highest SUCRA (0.74) followed by ibuprofen (0.67).

Sensitivity analysis

We conducted a sensitivity analysis of studies that specifically reported on infants born extremely preterm (less than 28 weeks of gestational age) and/or extremely low birth weight (less 1000 g of birth weight). 5 studies (n = 1335) that compared indomethacin versus placebo and 3 studies (n = 332) that compared ibuprofen versus placebo reported on severe IVH in infants in this specific gestational age and/or birth weight. Bayesian random-effects network meta-analysis showed no statistically significant difference between indomethacin versus placebo (Network RR 0.81, 95% CrIs 0.37, 2.0) as well as ibuprofen versus placebo (Network RR 0.46, 95% CrIs 0.14, 1.2) for the outcome of severe IVH. Ibuprofen (median rank 1, 95% CrI 1 to 3; mean SUCRA, 0.91) ranked as the best treatment for reduction of severe IVH followed by indomethacin (median rank 2, 95% CrI 1 to 3; mean SUCRA, 0.43) and placebo (median rank 2, 95% CrI 1 to 3; mean SUCRA), 0.16) in this specific gestational age and/or birth weight group.

Mortality (at discharge or at last reported follow-up, whichever is later)

Twenty-eight studies (n = 3999) reported on this outcome [Indomethacin versus placebo (19 studies, 2877 infants); ibuprofen versus placebo (7 studies, 914 infants) and

acetaminophen versus placebo (2 studies, 208 infants)]. The network diagram is presented in Figure 10.

Initial pairwise meta-analysis using Bayesian random-effects model showed no statistically significant differences in mortality with indomethacin compared to placebo (19 studies, 2877 infants; RR 0.82, 95% CrI 0.63 to 1.1) (Figure 11), ibuprofen versus placebo (7 studies, 914 infants; RR 0.83, 95% CrI 0.55 to 1.3) (Figure 12), or with acetaminophen versus placebo (2 studies, 208 infants; RR 0.43, 95% CrI 0.11 to 1.8) (Figure 13). Bayesian random-effects network meta-analysis showed no statistically significant reduction in mortality with indomethacin (Network RR 0.85, 95% CrIs 0.64, 1.05; moderate-certainty), ibuprofen (Network RR 0.83, 95% CrIs 0.57, 1.18; low-certainty) or acetaminophen (Network 0.49, 95% CrIs 0.16, 1.36; very low-certainty) compared to placebo. The relative treatment effects for all possible comparisons obtained from the network meta-analysis are shown in Figure 14; Table 2. Comparison-adjusted funnel plots were not suggestive of any small-study effects (Figure 15). We were unable to run any inconsistency models as there were no head-to-head trials between any of the three COX-I drugs. Acetaminophen (median rank 1, 95% CrI 1 to 4) ranked as the best treatment for reduction in mortality followed by ibuprofen (median rank 2, 95% CrI 1 to 4) and indomethacin (median rank 2, 95% CrI 1 to 4) (Figure 16). Based on the mean SUCRA values, acetaminophen had the highest SUCRA (0.87).

Sensitivity analysis

We conducted a sensitivity analysis of studies that specifically reported on infants born extremely preterm (less than 28 weeks of gestational age) and/or extremely low birth weight (less 1000 g of birth weight). 6 studies (n = 1421) that compared indomethacin versus placebo and 3 studies (n = 332) that compared ibuprofen versus placebo reported on mortality in infants in this specific gestational age and/or birth weight.

Bayesian random effects network meta-analysis showed no statistically significant difference between indomethacin versus placebo (Network RR 1.2, 95% CrIs 0.74, 1.9) as well as ibuprofen versus placebo (Network RR 0.78, 95% CrIs 0.42, 1.4) for the outcome of mortality. Ibuprofen (median rank 1, 95% CrI 1 to 3; mean SUCRA, 0.87) ranked as the best treatment for reduction in mortality followed by placebo (median rank 2, 95% CrI 1

to 3; mean SUCRA, 0.48) and indomethacin (median rank 3, 95% CrI 1 to 3; mean SUCRA, 0.15) in this specific gestational age and/or birth weight group.

Secondary outcomes

Receipt of pharmacotherapy for symptomatic patent ductus arteriosus (PDA)

Twenty-two studies (n = 3240) reported on this outcome [Indomethacin versus placebo (13 studies, 2117 infants); ibuprofen versus placebo (7 studies, 915 infants) and acetaminophen versus placebo (2 studies, 208 infants)]. The network diagram is presented in Figure 17.

Initial pairwise meta-analysis using Bayesian random-effects model showed a statistically significant reduction in treatment for symptomatic PDA with indomethacin versus placebo (13 studies, 2117 infants; RR 0.30, 95% CrI 0.19 to 0.47) (Figure 18) and ibuprofen versus placebo (7 studies, 915 infants; RR 0.18, 95% CrI 0.08 to 0.41) (Figure 19). No statistically significant difference in treatment for symptomatic PDA was noted with acetaminophen versus placebo (2 studies, 208 infants; RR 0.39, 95% CrI 0.08 to 1.8) (Figure 20).

Bayesian random-effects network meta-analysis showed a statistically significant reduction in treatment for symptomatic PDA with both indomethacin (Network RR 0.30, 95% CrIs 0.17, 0.43) as well as ibuprofen (Network RR 0.20, 95% CrIs 0.098, 0.33) compared to placebo. The relative treatment effects for all possible comparisons obtained from the network meta-analysis are shown in Figure 21; Table 3. No statistically significant difference in treatment for symptomatic PDA was noted with acetaminophen versus placebo (Network RR 0.32, 95% CrIs 0.13, 1.1) (Figure 21). Comparison-adjusted funnel plots were not suggestive of any small-study effects (Figure 22). We were unable to run any inconsistency models as there were no head- to-head trials between any of the three COX-I drugs. Ibuprofen (median rank 1, 95% CrI 1 to 3) ranked as the best treatment for reduction in need for PDA pharmacotherapy followed by indomethacin (median rank 2, 95% CrI 1 to 3) (Figure 23). Based on the mean SUCRA values, ibuprofen had the highest SUCRA (0.90).

Surgical or interventional patent ductus arteriosus (PDA) closure

Seventeen studies (n = 2673) reported on this outcome [Indomethacin versus placebo (11 studies, 1800 infants); ibuprofen versus placebo (6 studies, 873 infants). All studies used surgical PDA closure as the intervention. The network diagram is presented in Figure 24.

Initial pairwise meta-analysis using Bayesian random-effects model showed a statistically significant reduction in surgical PDA ligation with indomethacin versus placebo (11 studies, 1800 infants; RR 0.37, 95% CrI 0.18 to 0.77) (Figure 25) and ibuprofen versus placebo (6 studies, 873 infants; RR 0.17, 95% CrI 0.03 to 0.94) (Figure 26).

Bayesian random-effects network meta-analysis showed a statistically significant reduction in surgical PDA ligation with both indomethacin (Network RR 0.40, 95% CrIs 0.14, 0.66; moderate-certainty) as well as ibuprofen (Network RR 0.24, 95% CrIs 0.06, 0.64; moderate-certainty) compared to placebo. The relative treatment effects for all possible comparisons obtained from the network meta-analysis are shown in Figure 27; Table 4. Comparison-adjusted funnel plots were not suggestive of any small-study effects (Figure 28). We were unable to run any inconsistency models as there were no head-to-head trials between any of the three COX-I drugs. Ibuprofen (median rank 1, 95% CrI 1 to 2) ranked as the best treatment for reduction in surgical PDA ligation followed by indomethacin (median rank 2, 95% CrI 1 to 2) (Figure 29). Based on the mean SUCRA values, ibuprofen had the highest SUCRA (0.88).

Sensitivity analysis

We conducted a sensitivity analysis of studies that specifically reported on infants born extremely preterm (less than 28 weeks of gestational age) and/or extremely low birth weight (less 1000 g of birth weight). 3 studies (n = 1287) that compared indomethacin versus placebo and 3 studies (n = 332) that compared ibuprofen versus placebo reported on surgical PDA closure in infants in this specific gestational age and/or birth weight. Bayesian random-effects network meta-analysis showed a statistically significant reduction in surgical PDA closure with ibuprofen versus placebo (Network RR 0.07, 95% CrIs 0.001, 0.73) but not with indomethacin versus placebo (Network RR 0.56, 95% CrIs 0.13, 3.0). Ibuprofen (median rank 1, 95% CrI 1 to 2; mean SUCRA, 0.97) ranked as the best treatment for reduction in surgical PDA ligation followed by indomethacin (median

rank 2, 95% CrI 1 to 3; mean SUCRA, 0.45) and placebo (median rank 3, 95% CrI 2 to 3; mean SUCRA, 0.08) in this specific gestational age and/or birth weight group.

Necrotizing enterocolitis (NEC) (stage 2 or greater)

Twenty-two studies (n = 3496) reported on this outcome [Indomethacin versus placebo (14 studies, 2543 infants); ibuprofen versus placebo (7 studies, 905 infants) and acetaminophen versus placebo (1 study, 48 infants)]. The acetaminophen node had zero events for NEC and therefore was removed from the network meta-analysis as no continuity correction was applied. The network diagram is presented in Figure 30.

Initial pairwise meta-analysis using Bayesian random-effects model showed no statistically significant differences in NEC with indomethacin compared to placebo (14 studies, 2543 infants; RR 0.78, 95% CrI 0.45 to 1.4) (Figure 31) or ibuprofen versus placebo (7 studies, 905 infants; RR 0.63, 95% CrI 0.24 to 1.7) (Figure 32). Bayesian random effects network meta-analysis showed no statistically significant reduction in NEC with indomethacin (Network RR 0.76, 95% CrIs 0.35, 1.2; high- certainty) or ibuprofen (Network RR 0.73, 95% CrIs 0.31, 1.4; high-certainty) compared to placebo. The relative treatment effects for all possible comparisons obtained from the network meta-analysis are shown in Figure 33, Table 5. Comparison-adjusted funnel plots were not suggestive of any small-study effects (Figure 34). We were unable to run any inconsistency models as there were no head-to-head trials between any of the COX-I drugs. Ibuprofen (median rank 1, 95% CrI 1 to 3) ranked as the best treatment for reduction in NEC followed by indomethacin (median rank 2, 95% CrI 1 to 3) (Figure 35). Based on the mean SUCRA values, ibuprofen had the highest SUCRA (0.69).

Sensitivity analysis

We conducted a sensitivity analysis of studies that specifically reported on infants born extremely preterm (less than 28 weeks of gestational age) and/or extremely low birth weight (less 1000 g of birth weight). 4 studies (n = 1344) that compared indomethacin versus placebo and 3 studies (n = 323) that compared ibuprofen versus placebo reported on necrotizing enterocolitis in infants in this specific gestational age and/or birth weight. Bayesian random effects network meta-analysis showed no statistically significant

difference between indomethacin versus placebo (Network RR 0.95, 95% CrIs 0.32, 2.4) as well as ibuprofen versus placebo (Network RR 1.0, 95% CrIs 0.30, 3.0) for the outcome of necrotizing enterocolitis. There were no differences in the median ranks between any of the interventions [Indomethacin (median rank 2, 95% CrI 1 to 3; mean SUCRA, 0.55), ibuprofen (median rank 2, 95% CrI 1 to 3; mean SUCRA, 0.48) and placebo (median rank 2, 95% CrI 1 to 3; mean SUCRA, 0.47) in this specific gestational age and/or birth weight group.

Gastrointestinal perforation

Four studies (n = 1398) reported on this outcome [Indomethacin versus placebo (2 studies, 1221 infants); ibuprofen versus placebo (2 studies, 177 infants). The network diagram is presented in Figure 36.

Initial pairwise meta-analysis using Bayesian random-effects model showed no statistically significant differences in gastrointestinal perforation with indomethacin compared to placebo (2 studies, 1221 infants; RR 1.1, 95% CrI 0.66 to 1.7) (Figure 37) or ibuprofen versus placebo (2 studies, 177 infants; RR 2.7, 95% CrI 0.40 to 18.00) (Figure 38).

Bayesian random-effects network meta-analysis showed no statistically significant difference in gastrointestinal perforation with indomethacin (Network RR 0.92, 95% CrIs 0.11, 3.9; moderate-certainty) or ibuprofen (Network RR 2.6, 95% CrIs 0.42, 20; very low-certainty) compared to placebo. The relative treatment effects for all possible comparisons obtained from the network meta-analysis are shown in Figure 39, Table 6. We were unable to run any inconsistency models as there were no head-to-head trials between any of the three COX-I drugs. Indomethacin (median rank 1, 95% CrI 1 to 3, mean SUCRA 0.70) ranked as the best treatment for reduction in gastrointestinal perforation (Figure 40).

Sensitivity Analysis

All four studies mentioned above were conducted in infants born extremely preterm (less than 28 weeks of gestational age) and/or extremely low birth weight (less 1000 g of birth weight). Therefore, no separate sensitivity analysis was conducted for this outcome.

Chronic lung disease (CLD) (defined as use of oxygen or respiratory support at 36 weeks' postmenstrual age)

Eighteen studies (n = 3058) reported on this outcome [Indomethacin versus placebo (10 studies, 2106 infants); ibuprofen versus placebo (7 studies, 904 infants) and acetaminophen versus placebo (1 study, 48 infants)]. The acetaminophen node had zero events for CLD and therefore was removed from the network meta-analysis as no continuity correction was applied. The network diagram is presented in Figure 41.

Initial pairwise meta-analysis using Bayesian random-effects model showed no statistically significant differences in CLD with indomethacin compared to placebo (10 studies, 2106 infants; RR 1.1, 95% CrI 0.91 to 1.3) (Figure 42) or ibuprofen versus placebo (7 studies, 904 infants; RR 1.00, 95% CrI 0.74 to 1.4) (Figure 43).

Bayesian random-effects network meta-analysis showed no statistically significant difference in CLD with indomethacin (Network RR 1.09, 95% CrIs 0.93, 1.29; low-certainty) or ibuprofen (Network RR 1.05, 95% CrIs 0.83, 1.32; low-certainty) compared to placebo. The relative treatment effects for all possible comparisons obtained from the network meta-analysis are shown in Figure 44, Table 7. Comparison-adjusted funnel plots were not suggestive of any small-study effects (Figure 45). We were unable to run any inconsistency models as there were no head-to-head trials between any of the three COX-I drugs. Placebo (median rank 1, 95% CrI 1 to 3, mean SUCRA 0.77) ranked as the best option for reduction in CLD followed by ibuprofen (median rank 2, 95% CrI 1 to 3, mean SUCRA 0.47) (Figure 46).

Sensitivity Analysis

We conducted a sensitivity analysis of studies that specifically reported on infants born extremely preterm (less than 28 weeks of gestational age) and/or extremely low birth weight (less 1000 g of birth weight). 4 studies (n = 1179) that compared indomethacin versus placebo and 3 studies (n = 322) that compared ibuprofen versus placebo reported on chronic lung disease in infants in this specific gestational age and/or birth weight. Bayesian random effects network meta-analysis showed no statistically significant difference between indomethacin versus placebo (Network RR 1.2, 95% CrIs 0.88, 1.9) as

well as ibuprofen versus placebo (Network RR 0.99, 95% CrIs 0.60, 1.7) for the outcome of chronic lung disease. Ibuprofen (median rank 1, 95% CrI 1 to 3; mean SUCRA, 0.65) ranked as the best treatment for reduction in chronic lung disease followed by placebo (median rank 2, 95% CrI 1 to 3; mean SUCRA, 0.70) and indomethacin (median rank 3, 95% CrI 1 to 3; mean SUCRA, 0.15) in this specific gestational age and/or birth weight group.

Oliguria

Twelve studies (n = 2864) reported on this outcome [Indomethacin versus placebo (8 studies, 2115 infants); ibuprofen versus placebo (3 studies, 701 infants) and acetaminophen versus placebo (1 study, 48 infants)]. The network diagram is presented in Figure 47.

Initial pairwise meta-analysis using Bayesian random-effects model showed a statistically significant increase in oliguria with indomethacin versus placebo (8 studies, 2115 infants; RR 1.7, 95% CrI 1.2 to 2.4) (Figure 48). No statistically significant difference in oliguria was noted with ibuprofen versus placebo (3 studies, 701 infants; RR 1.3, 95% CrI 0.83 to 2.1) (Figure 49), or with acetaminophen versus placebo (1 study, 48 infants; RR 0.78, 95% CrI 0.28 to 2.16).

Bayesian random effects network meta-analysis showed a statistically significant increase in oliguria with indomethacin (Network RR 1.7, 95% CrIs 1.2, 2.3) (Figure 50). No statistically significant differences in oliguria were noted with ibuprofen (Network RR 1.32, 95% CrIs 0.85, 2.02) or acetaminophen (Network RR 0.68, 95% CrIs 0.20, 1.97) compared to placebo (Figure 50). The relative treatment effects for all possible comparisons obtained from the network meta-analysis are shown in Table 8. Comparison-adjusted funnel plots were not suggestive of any small-study effects (Figure 51). We were unable to run any inconsistency models as there were no head- to-head trials between any of the three COX-I drugs. Acetaminophen (median rank 1, 95% CrI 1 to 4) ranked as the best treatment option for the outcome of oliguria followed by placebo (median rank 2, 95% CrI 1 to 3), ibuprofen (median rank 3, 95% CrI 1 to 4) and lastly indomethacin (median rank 4, 95% CrI 3 to 4) (Figure 52). Based on the mean SUCRA values, acetaminophen had the highest SUCRA (0.86).

Intraventricular haemorrhage (IVH) of any grade

Twenty-two studies (n = 3543) reported on this outcome [Indomethacin versus placebo (16 studies, 2674 infants); ibuprofen versus placebo (5 studies, 821 infants) and acetaminophen versus placebo (1 study, 48 infants)]. The network diagram is presented in Figure 53.

Initial pairwise meta-analysis using Bayesian random-effects model showed a statistically significant reduction in IVH (any grade) with indomethacin versus placebo (16 studies, 2674 infants; RR 0.75, 95% CrI 0.61 to 0.92) (Figure 54). No statistically significant difference in IVH (any grade) was noted with ibuprofen versus placebo (5 studies, 821 infants; RR 0.93, 95% CrI 0.63 to 1.4) (Figure 55), or with acetaminophen versus placebo (1 study, 48 infants; RR 0.65, 95% CrI 0.28 to 1.54).

Bayesian random-effects network meta-analysis showed a statistically significant reduction in IVH (any grade) with indomethacin (Network RR 0.77, 95% CrIs 0.62, 0.90) (Figure 56). No statistically significant differences in IVH (any grade) were noted with ibuprofen (Network RR 0.94, 95% CrIs 0.66, 1.31) or acetaminophen (Network RR 0.60, 95% CrIs 0.20, 1.59) compared to placebo. The relative treatment effects for all possible comparisons obtained from the network meta-analysis are shown in Figure 56, Table 9. Comparison-adjusted funnel plots were not suggestive of any small-study effects (Figure 57). We were unable to run any inconsistency models as there were no head-to-head trials between any of the three COX-I drugs. Acetaminophen (median rank 1, 95% CrI 1 to 4) ranked as the best treatment option for reduction of IVH (any grade) followed by indomethacin (median rank 2, 95% CrI 1 to 3), ibuprofen (median rank 3, 95% CrI 1 to 4) and placebo (median rank 4, 95% CrI 2 to 4) (Figure 58). Based on the mean SUCRA values, acetaminophen had the highest SUCRA (0.78).

Periventricular leukomalacia (PVL) of any grade)

Eight studies (n = 2216) reported on this outcome [Indomethacin versus placebo (4 studies, 1469 infants); ibuprofen versus placebo (4 studies, 747 infants). The network diagram is presented in Figure 59.

Initial pairwise meta-analysis using Bayesian random-effects model showed no statistically significant differences in PVL with indomethacin compared to placebo (4 studies, 1469

infants; RR 0.69, 95% CrI 0.29 to 1.6) (Figure 60) or with ibuprofen versus placebo (4 studies, 747 infants; RR 0.94, 95% CrI 0.46 to 1.9) (Figure 61).

Bayesian random effects network meta-analysis showed no statistically significant difference in PVL with indomethacin (Network RR 0.74, 95% CrIs 0.30, 1.35) or ibuprofen (Network RR 0.94, 95% CrIs 0.40, 2.02) compared to placebo. The relative treatment effects for all possible comparisons obtained from the network meta-analysis are shown in Figure 62, Table 10. We were unable to run any inconsistency models as there were no head-to-head trials between any of the three COX-I drugs. Indomethacin (median rank 1, 95% CrI 1 to 3) ranked as the best treatment option for PVL followed by ibuprofen (median rank 2, 95% CrI 1 to 3) and placebo (median rank 2, 95% CrI 1 to 3)(Figure 63). Based on the mean SUCRA values, indomethacin had the highest SUCRA (0.80).

Neurodevelopmental outcome (at 18 to 24 months of age)

Due to absence of data on multiple COX-I drugs network meta-analysis was not possible for this outcome.

Cerebral palsy (CP)

Five studies (n =1402) reported on this outcome [Indomethacin versus placebo (4 studies, 1367 infants); acetaminophen versus placebo (1 study, 35 infants). The network diagram is presented in Figure 64.

Initial pairwise meta-analysis using Bayesian random-effects model showed no statistically significant differences in CP with indomethacin compared to placebo (4 studies, 1367 infants; RR 0.97, 95% CrI 0.46 to 2.0) (Figure 65), or with acetaminophen versus placebo (1 study, 35 infants; RR 0.84, 95% CrI 0.05 to 13.75).

Bayesian random-effects network meta-analysis showed no statistically significant difference in CP with indomethacin (Network RR 0.97, 95% CrIs 0.44, 2.11; low-certainty) or acetaminophen (Network RR 0.36, 95% CrIs 0.01, 6.31; very low-certainty) compared to placebo. The relative treatment effects for all possible comparisons obtained from the network meta-analysis are shown in Figure 66; Table 11. We were unable to run any inconsistency models as there were no head-to-head trials between any of the three

COX-I drugs. Acetaminophen (median rank 1, 95% CrI 1 to 3) ranked as the best treatment option for CP followed by indomethacin (median rank 2, 95% CrI 1 to 3) and placebo (median rank 2, 95% CrI 1 to 3)(Figure 67). Based on the mean SUCRA values, acetaminophen had the highest SUCRA (0.76).

Major neurodevelopmental disability

Due to absence of data on multiple COX-I drugs network meta-analysis was not possible for this outcome.

Network meta-regression

The included studies were conducted between 1985 and 2018. Therefore, as planned a priori, we conducted a network meta-regression, assuming a common fixed coefficient across comparisons to explore the effect of year of publication on the following clinical outcomes:

Severe Intraventricular haemorrhage (IVH)

Bayesian random effects network meta-regression showed that indomethacin significantly reduced severe IVH compared to placebo (Network RR 0.59, 95% CrIs 0.39, 0.80). There were no statistically significant differences observed with either Ibuprofen (Network RR 0.64, 95% CrIs 0.34, 1.1) or acetaminophen (Network RR 0.48, 95% CrIs 0.02, 6.6) compared to placebo. Acetaminophen (median rank 1, 95% CrI 1 to 4; mean SUCRA, 0.60) had the best median rank for reduction of severe IVH followed by indomethacin (median rank 2, 95% CrI 1 to 3; mean SUCRA, 0.68), ibuprofen (median rank 2, 95% CrI 1 to 4; mean SUCRA, 0.59) and placebo (median rank 4, 95% CrI 3 to 4; mean SUCRA, 0.12).

Mortality

Bayesian random effects network meta-regression showed no statistically significant differences in mortality with indomethacin (Network RR 0.85, 95% CrIs 0.61, 1.1), ibuprofen (Network RR 0.81, 95% CrIs 0.54, 1.2) or acetaminophen (Network RR 0.45,

95% CrIs 0.13, 1.5) compared to placebo. Acetaminophen (median rank 1, 95% CrI 1 to 4; mean SUCRA, 0.85) had the best median rank for reduction of mortality followed by ibuprofen (median rank 2, 95% CrI 1 to 4; mean SUCRA, 0.53), indomethacin (median

rank 3, 95% CrI 1 to 4; mean SUCRA, 0.51) and placebo (median rank 4, 95% CrI 2 to 4; mean SUCRA, 0.12).

Chronic lung disease (CLD)

Bayesian random-effects network meta-regression showed no statistically significant differences in CLD with indomethacin (Network RR 1.1, 95% CrIs 0.94, 1.5) or ibuprofen (Network RR 0.96, 95% CrIs 0.65, 1.3) compared to placebo. Ibuprofen (median rank 1, 95% CrI 1 to 3; mean SUCRA, 0.70) had the best median rank for reduction of CLD followed by placebo (median rank 2, 95% CrI 1 to 3; mean SUCRA, 0.66) and indomethacin (median rank 3, 95% CrI 1 to 3; mean SUCRA, 0.14).

Necrotizing enterocolitis (NEC)

Bayesian random effects network meta-regression showed no statistically significant differences in NEC with indomethacin (Network RR 0.73, 95% CrIs 0.32, 1.2) or ibuprofen (Network RR 0.74, 95% CrIs 0.26, 1.7) compared to placebo. Indomethacin (median rank 2, 95% CrI 1 to 3; mean SUCRA, 0.68) and ibuprofen (median rank 2, 95% CrI 1 to 3; mean SUCRA, 0.63) had the best median ranks for reduction of NEC followed by placebo (median rank 3, 95% CrI 2 to 3; mean SUCRA, 0.19).

Gastrointestinal perforation

Bayesian random effects network meta-regression showed no statistically significant differences in gastrointestinal perforation with indomethacin (Network RR 0.61, 95% CrIs 0.04, 4.1) or ibuprofen (Network RR 2.7, 95% CrIs 0.43, 22.0) compared to placebo. Indomethacin (median rank 1, 95% CrI 1 to 3; mean SUCRA, 0.79) had the best median rank for reduction of gastrointestinal perforation followed by placebo (median rank 2, 95% CrI 1 to 3; mean SUCRA, 0.58) and ibuprofen (median rank 3, 95% CrI 1 to 3; mean SUCRA, 0.13).

Planned sensitivity analysis

We did not perform the planned sensitivity analysis including only low risk of bias studies as majority of information in all the three networks (indomethacin versus placebo, ibuprofen versus placebo and acetaminophen versus placebo) was derived from studies at

low risk of bias with minimal statistical heterogeneity demonstrated in the direct comparisons.

Discussion

Summary of main results

Twenty-eight randomized controlled trials (RCTs) completed to date have reported on 3999 infants. Nineteen studies that enrolled 2877 infants compared prophylactic indomethacin versus placebo/no treatment, seven studies that enrolled 914 infants compared prophylactic ibuprofen versus placebo/no treatment and two studies that enrolled 208 infants compared prophylactic acetaminophen versus placebo/no treatment. No head-to-head RCTs that directly compared two or more of the three active interventions were identified for inclusion in our review.

Based on the decision thresholds defined by the authoring team, Bayesian random- effects network meta-analysis (NMA) of eligible RCTs showed that prophylactic indomethacin probably results in a small reduction in severe intraventricular haemorrhage (IVH), a moderate reduction in mortality and need for surgical patent ductus arteriosus (PDA) closure (moderate certainty). Prophylactic indomethacin may result in a small increase in chronic lung disease (CLD) (low certainty) and results in trivial differences in necrotizing enterocolitis (NEC) (high certainty), gastrointestinal perforation (moderate certainty) and cerebral palsy (low certainty) compared to placebo or no treatment.

Prophylactic ibuprofen probably results in a small reduction in severe IVH and a moderate reduction in need for surgical PDA closure (moderate certainty). Prophylactic ibuprofen may also result in a moderate reduction in mortality (low certainty), and trivial differences in CLD (low certainty) and NEC (high certainty) compared to placebo or no treatment.

The evidence is very uncertain about the effect of acetaminophen on any of the clinically relevant outcomes. Indirect comparisons, where possible, between the three cyclooxygenase inhibitors (COX-I) drugs revealed no statistically significant differences for any of the clinical outcomes.

Overall completeness and applicability of evidence

This is the first systematic review and NMA comparing prophylactic COX-I drugs in preterm infants. We used Bayesian random-effects NMA to derive relative treatment effects and relative treatment rankings for the four possible pharmacoprophylactic options (indomethacin, ibuprofen, acetaminophen, and placebo/no treatment) for each clinical outcome, where possible. Although the use of NMA has allowed us to derive more precise effect estimates for each of the COX-I drugs versus placebo and to generate effect estimates against each other through indirect comparisons, we recommend cautious interpretation of the relative treatment rankings, especially for acetaminophen.

This is primarily due to the fact that majority of the evidence in the network was contributed by randomized controlled trials comparing indomethacin versus placebo (19 studies, 2877 infants) and ibuprofen versus placebo (7 studies, 914 infants). Only 208 participants out of 3999 in the entire network were contributed by studies that used prophylactic acetaminophen (2 studies). This has resulted in imprecise effect estimates for acetaminophen. Although this imprecision is adequately accounted for in the GRADE certainty of evidence, resulting in very low certainty for all the acetaminophen estimates, the median ranks and surface under the cumulative ranking curve (SUCRA) values in such sparse networks could be misleading. For example, for the outcome of mortality, acetaminophen ranks as the best intervention (median rank 1) ahead of indomethacin and ibuprofen, with the best mean SUCRA value (0.87). This is primarily because the network risk ratio (RR) point estimate for acetaminophen (0.49) is substantially better than either indomethacin (0.85) or ibuprofen (0.83). However, the median rank and mean SUCRA value fail to account for the imprecision around this point estimate (acetaminophen network RR for mortality: 0.49, 95% credible intervals (CrIs) 0.16 to 1.4), which is demonstrated by the 95% CrIs around the median rank (1- 4, in the case of acetaminophen for mortality). Therefore, simply stating that acetaminophen is the best intervention for the critical outcome of mortality would be an oversimplification of the interpretation of NMA results. Hence, readers should consider the imprecision (95% CrIs) around the network effect estimates and median ranks while determining the relative benefit or harm of an intervention with respect to a particular outcome.

Subgroup considerations

There is considerable debate on the use of prophylactic COX-I drugs in preterm infants. Based on existing evidence, the American Academy of Pediatrics (Hamrick 2020)[146] and the Canadian Pediatric Society (Ryan 2019)[147] recently suggested considering the use of prophylactic indomethacin in extremely low gestational age neonates (ELGANs, born less than 28 weeks of gestational age), or extremely low birth weight (ELBW, birth weight less than 1000 g) infants, especially if they are at a high risk of severe IVH (such as gestational age at birth <26 weeks, lack of antenatal corticosteroids, and male sex). We conducted a sensitivity analysis to specifically explore the effect of COX-I drugs in ELGAN and/or ELBW infants. The notable differences with the primary analysis results that may affect clinical decision-making on prophylactic indomethacin use were the following.

a) Severe IVH: prophylactic indomethacin no longer had a statistically significant benefit for reduction of severe IVH in this group (Network RR 0.81, 95% CrIs 0.37, 2.0). Prophylactic ibuprofen (Network RR 0.46, 95% CrIs 0.14, 1.2) ranked higher (median rank 1, 95% CrI 1 to 3; mean SUCRA, 0.91) than prophylactic indomethacin (median rank 2, 95% CrI 1 to 3; mean SUCRA, 0.43) in this gestational age and/or birth weight group. This result might be an important practice consideration for centers that routinely use prophylactic indomethacin for prevention of IVH in extremely preterm or ELBW infants.

b) Mortality: similar to the results of severe IVH above, prophylactic indomethacin no longer demonstrated a statistically significant benefit for reduction in mortality in this gestational age/birthweight (GA/BW) group (Network RR 1.2, 95% CrIs 0.74, 1.9). Both prophylactic ibuprofen (median rank 1, 95% CrI 1 to 3; mean SUCRA, 0.87) as well as placebo (median rank 2, 95% CrI 1 to 3; mean SUCRA, 0.48) ranked higher than prophylactic indomethacin (median rank 3, 95% CrI 1 to 3; mean SUCRA, 0.15) in this specific gestational age and/or birth weight group.

c) Surgical PDA closure: prophylactic indomethacin no longer demonstrated a statistically significant reduction in need for surgical PDA closure in this GA/BW group (Network RR 0.56, 95% CrIs 0.13, 3.0). Prophylactic ibuprofen (Network RR 0.07, 95% CrIs 0.001, 0.73) still demonstrated a statistically significant reduction in need for PDA ligation and therefore maintained a higher rank (median rank 1, 95% CrI 1 to 2; mean

SUCRA, 0.97) than prophylactic indomethacin (median rank 2, 95% CrI 1 to 3; mean SUCRA, 0.45) in this specific gestational age and/or birth weight group.

Moreover, both the primary and the sensitivity analysis demonstrated that indomethacin ranked as the least preferable option for reduction of CLD. Given that prophylactic indomethacin is unlikely to significantly reduce severe IVH, mortality or surgical PDA ligation and, in addition may lead to a small increase in risk of CLD, caution should be exercised while considering routine use of prophylactic indomethacin in ELGAN and/or ELBW infants. Current evidence, thus, fails to demonstrate benefit of any of the COX-I drugs in improving critical outcomes such as severe IVH or mortality in ELGAN and/or ELBW infants.

Quality of the evidence

The certainty of evidence for the primary outcome of severe IVH was moderate for the comparisons of indomethacin versus placebo and ibuprofen versus placebo while it was very low for acetaminophen versus placebo. The certainty of evidence for the primary outcome of mortality was moderate for the comparison of indomethacin versus placebo, low for ibuprofen versus placebo and very low for acetaminophen versus placebo. We used the 'GRADE guidelines on informative statements to communicate the findings of systematic reviews of interventions' by Santesso 2020[1] to formulate statements on the size of the effect estimate and certainty of evidence in our result summaries.

Readers should consider the following while interpreting the certainty of evidence as determined in this review.

a) Imprecision: prior to assessing the certainty of evidence, the authoring team adopted a partially contextualized approach for addressing imprecision in the NMA estimates following the GRADE guidance by Brignardello-Petersen 2021[148]. We defined thresholds for benefit or harm for each outcome (listed in the protocol for certainty assessment) and assessed the imprecision in the context of these thresholds. For the outcome of mortality, 'small' benefit/harm was defined as < 20 fewer or more per 1000, respectively; 'moderate' benefit/harm was defined as 20 to 50 fewer or more per 1000, respectively; 'large' benefit/harm was defined as > 50 fewer or more per 1000,

respectively. For all other outcomes listed in the summary of findings table, any effect < 20 fewer or more per 1000 was defined as a trivial benefit or harm. No direction of effect was specified for trivial effects. A 'small' benefit/harm was defined as 20 to 50 fewer or more per 1000, respectively, 'moderate' benefit/harm was defined as 50-100 fewer or more per 1000 respectively and 'large' benefit/harm was defined as >100 fewer or more per 1000 respectively. A moderate or large effect was considered as an 'appreciable' effect. If the 95% CrIs included an appreciable effect at one end of the 95% CrI (i.e. small benefit-appreciable harm or small harm-appreciable benefit), the certainty was rated down by one-level. If the 95% CrIs included both appreciable benefit and harm, the certainty was rated down by 2 levels. Further, in sparse networks (such as with acetaminophen versus placebo) where the 95% CrIs included implausible benefit/harm, we chose to rate the certainty of evidence down by 3 levels as per the recent GRADE guidance by Brignardello-Petersen 2021. Decision-makers and guideline panels may choose to use different decision thresholds and appropriately update the certainty of evidence prior to formulating guideline recommendations.

b) Inconsistency: the networks for none of the outcomes in our review had closed loops as there were no head-to-head RCTs between the active interventions; all RCTs had compared an active intervention against placebo/no treatment. Therefore, in the NMA, we were unable to obtain both direct and indirect estimates for any set of comparisons; we either had only direct or only indirect estimates. As a result, we were unable to run any inconsistency models and hence we were unable to judge the NMA inconsistency domain for GRADE. In our protocol we had specified that "when assessment of statistical inconsistency is not possible due to absence of head-to-head comparisons between interventions, we will not rate down the certainty of evidence any further due to presumed inconsistency, as the NMA would have been conducted under the strict assumption of transitivity thereby ensuring clinical and methodological homogeneity between the indirect comparisons". Therefore, the certainty of evidence for none of the comparisons were rated down for inconsistency.

Potential biases in the review process

We are not aware of any biases in the review process. Review authors were not involved with any of the included trials. All included studies strictly met our pre-defined criteria for transitivity defined by the inclusion of only preterm or low birth weight infants, within the first 72 hours of birth and without a prior clinical or echocardiographic diagnosis of a PDA. However, we were unable to run any inconsistency models as there were no head-to-head trials between any of the three COX-I drugs. Therefore, though the transitivity assumption was met, we could not statistically assess consistency of our NMA models.

Agreements and disagreements with other studies or reviews

Three previous Cochrane Reviews have separately compared placebo/no treatment against prophylactic indomethacin, ibuprofen, or acetaminophen, respectively (Fowlie 2010; Ohlsson 2020b; Ohlsson 2020c)[25,27,28]. All three previous reviews used a fixed-effect model for their statistical analysis, whereas we used a Bayesian random-effects model for both our direct and indirect comparisons.

The review by Fowlie 2010[27] on use of prophylactic intravenous indomethacin was last updated in 2010 and did not include any assessment of certainty of evidence. The Fowlie 2010 review demonstrated that prophylactic indomethacin resulted in a statistically significant reduction in severe IVH and has subsequently formed the basis of its routine prophylactic use in many neonatal centers. In our review, we found four additional studies (Jannatdoust 2014; Kumar Nair 2004; Maruyama 2012; Vogtmann 1988)[80,82,84,106] comparing prophylactic indomethacin versus placebo that met our inclusion criteria and were added to the indomethacin versus placebo arm. Our overall network effect estimates were similar to those from the Fowlie review, and we also demonstrated that prophylactic indomethacin overall results in a statistically significant reduction in severe IVH. We further added a sensitivity analysis for ELGAN and/or ELBW infants which showed that in this particular subgroup prophylactic indomethacin may not reduce the incidence of severe IVH. This finding may have important practice implications.

The updated review by Ohlsson 2020c on the use of prophylactic ibuprofen included nine trials (n = 1070) while our review included seven trials (n = 914)[28]. Two studies included in the Ohlsson 2020c review were not included in our review, as they did not meet our inclusion criteria. The study by Sangtawesin 2008[149] included only infants who were

diagnosed with a PDA within the first 24 hours after birth which did not meet our definition of prophylactic therapy. The study by Kalani 2016[73] was placed in Characteristics of studies awaiting classification as their methods section suggested that it was a retrospective study, and we were unable to establish contact with the primary author to clarify this discrepancy. However, the effect estimates and certainty of evidence for clinically relevant outcomes in the Ohlsson 2020c[28] review were similar to our review.

The updated review by Ohlsson 2020b[25] on use of prophylactic acetaminophen included two trials (n = 80), while our review included two trials (n = 208). We did not include the study by Akbari Asbagh 2015[72] as we were unable to contact the corresponding author to obtain clarifying information on outcome data. Hence, this study has been placed in Characteristics of studies awaiting classification. Due to overall paucity of data, neither the Ohlsson 2020b[25] review nor our review could precisely establish or refute any clinically meaningful benefit/harm with use of prophylactic acetaminophen.

Authors' conclusions

Implications for practice

Prophylactic indomethacin probably results in a small reduction in severe intraventricular haemorrhage (IVH) and a moderate reduction in mortality and need for surgical patent ductus arteriosus (PDA) closure (moderate certainty), may result in a small increase in chronic lung disease (CLD) (low certainty) and results in trivial differences in necrotizing enterocolitis (NEC) (high certainty), gastrointestinal perforation (moderate certainty) and cerebral palsy (CP) (low certainty) compared to placebo. In the subgroup of extremely preterm and/or extremely low birth weight infants, prophylactic indomethacin is unlikely to reduce severe IVH, mortality, or need for PDA ligation.

Prophylactic ibuprofen probably results in a small reduction in severe IVH and a moderate reduction in need for surgical PDA closure (moderate certainty), may result in a moderate reduction in mortality (low certainty) and trivial differences in CLD (low certainty) and NEC (high certainty) compared to placebo. In the subgroup of extremely preterm and/or extremely low birth weight infants, prophylactic ibuprofen may reduce need for PDA ligation, but is unlikely to reduce severe IVH or mortality.

The evidence is very uncertain about the effect of acetaminophen on any of the clinically relevant outcomes.

Implications for research

Given that extremely preterm infants born < 26 weeks' of gestation are at the highest risk of mortality and major morbidity such as severe IVH, CLD, NEC and neurodevelopmental impairment, future COX-I pharmacoprophylaxis trials should be designed to explore the effectiveness and safety of the COX-I drugs specifically in this high-risk population. Out of the three COX-I medications, acetaminophen clearly lacks good quality evidence for its use as pharmacoprophylaxis. Therefore, additional large trials specifically on acetaminophen pharmacoprophylaxis in extremely low gestational age neonates are warranted. There are currently two ongoing randomized controlled trials on prophylactic use of acetaminophen in extremely preterm infants born less than 28 weeks of gestational age (NCT03641209; NCT04459117). In addition, large, well-designed, prospective observational studies might provide useful data for potential harms of these COX-I medications in extremely preterm infants. Given the low rate of adverse clinical outcomes, lack of clear benefit and potential for harm with routine use, there is no clinical equipoise for use of prophylactic COX-I medications in older preterm infants. Therefore, we do not recommend any further research on COX-I prophylaxis in older preterm infants, especially those born after 28 weeks' of gestation.

Acknowledgements

We would like to thank Cochrane Neonatal: Colleen Ovelman (Managing Editor), Jane Cracknell (Assistant Managing Editor), Roger Soll (Co-coordinating editor), and Bill McGuire (Co-coordinating Editor), who provided editorial and administrative support.

We would also like to thank Robin Parker (WK Kellogg Health Sciences Library, Dalhousie University), as the creator of these searches, and Leah Boulos (Evidence Synthesis Coordinator, Maritime SPOR SUPPORT Unit), for her peer review of the MEDLINE search strategy.

Menelaos Konstantinidis, Kerry Dwan (Cochrane Methods Support Unit) and Prakeshkumar Shah (Cochrane Neonatal Senior Editor) peer-reviewed and offered feedback for this protocol.

The methods section of the protocol is based on a standard template used by Cochrane Neonatal.

History

Protocol first published: Issue 1, 2021

Declarations of interest

SM is the principal investigator of a Canadian Institutes of Health Research (CIHR)-funded prospective study on the relative effectiveness and safety of pharmacotherapeutic agents for treatment of patent ductus arteriosus (PDA) in preterm infants. SM reports working as a neonatologist at a tertiary care neonatal intensive care unit in IWK Health Center (Halifax, Nova Scotia, Canada) where they attend to preterm infants diagnosed with a PDA.

CEG declares no conflict of interest. AM declares no conflict of interest. TD declares no conflict of interest.

DMS reports working as a Fellow (Resident PGY6) Neonatal-Perinatal Medicine at Dalhousie University/IWK Health Center.

MCY declares no conflict of interest. SK declares no conflict of interest.

BCJ declares no conflict of interest.

JD reports working at IWK Health as Neonatologist and therefore sometimes treat PDAs in preterm infants.

Sources of support

Internal sources

No sources of support provided

External sources

Vermont Oxford Network, USA

Cochrane Neonatal Reviews are produced with support from Vermont Oxford Network, a worldwide collaboration of health professionals dedicated to providing evidence-based care of the highest quality for newborn infants and their families.

Differences between protocol and review

2021

We made the following changes to the published protocol.

1. Statistical software for analysis: in the protocol we had mentioned that "We will undertake all analyses (both pairwise meta-analyses and NMA) using the R (R Core Team 2020)[63] package gemtc on the MetaInsight application, developed by the Cochrane Complex Review Support Unit (CRSU)". However, the MetaInsight application was unable to generate all the pre-defined statistical outputs such as rankograms and comparison-adjusted forest plots. Therefore, we used the GEMTC GUI interface (van Valkenhoef 2012)[49] which also uses the same R package gemtc to run all the analyses.
2. Presentation of relative treatment effects: in the protocol we had mentioned that the relative treatment effects "will be summarized in forest plots displaying the results from pairwise, indirect and network (combining direct and indirect) analyses". However, the R package gemtc that was used to conduct the Bayesian random effects meta-analysis only provided forest plot outputs for direct and network

estimates. Hence, forest plots for indirect estimates were not presented in the results.

3. Heterogeneity priors for the Bayesian NMA: prior distributions for the relative effect estimates were determined heuristically based on the following: N(0, (15 · S)2), where N denotes normal distribution and S denotes the outcome scale. The outcome scale is meant to represent an unreasonably large deviation on the scale of measurement which was determined heuristically based on available data. The heterogeneity priors for the primary analyses of each of the 11 outcomes are presented in Table 12.
4. Subgroup and sensitivity analysis: none of the pre-defined subgroup analysis (based on gestational age, birth weight or timing of initiation of prophylaxis) was possible due to lack of complete data in either subgroup in each category. Instead, we performed a post-hoc sensitivity analysis of studies that specifically reported on infants born extremely preterm (less than 28 weeks of gestational age) and/or extremely low birth weight (less 1000 g of birth weight). We reported the sensitivity analysis results for those clinically relevant outcomes where subgroup analyses were planned a priori. Further, we did not perform the planned sensitivity analysis including only low risk of bias studies as majority of information in all the three networks (indomethacin versus placebo, ibuprofen versus placebo and acetaminophen versus placebo) was derived from studies at low risk of bias with minimal statistical heterogeneity demonstrated in the direct comparisons.
5. Outcomes for assessment of GRADE certainty of the evidence: in our protocol we had planned to include severe neurodevelopmental impairment as one of the seven outcomes for assessment of GRADE certainty of evidence. However, an NMA could not be conducted for the said outcome as this was only reported for the indomethacin versus placebo arm. Out of the listed neurodevelopmental outcomes, an NMA could be conducted for the outcome of CP. Therefore, we replaced neurodevelopmental impairment with CP as the 7th outcome for assessment of GRADE certainty of evidence.
6. Interpretation of magnitude of effect sizes for assessment of certainty of evidence: prior to assessing the certainty of evidence, the authoring team used a partially

contextualized approach to define the magnitude of effect sizes for each outcome (Zeng 2021)[150]. Interpretation of effect sizes were based on a priori defined thresholds as follows: (a) For the outcome of mortality: small benefit/harm was defined as < 20 fewer or more per 1000, respectively. Moderate benefit/harm was defined as 20 to 50 fewer or more per 1000, respectively. Large benefit/harm was defined as > 50 fewer or more per 1000, respectively; (b) For all other outcomes listed in the summary of findings table: any effect < 20 fewer or more per 1000 was defined as a trivial benefit or harm. No direction of effect was specified for trivial effects. Small benefit/harm was defined as 20 to 50 fewer or more per 1000, respectively. Moderate benefit/harm was defined as 50 to 100 fewer or more per 1000, respectively. Large benefit/harm was defined as >100 fewer or more per 1000, respectively. Language for interpretation used in this column is based on the GRADE informative statements to communicate the findings of systematic reviews of interventions by Santesso 2020[1].

Summary of Findings

Outcome	Effects and confidence in the effect estimates						Comments**
	Indomethacin		Ibuprofen		Acetaminophen		
Severe Intraventricular Haemorrhage							
Placebo comparator 127 per 1000 (12.7%)	*Network RR* 0.66 (0.49, 0.87)	*Network absolute risk difference** 43 fewer per 1000 (from 65 fewer to 16 fewer)	*Network RR* 0.69 (0.41, 1.14)	*Network absolute risk difference* 39 fewer per 1000 (from 75 fewer to 18 more)	*Network RR* 1.17 (0.04, 55.2)	*Network absolute risk difference* 22 more per 1000 (from 122 fewer to 1000 more)	Prophylactic indomethacin probably results in a small reduction in severe IVH Prophylactic ibuprofen probably results in a small reduction in severe IVH The evidence is very uncertain about the effect of prophylactic acetaminophen on severe IVH
	Moderate ⊕⊕⊕◯ Confidence in estimate due to imprecision[1]		**Moderate** ⊕⊕⊕◯ Confidence in estimate due to imprecision[2]		**Very Low** ⊕◯◯◯ Confidence in estimate due to imprecision[3]		
Rank [Median (95% CrIs)] 3 (2-4)	**Rank** 2 (1-3)		**Rank** 2 (1-4)		**Rank** 4 (1-4)		
	Based on 2629 infants (16 RCTs)		Based on 863 infants (6 RCTs)		Based on 48 infants (1 RCT)		
Mortality							
Placebo comparator 161 per 1000 (16.1%)	*Network RR* 0.85 (0.64 to 1.1)	*Network absolute risk difference** 24 fewer per 1000 (from 58 fewer to 16 more)	*Network RR* 0.83 (0.57 to 1.2)	*Network absolute risk difference* 27 fewer per 1000 (from 69 fewer to 32 more)	*Network RR* 0.49 (0.16 to 1.4)	*Network absolute risk difference* 82 fewer per 1000 (from 135 fewer to 64 more)	Prophylactic indomethacin probably results in a moderate reduction in mortality Prophylactic ibuprofen may result in a moderate reduction in mortality The evidence is very uncertain about the effect of prophylactic acetaminophen on mortality
	Moderate ⊕⊕⊕◯ Confidence in estimate due to imprecision[4]		**Low** ⊕⊕◯◯ Confidence in estimate due to imprecision[5]		**Very Low** ⊕◯◯◯ Confidence in estimate due to risk of bias and imprecision[6]		
Rank [Median (95% CrIs)] 4 (3-4)	**Rank** 2 (1-4)		**Rank** 2 (1-4)		**Rank** 1 (1-4)		
	Based on 2877 infants (19 RCTs)		Based on 914 infants (7 RCTs)		Based on 208 infants (2 RCTs)		
Surgical PDA closure							
Placebo comparator 87 per 1000 (8.7%)	*Network RR* 0.40 (0.14 to 0.66)	*Network absolute risk difference** 52 fewer per 1000 (from	*Network RR* 0.24 (0.06 to 0.64)	*Network absolute risk difference* 66 fewer per 1000 (from	_____	_____	Prophylactic indomethacin probably results in a moderate reduction in need for surgical PDA closure

Outcome	Effects and confidence in the effect estimates						Comments**
	Indomethacin		Ibuprofen		Acetaminophen		
		75 fewer to 30 fewer)		82 fewer to 31 fewer)			Prophylactic ibuprofen may result in a moderate reduction in need for surgical PDA closure There is no evidence on the effect of prophylactic acetaminophen on need for surgical PDA closure
	Moderate ⊕⊕⊕◯ Confidence in estimate due to imprecision[7]		**Moderate** ⊕⊕⊕◯ Confidence in estimate due to imprecision[8]		_____		
Rank [Median (95% CrIs)] 3 (3-3)	**Rank** 2 (1-2)		**Rank** 1 (1-2)		_____		
	Based on 1800 infants (11 RCTs)		Based on 873 infants (6 RCTs)		_____		
Necrotizing Enterocolitis							
Placebo comparator 65 per 1000 (6.5%)	*Network RR* 0.76 (0.35 to 1.2)	*Network absolute risk difference** 16 fewer per 1000 (from 42 fewer to 13 more)	*Network RR* 0.73 (0.31 to 1.4)	*Network absolute risk difference* 18 fewer per 1000 (from 45 fewer to 26 more)	_____	_____	Prophylactic indomethacin results in trivial difference in NEC Prophylactic ibuprofen results in trivial difference in NEC There is no evidence on the effect of prophylactic acetaminophen on NEC
	High ⊕⊕⊕⊕ Confidence in estimate		**High** ⊕⊕⊕⊕ Confidence in estimate		_____		
Rank [Median (95% CrIs)] 3 (3-3)	**Rank** 2 (1-3)		**Rank** 1 (1-3)		_____		
	Based on 2543 infants (14 RCTs)		Based on 905 infants (7 RCTs)		_____		
Gastrointestinal perforation							
Placebo comparator 47 per 1000 (4.7%)	*Network RR* 0.92 (0.11 to 3.9)	*Network absolute risk difference** 4 fewer per 1000 (from 42 fewer to 137 more)	*Network RR* 2.6 (0.42 to 20.0)	*Network absolute risk difference* 76 more per 1000 (from 27 fewer to 897 more)	_____	_____	Prophylactic indomethacin probably results in trivial difference in gastrointestinal perforation The evidence is very uncertain about the effect of prophylactic ibuprofen on gastrointestinal perforation There is no evidence on the effect of prophylactic acetaminophen
	Moderate ⊕⊕⊕◯ Confidence in estimate due to imprecision[9]		**Very Low** ⊕◯◯◯ Confidence in estimate due to imprecision[10]		_____		
Rank [Median (95% CrIs)] 2 (1-3)	**Rank** 1 (1-3)		**Rank** 3 (1-3)		_____		
					_____		

Outcome	Effects and confidence in the effect estimates						Comments**
	Indomethacin		Ibuprofen		Acetaminophen		
	Based on 1221 infants (2 RCTs)		Based on 177 infants (2 RCTs)				on gastrointestinal perforation
Chronic Lung Disease							
Placebo comparator 359 per 1000 (35.9%)	*Network RR* 1.10 (0.93 to 1.3)	*Network absolute risk difference** 36 more per 1000 (from 25 fewer to 108 more)	*Network RR* 1.00 (0.83 to 1.3)	*Network absolute risk difference* 0 fewer per 1000 (from 61 fewer to 108 more)	_____	_____	Prophylactic indomethacin may result in a small increase in chronic lung disease Prophylactic ibuprofen may result in trivial difference in chronic lung disease There is no evidence on the effect of prophylactic acetaminophen on chronic lung disease
	Low ⊕⊕◯◯ Confidence in estimate due to inconsistency and imprecision[11]		**Low** ⊕⊕◯◯ Confidence in estimate due to imprecision[12]		_____		
Rank [Median (95% CrIs)] 1 (1-3)	**Rank** 3 (1-3)		**Rank** 2 (1-3)		_____		
	Based on 2106 infants (10 RCTs)		Based on 904 infants (7 RCTs)		_____		
Cerebral Palsy							
Placebo comparator 110 per 1000 (11%)	*Network RR* 0.97 (0.44 to 2.1)	*Network absolute risk difference** 3 fewer per 1000 (from 62 fewer to 121 more)	_____	_____	*Network RR* 0.36 (0.01 to 6.3)	*Network absolute risk difference* 70 fewer per 1000 (from 109 fewer to 583 more)	Prophylactic indomethacin may result in trivial difference in cerebral palsy There is no evidence on the effect of prophylactic ibuprofen on cerebral palsy The evidence is very uncertain about the effect off prophylactic acetaminophen on cerebral palsy
	Low ⊕⊕◯◯ Confidence in estimate due to imprecision[13]		_____		**Very Low** ⊕◯◯◯ Confidence in estimate due to imprecision[14]		
Rank [Median (95% CrIs)] 2 (1-3)	**Rank** 2 (1-3)		_____		**Rank** 1 (1-3)		
	Based on 1367 infants (4 RCTs)		_____		Based on 35 infants (1 RCT)		

Footnotes:

1. In the direct comparison, the credible intervals include moderate benefit (73 fewer per 1000) to small benefit (27 fewer per 1000). Therefore, the certainty of evidence was rated down by one level for imprecision. No further change was made based on the network estimates

2. In the direct comparison, the credible intervals include moderate benefit (82 fewer per 1000) to small harm (33 more per 1000). Therefore, the certainty of evidence was rated down by one level for imprecision. No further change was made based on the network estimates

3. 95% CrIs include appreciable benefit and very large harm. In the direct comparison, the certainty of evidence was rated down by one-level for serious imprecision. Based on the network estimates, the certainty was rated down by two more levels due to very serious imprecision (implausible effect sizes) in the network estimates

4. In the direct comparison, the credible intervals include moderate benefit (61 fewer per 1000) to small harm (17 more per 1000). Therefore, the certainty of evidence was rated down by one level for imprecision. No further change was made based on the network estimates

5. In the direct comparison, the credible intervals include appreciable benefit (72 fewer per 1000) and harm (48 more per 1000). Therefore, the certainty of evidence was rated down by two levels for very serious imprecision. No further change was made based on the network estimates.

6. In the direct comparison, the certainty of evidence was rated down due to substantial risk of bias in the included studies; the certainty was further rated down two levels for very serious imprecision as the credible intervals include appreciable benefit (85 fewer per 1000) and harm (76 more per 1000). Therefore, the overall certainty of evidence for the direct estimate was rated as very low. No further change was made based on the network estimates.

7. In the direct comparison, the credible intervals include moderate benefit (88 fewer per 1000) to small benefit (25 fewer per 1000). Therefore, the certainty of evidence was rated down by one level for imprecision. No further change was made based on the network estimates

8. The certainty of evidence for the direct comparison was high. However, the 95% credible intervals in the network estimates include appreciable benefit (82 fewer) to small benefit (31 fewer). Hence, the certainty of evidence was rated down by one level due to imprecision

9. 95% CrIs of the network estimates include small benefit (42 fewer) to appreciable harm (137 more). Hence, the certainty of evidence was rated down by one level due to imprecision

10. In the direct comparison, the credible intervals included trivial benefit (7 fewer per 1000) to appreciable harm (191 fewer per 1000). Therefore, the certainty of evidence was rated down by one level for imprecision. 95% CrIs of the network estimates include small benefit (27 fewer) to very large harm (897 more). Hence, the certainty was rated down by two more levels due to very serious imprecision (implausible effect sizes) in the network estimates.

11. In the direct comparison, the certainty of evidence was rated down one level due to serious inconsistency; the certainty was further rated down one level for imprecision as the credible intervals include small benefit (33 fewer per 1000) to appreciable harm (111 more per 1000). Therefore, the overall certainty of evidence for the direct estimate was rated as low. No further change was made based on the network estimates.

12. In the direct comparison, the credible intervals include moderate benefit (86 fewer per 1000) to large harm (132 more per 1000). Therefore, the certainty of evidence was rated down by two levels for imprecision (as the confidence limits include appreciable benefit or harm). No further change was made based on the network estimates

13. In the direct comparison, the credible intervals include moderate benefit (60 fewer per 1000) to large harm (111 more per 1000). Therefore, the certainty of evidence was rated down by two levels for imprecision

(as the credible intervals include appreciable benefit and harm). No further change was made based on the network estimates

14. In the direct comparison, the credible intervals include moderate benefit (59 fewer per 1000) to very large harm (797 more per 1000). Therefore, the certainty of evidence was rated down by two levels for imprecision (as the credible intervals include appreciable benefit and harm). The 95% CrIs of the network estimates include large benefit (109 fewer) to very large harm (583 more). Hence the certainty of evidence was rated down by one more level due to very serious imprecision (implausible effect sizes) in the network estimates

* A network absolute risk difference was calculated from the network RR estimates using an assumed control risk that was derived by dividing the total event number by the total infant number in the control groups in the network

**Comments on interpretation of effect sizes are based on a priori defined thresholds as follows: (a) For the outcome of *mortality*: small benefit/harm was defined as <20 fewer or more per 1000, respectively. Moderate benefit/harm was defined as 20 to 50 fewer or more per 1000, respectively. Large benefit/harm was defined as >50 fewer or more per 1000 respectively; (b) *For all other outcomes* listed in the summary of findings table: Any effect <20 fewer or more per 1000 was defined as a trivial benefit or harm. No direction of effect was specified for trivial effects. Small benefit/harm was defined as 20-50 fewer or more per 1000 respectively. Moderate benefit/harm was defined as 50-100 fewer or more per 1000 respectively. Large benefit/harm was defined as >100 fewer or more per 1000, respectively. Language for interpretation used in this column is based on the GRADE informative statements to communicate the findings of systematic reviews of interventions by Santesso 2020[1].

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Characteristics of studies

Characteristics of included studies [ordered by study ID]

Bada 1989		
Study characteristics		
Methods	Single-center randomized controlled trial	
Participants	**Inclusion criteria** Birth weight ≤1500g; periventricular-intraventricular haemorrhage ≤ grade 1 at 1 hour **Exclusion criteria** 1. Congenital malformations 2. Thrombocytopenia 3. Bleeding from puncture site or orifices 4. Plasma creatinine level ≥ than 1.8mg/dL	
Interventions	**Active intervention (n = 71)** Prophylactic IV indomethacin 0.2 mg/kg at 6 hours of age; and 0.1 mg/kg at 18 hours and 30 hours of age **Control (n = 70)** IV placebo (no description available)	
Outcomes	Relevant outcomes for this study included 1. Death before hospital discharge 2. IVH 3. CLD (oxygen supplementation beyond 28 days) 4. NEC (Bell stage 2 or 3 disease) 5. Oliguria	
Notes	**Primary study location:** Regional Medical Center, Memphis, Tenessee, USA **Study period:** not specified **Trial registration:** not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Bada 1989		
Study characteristics		
Random sequence generation (selection bias)	Unclear risk	It was not stated how randomization was done
Allocation concealment (selection bias)	Unclear risk	No information provided on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was used suggesting personnel were blinded during the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome assessed by one investigator blinded to the allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomized infants accounted for
Selective reporting (reporting bias)	Unclear risk	No protocol available for comparison
Other bias	Unclear risk	No specific issues noted.

Bagheri 2018	
Study characteristics	
Methods	Single-center randomized controlled trial
Participants	**Inclusion criteria** 1. Gestational age of ≤ 34 weeks **Exclusion criteria** 1. Pulmonary artery atresia 2. Aortic coarctation 3. Genetic disorders 4. Persistent pulmonary hypertension 5. Severe asphyxia 6. Hepatic failure 7. 5th minute Apgar score < 5 8. Cord blood pH < 7

Bagheri 2018		
Study characteristics		
Interventions	**Active intervention (n = 80)** Prophylactic IV acetaminophen, 1st dose 20 mg/kg at 12 hours, then 7.5 mg/kg every 6 hours up to <4 days old **Control (n = 80)** No placebo	
Outcomes	Relevant outcomes for this study included 1. Mortality	
Notes	**Primary study location:** Kerman, Iran **Study period:** November 2015 to November 2016 **Trial registration:** IR.KMU.REC.1395.841 and IRCT2017012718994N2	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	It was not stated how randomization sequence was generated
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	The authors say the nurses giving injections were unaware of case-control division as paracetamol can be used as analgesic. Following first dose of paracetamol the infants were examined closely for any new symptoms prompting exclusion or further testing. This detailed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Cardiologists evaluating echocardiograms were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data reported for all randomized infants

Bagheri 2018		
Study characteristics		
Selective reporting (reporting bias)	Unclear risk	The trial was registered with Iranian Registry of Clinical Trials (IRCT2017012718994N2) in 2017 retrospectively following complete recruitment (2015-2016). There does not seem to be any obvious protocol deviations.
Other bias	Low risk	none noted

Couser 1996	
Study characteristics	
Methods	Single-center randomized controlled trial
Participants	**Inclusion criteria** 1. Preterm infants 23 to 29 weeks GA; 600 g to 1250 g BW; received prophylactic surfactant in delivery room **Exclusion criteria** 1. Congenital anomalies 2. Parental refusal 3. Inability to obtain parental consent within first 24 hours of life 1. Infants with small muscular ventricular septal defects and congenital heart disease were later excluded following diagnosis in echo
Interventions	**Active intervention (n = 43)** Prophylactic IV indomethacin sodium trihydrate (Indocin) 0.1mg/kg every 24 hours for 6 doses slow IV infusion over 20 minutes; initiated within 24 hours of birth **Control (n = 47)** IV placebo (0.9% saline solution given at same times as indomethacin treatment group)
Outcomes	Relevant outcomes for this study included: 1. Neurodevelopmental impairment including cerebral palsy at 36 months corrected age 2. Clinically significant PDA 3. IVH grade 3 or 4 4. Mortality 5. Chronic lung disease (supplementary oxygen at 28 days plus chest Xray changes) 6. NEC 7. Urine output reduced to < 1.0 mL/kg/hour at any time during first 7 days
Notes	**Primary study location:** Abbott-Northwestern Hospital and Children's Health Care, Minneapolis, USA **Study period:** 3 June 1994 to 18 Oct 1995 **Trial registration:** Not reported

Couser 1996		
Study characteristics		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Unclear if allocation was concealed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Individuals administering the treatment were blinded, staff examining and caring for infants were blinded. Hospital pharmacists prepared blinded indomethacin and blinded placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Cardiologists blinded to patient assignment and not involved in patient management. Examiners blinded to patient assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 93 enrolled infants accounted for (3 excluded due to ventricular septal defect before analysis).
Selective reporting (reporting bias)	Unclear risk	Study protocol unavailable for comparison.
Other bias	Low risk	Appeared free of other bias.

Dani 2000	
Study characteristics	
Methods	Two-center randomized controlled trial
Participants	**Inclusion criteria** 1. GA < 34 weeks 2. Treatment with nasal continuous positive airway pressure with FiO2 >0.3 or with mechanical ventilation (synchronized mechanical ventilation or high-frequency ventilation) due to RDS 3. Platelet count ≥ 75,000/cm, serum creatinine ≤ 1.5 mg/dL, absence of clinical manifestation of abnormal clotting function 4. Absence of grade 3 or 4 IVH before randomization 5. Enrolled within first 24 hours after birth **Exclusion criteria** 2. Major congenital malformations including congenital heart defects, persistent pulmonary hypertension of the newborn or hydrops fetalis
Interventions	**Active intervention (n = 40)** Prophylactic IV ibuprofen lysine (Arfen, Lisapharma, Italy) 10 mg/kg within first 24 hours of life, followed by 5 mg/kg after 24 and 48 hours **Control (n = 40)**

Dani 2000		
Study characteristics		
	The control group received no prophylactic therapy. The control group received same pharmacological treatment after echocardiographic diagnosis of PDA	
Outcomes	Relevant outcomes for this study included 1. Mortality 2. IVH 3. CLD (oxygen supplementation beyond 28 days) 4. NEC 5. Treatment for symptomatic PDA 6. Surgical PDA ligation	
Notes	**Primary study location:** Careggi University Hospital of Florence and Sant'Anna University Hospital of Turin, Italy **Study period:** February 1995 to January 1996 **Trial registration:** not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation method not specified.
Allocation concealment (selection bias)	Low risk	Sealed envelope technique used.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo and no indication of blinding efforts.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is unclear if the assessors for reported outcomes were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all enrolled infants.
Selective reporting (reporting bias)	Unclear risk	Study protocol was unavailable. Unclear if there were any deviations from the protocol.
Other bias	Low risk	Appeared free of other bias.

Dani 2005	
Study characteristics	
Methods	Multi-center (7 centers) randomized controlled trial
Participants	**Inclusion criteria** 1. Gestational age of < 28 weeks, postnatal age < 6 hours. **Exclusion criteria**

Dani 2005		
Study characteristics		
	1. Presence of major congenital malformations 2. Hydrops fetalis 3. Persistent pulmonary hypertension of the newborn 4. Grade 2 to 4 IVH 5. Platelet count of < 50 000 platelets per mm^3 6. Tendency to bleed as revealed by hematuria, blood in endotracheal aspirate, gastric aspirate, or stools, or oozing from puncture sites 7. Serum creatinine >1.5mg/dL	
Interventions	**Active intervention (n = 77)** Prophylactic IV ibuprofen lysine; 3 doses (10 mg/kg within 6 hours after birth, followed by 5 mg/kg after 24 and 48 hours). The medications were infused continuously over a 15-minute period. **Control (n = 78)** Indistinguishable placebo infused continuously over a 15-minute period.	
Outcomes	Relevant outcomes for this study included 1. Mortality 2. IVH 3. CLD (oxygen supplementation beyond 28 days) 4. NEC 5. Treatment for symptomatic PDA 6. Surgical PDA ligation 7. Oliguria 8. Periventricular leukomalacia	
Notes	**Primary study location:** the primary study location was Careggi University Hospital of Florence, Italy. The study was conducted across 7 tertiary neonatal care units across Italy **Study period:** February 1995 to January 1996 **Trial registration:** not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation unspecified.
Allocation concealment (selection bias)	Low risk	Allocation concealment via sealed-envelope technique, with envelopes prepared and distributed to participating study sites.
Blinding of participants and personnel (performance bias)	Low risk	Indistinguishable placebo was administered to control group to ensure blinding of participants and personnel.

Dani 2005		
Study characteristics		
All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were unaware of group assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 were excluded after randomization due to incomplete data entry (4 from ibuprofen). No other missing outcome data noted.
Selective reporting (reporting bias)	Unclear risk	Study protocol was unavailable. Unclear if there were any deviations from the protocol.
Other bias	Low risk	Appears free of other bias.

De Carolis 2000	
Study characteristics	
Methods	Single-center randomized controlled trial
Participants	**Inclusion criteria** 1. Gestational age of <31 weeks **Exclusion criteria** 1. BW < 500 g 2. Receipt of antenatal indomethacin 3. Congenital heart defect 4. Persistent pulmonary hypertension 5. Severe thrombocytopenia (platelet count < 50 x10^9/L) 6. Major congenital malformations
Interventions	**Active intervention (n = 23)** Prophylactic IV ibuprofen lysine; 3 doses (10 mg/kg within 2 hours after birth, followed by 5 mg/kg after 24 and 48 hours). The medications were infused continuously over a 20-minute period. **Control (n = 23)** No placebo
Outcomes	Relevant outcomes for this study included 1. Mortality 2. IVH 3. CLD (oxygen supplementation beyond 28 days) 4. NEC 5. Treatment for symptomatic PDA 6. Surgical PDA ligation 7. Periventricular leukomalacia
Notes	**Primary study location:** Catholic University of the Sacred Heart, Rome, Italy **Study period:** 1 April 1996 to 30 July 1997 **Trial registration:** not reported

De Carolis 2000		
Study characteristics		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Used random permuted blocks.
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Placebo not used for control group. No mention of other blinding efforts.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Echocardiography outcome assessor was blinded to treatment arm.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomized infants accounted for.
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable. Unclear if any deviations from protocol exist.
Other bias	Low risk	Apart from lack of placebo, appears free of other bias.

Gournay 2004	
Study characteristics	
Methods	Multi-center (11 centers) randomized controlled trial
Participants	**Inclusion criteria** 1. Gestational age < 28 weeks, postnatal age less than 6 hours, signed parental consent. **Exclusion criteria** 1. Major congenital malformations 2. Proven severe congenital maternal-fetal infection 3. Hydrops fetalis 4. IVH grade 3 to 4 5. Clinical bleeding 6. Shock or right-to-left ductal shunt evidenced by differential cyanosis (pre-post SpO2 difference>5%) 7. Cerebral complications (convulsions; coma) 8. Bleeding disorders
Interventions	**Active intervention (n = 65)**

Gournay 2004		
Study characteristics		
	Prophylactic IV ibuprofen lysine; loading dose 10 mg/kg followed by 2 maintenance doses of 5 mg/kg at 24-hour intervals (equivalent volumes for placebo), each infused over 20 minutes **Control (n = 66)** Blinded IV placebo (2 mL vials with 0.9% saline)	
Outcomes	Relevant outcomes for this study included 1. Mortality 2. IVH 3. CLD (oxygen supplementation beyond 28 days) 4. NEC 5. Gastrointestinal perforation 6. Treatment for symptomatic PDA 7. Surgical PDA ligation 8. Periventricular leukomalacia 9. Oliguria	
Notes	**Primary study location:** the primary study location was Nantes, France. The study was conducted across 11 tertiary neonatal care units across France **Study period:** March 2001 to December 2001 **Trial registration:** not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation method not specified.
Allocation concealment (selection bias)	Low risk	Sealed envelope allocation kept at hospital pharmacy.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo (0.9% saline) was used suggesting that personnel were blinded to the allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo (0.9% saline) was used suggesting that outcome assessors were blinded to the allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	135 infants were included in the study; 4 infants were not randomized due to errors in study drug allocation (3 mistakenly received open-label ibuprofen during their prophylactic course, and one 10-day-old with diagnosis of PDA was mistakenly given 2 doses of placebo instead of open-label therapeutic ibuprofen. Per-protocol analyses were performed on 131 infants. No participants were lost to follow-up
Selective reporting (reporting bias)	Unclear risk	The trial was not pre-registered in any trials registry

Gournay 2004		
Study characteristics		
Other bias	Unclear risk	The study was sponsored by the manufacturers of the intervention drug ibuprofen lysine (Orphan Europe, Paris, France). The sponsors were involved in the study design, data management, data analysis and data interpretation. All final data analyses were double checked by one of the co-authors (JCR) who had free access to the raw data.

Hanigan 1988		
Study characteristics		
Methods	Single-center randomized controlled trial	
Participants	**Inclusion criteria** 1. birth weight of ≤1500 g, negative sonogram for PVH-IVH and written parental consent. **Exclusion criteria** 1. Gestational age >34 weeks 2. Platelet counts of <60,000/mm^3 3. Clinical evidence of a bleeding diathesis 4. Significant congenital abnormalities 5. Lack of a baseline cranial sonogram obtained before 12 hours of age 6. Birth weight less than 500 g	
Interventions	**Active intervention (n = 56)** Blinded IV indomethacin as reconstituted lyophilized sodium salt; 0.1mg/kg at <12 hours, and 24, 48 and 72 hours IV, over 2 minutes **Control (n = 55)** Blinded IV placebo (Placebo identical quantity of saline solution)	
Outcomes	Relevant outcomes for this study included 1. Mortality 2. IVH 3. Treatment for symptomatic PDA	
Notes	**Primary study location:** Illinois, USA **Study period:** 1 May 1984 to 30 April 1986 **Trial registration:** not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not specified.
Allocation concealment (selection bias)	Low risk	Used random-sized block allocation, and opaque sealed envelopes available only by the pharmacist

Hanigan 1988		
Study characteristics		
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Personnel involved in care were blinded to participants' study arm
Blinding of outcome assessment (detection bias) All outcomes	Low risk	States that only biostatistician and pharmacist had access to study arms, implying that outcome assessors were also blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	11 infants enrolled were withdrawn from study before statistical analysis, six due to oliguria or thrombocytopenia, one withdrew consent, four due to false-negative baseline sonograms. No enrolled infants were unaccounted for.
Selective reporting (reporting bias)	Unclear risk	Study protocol unavailable, unclear if there were any deviations to the original protocol.
Other bias	Low risk	None noted

Harkin 2016	
Study characteristics	
Methods	Single-center randomized controlled trial
Participants	**Inclusion criteria** 1. Gestational age < 32 weeks, admitted to NICU **Exclusion criteria** 1. Septic shock 2. Major malformation 3. Chromosomal abnormality
Interventions	**Active intervention (n = 23)** Blinded IV acetaminophen initiated within 24 hours after birth; loading dose: 20 mg/kg then maintenance dose 7.5 mg/kg every 6 hours for 4 days (given as 15- minute IV infusions). **Control (n = 25)** Blinded IV placebo
Outcomes	Relevant outcomes for this study included 1. Mortality 2. IVH 3. CLD (oxygen supplementation beyond 28 days) 4. NEC 5. Treatment for symptomatic PDA 6. Neurodevelopmental impairment 7. Oliguria

Harkin 2016		
Study characteristics		
Notes	**Primary study location:** Oulu University Hospital, Finland **Study period:** 18 September 2013 to 2 January 2015 **Trial registration:** ClinicalTrials.gov: NCT01938261; European Clinical Trials Database: EudraCT 2013-008142-33	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computed randomization with 4-block design was used.
Allocation concealment (selection bias)	Low risk	Sealed-envelop technique used.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was placebo-controlled and all nurses and doctors involved in treatment and study of infants were blinded to study medication.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All doctors and nurses involved with the study of the infants were blinded to study medication.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported for all randomized infants.
Selective reporting (reporting bias)	Low risk	Clinical trial was registered with European Clinical Trials Database (2013-008142-33) and ClinicalTrials.gov (NCT01938261). Access to ClinicalTrials.gov showed no major deviations from protocol.
Other bias	Low risk	Paracetamol preparation changed mid-study due to hospital protocol.

Jannatdoust 2014	
Study characteristics	
Methods	Single-center randomized controlled trial
Participants	**Inclusion criteria** 1. GA less than 32 weeks and birth weight 800 g to 1500 g **Exclusion criteria** 1. Congenital abnormalities 2. severe asphyxia (5-minute Apgar score < 7 or initial pH < 7.1) 3. Moderate thrombocytopenia (50,000/μL) 4. High serum creatinine (1.8 mg/dL) 5. Obvious bleeding (respiratory, skin, digestive, urinary, mucous)

Jannatdoust 2014		
Study characteristics		
	6. Antenatal receipt of indomethacin	
Interventions	**Active intervention (n = 35)** IV indomethacin; initial dose 0.2 mg/kg administered between 2 to 12 hours followed by 2 doses of 0.1 mg/kg each at 24 and 48 hours **Control (n = 35)** No placebo	
Outcomes	Relevant outcomes for this study included 1. Mortality 2. IVH 3. Treatment for symptomatic PDA	
Notes	**Primary study location:** Alzahra Educational-Medical Center, Tabriz, Iran **Study period:** June 2010 to December 2012 **Trial registration:** IRCT201107117010N1	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerized randomized number generator used
Allocation concealment (selection bias)	Low risk	Random allocation determined by Rand List Software
Blinding of participants and personnel (performance bias) All outcomes	High risk	No mention of placebo use in control group and no mention of blinding efforts.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No mention of placebo use in control group and no mention of blinding efforts.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported for all randomized infants.
Selective reporting (reporting bias)	Unclear risk	Trial was registered retrospectively with the Iranian Registry of Clinical Trials (IRCT201107117010N1).
Other bias	Unclear risk	Given this was an unblinded study and it was retrospectively registered, difficult to assess if there were other sources of bias.

Kanmaz 2013	
Study characteristics	
Methods	Single-center randomized controlled trial
Participants	**Inclusion criteria**

Kanmaz 2013		
Study characteristics		
	1. GA less than <2 8 weeks, and/or birth weight < 1000 g. **Exclusion criteria** 1. Major congenital abnormalities 2. Life-threatening infection 3. Grade 3 or 4 IVH 4. Urine output of < 1mL/Kg/hour during the preceding 8 hours 5. Serum creatinine of >1.6 mg/dL 6. Platelet count of < 60000/mm^3 7. Tendency to bleed 8. Hyperbilirubinaemia requiring exchange transfusion 9. Persistent pulmonary hypertension 10. Patients whose early enteral feeding and enteral drug use were inappropriate due to contraindications (such as congenital anomalies, meconium ileus, severe hypotension and asphyxia) were also excluded	
Interventions	**Active intervention (n = 23)** Oral ibuprofen,10mg/kg within 12 to 24 hours after birth followed by 5 mg/kg at 24 and 48 hours. **Control (n = 23)** No placebo	
Outcomes	Relevant outcomes for this study included 1. Mortality 2. IVH 3. CLD 4. NEC 5. Gastrointestinal perforation 6. Treatment for symptomatic PDA 7. Surgical PDA ligation	
Notes	**Primary study location:** Zekai Tahir Burak Maternity Teaching Hospital, Ankara, Turkey **Study period:** July 2011 and November 2011 **Trial registration:** NCT01400737	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation method not specified
Allocation concealment (selection bias)	Low risk	Patients allocated using sealed opaque envelopes.

Kanmaz 2013		
Study characteristics		
Blinding of participants and personnel (performance bias) All outcomes	High risk	The control group received no treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Cardiologist blinded to allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all enrolled infants
Selective reporting (reporting bias)	Low risk	All outcomes described in protocol were reported. The trial was registered with ClinicalTrials.gov (NCT01400737).
Other bias	Unclear risk	Trial was ended prematurely due to high incidence of adverse effects.

Krueger 1987	
Study characteristics	
Methods	Single-center randomized controlled trial
Participants	**Inclusion criteria** 1. Preterm infants admitted to the hospital NICU weighing between 750 g and 1500 g and who had Hyaline membrane disease. and required mechanical ventilation at 24 hours postnatal age 2. Platelet count must be $\geq$ 75,000/μL 3. Serum creatinine concentration $\leq$ 1.5 mg/dL 4. Birth weight appropriate for gestational age 5. Absence of clinical manifestations of abnormal clotting function 6. No evidence of intraventricular haemorrhage (based on clinical grounds when cranial ultrasonography was not available) 7. Absence of radiographic evidence of disseminated pulmonary interstitial air dissection, and venous admixture at 24 hours after birth of no more than 35% as calculated from FiO_2 and blood gas data. **Exclusion criteria** 1. Patients weighing less than 750 g at birth
Interventions	**Active intervention (n = 15)** Indomethacin IV single dose of 0.2mg/kg at 24 hours of age **Control (n = 17)** No placebo
Outcomes	Relevant outcomes for this study included 1. Mortality

Krueger 1987		
Study characteristics		
	2. IVH 3. CLD 4. NEC 5. Treatment for symptomatic PDA 6. Surgical PDA ligation	
Notes	**Primary study location:** Vanderbilt Hospital, Nashville, Tennessee, USA **Study period:** not reported **Trial registration:** not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation method not specified.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not specified.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo used for control group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No placebo was used for control group and there was no indication of blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Several infants excluded from analyses following early death, which was clearly described. No other missing outcomes noted.
Selective reporting (reporting bias)	Unclear risk	We could not judge if there were any deviations from the original protocol.
Other bias	Low risk	No other obvious sources of bias

Kumar Nair 2004	
Study characteristics	
Methods	Single-center randomized controlled trial
Participants	**Inclusion criteria** 1. Inborn infants with birth weight between 750 g and 1250 g, absence of major congenital anomalies, informed consent, absence of intraventricular haemorrhage prior to randomization **Exclusion criteria** 1. Gestational age < 26 weeks 2. Severely asphyxiated at birth (Apgar score < 5 at 5 minutes)

Kumar Nair 2004		
Study characteristics		
	3. Chromosomal aberrations 4. Evidence of intrauterine or intrapartum sepsis on initial investigations 5. Haematological or renal profiles contraindicating indomethacin administration	
Interventions	**Active intervention (n = 56)** Indomethacin IV for a total of 3 doses at 0.1 mg/kg/dose. First dose administered over period of no less than 30 minutes between 6 and 12 hours of age, second and third dose administered at 24-hour intervals if initial ultrasound detected no IVH. **Control (n = 59)** No placebo	
Outcomes	Relevant outcomes for this study included 1. Mortality 2. IVH 3. CLD 4. NEC 5. Surgical PDA ligation 6. Periventricular leukomalacia	
Notes	**Primary study location:** Royal Hospital, Oman **Study period:** March 1998 to March 2001 **Trial registration:** not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Simple random sampling method used for randomization.
Allocation concealment (selection bias)	Low risk	Sealed envelopes were used, mixed up, and stored in locked box.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No evidence of blinding or placebo used for control
Blinding of outcome assessment (detection bias) All outcomes	High risk	No evidence of blinding or placebo used for control and no evidence of blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data were noted
Selective reporting (reporting bias)	Unclear risk	No protocol available for comparison
Other bias	Unclear risk	Study terminated prematurely.

Mahony 1985		
Study characteristics		
Methods	Single-center double-blind randomized controlled trial	
Participants	**Inclusion criteria** 1. Birth weight between 700 g and 1300 g, admitted before 12 hours of age to the NICU **Exclusion criteria** 1. Small for gestational age 2. Presence of major congenital anomalies 3. Evidence of congenital infection 4. Platelet count < 75,000/μL 5. Serum creatinine concentration >1.6 mg/dL (140 μmol/L) 6. Echocardiographic evidence of structural heart disease 7. Hematocrit <35% 8. Permission refused or not requested due to mitigating social factors, and in the judgement of the attending neonatologist 9. Moribund clinical condition	
Interventions	**Active intervention (n = 51)** Blinded IV Indomethacin, first dose (given at 12 to 18 hours) was 0.2 mg/kg body weight and second dose (given 12 hours later) was 0.1 mg/kg and third dose (given 36 hours after the first) was 0.1 mg/kg. **Control (n = 53)** Blinded IV placebo	
Outcomes	Relevant outcomes for this study included 1. Mortality 2. IVH 3. NEC 4. Treatment for symptomatic PDA 5. Surgical PDA ligation	
Notes	**Primary study location:** James Whitcomb Riley Hospital, Indiana, USA **Study period:** March 1982 to October 1983 **Trial registration:** not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Infants were randomly allocated by a statistician otherwise uninvolved with the study, however the method of sequence generation was not specified.
Allocation concealment (selection bias)	Low risk	Allocation was concealed by placing identical vials of either indomethacin or placebo into envelopes
Blinding of participants and personnel (performance bias)	Low risk	Persons evaluating and caring for infants were unaware of study drug assignment.

Mahony 1985		
Study characteristics		
All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Allocation of infants was not revealed until after discharge and outcome data collection was complete.
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 infants were excluded from the analysis due to death before receiving all 3 doses of study drug. Outcomes were reported for all other randomized infants.
Selective reporting (reporting bias)	Unclear risk	We could not judge if there were any deviations from the protocol.
Other bias	Unclear risk	Study was stopped early due to lack of power to prove desired results; unclear if this was pre-specified

Maruyama 2012	
Study characteristics	
Methods	Multi-center (21 centers) randomized controlled trial
Participants	**Inclusion criteria** 1. Newborn infants ≤ 6 hours of age with gestational age ≥ 22 weeks and birthweight of 400 g to 999 g **Exclusion criteria** 1. Birthweight of ≤ -2 SD for gestational age 2. Grade 3 or 4 IVH 3. PDA necessitating treatment 4. Hemorrhagic tendency 5. Platelet count < 50000/μL 6. NEC 7. Major anomalies 8. Abnormal visceral morphology 9. Hydrops fetalis 10. Treatment of mother with anti-prostaglandins (including indomethacin) ≤48 hours before delivery 11. Infants judged by their physician as inappropriate
Interventions	**Active intervention (n = 10)** IV Indomethacin (0.1 mg/kg/dose) admixed with menatetrenone given as IV for a total of 3 doses (0.0125 mg/mL indomethacin and 0.0625 mg/mL menatetrenone continuous 6 hours IV infusions every 24 hours with first dose within 6 hours of birth) **Control (n = 9)** IV Placebo (0.0625 mg/mL menatetrenone as a 6-hour continuous intravenous infusion every 24 hours)

Maruyama 2012		
Study characteristics		
Outcomes	Relevant outcomes for this study included 1. Mortality 2. IVH 3. NEC 4. Gastrointestinal perforation 5. Treatment for symptomatic PDA 6. Surgical PDA ligation	
Notes	**Primary study location:** the primary study location was Gunma Children's Medical Center, Hokkitsu, Japan. The study was conducted across 21 level III NICUs in Japan. **Study period:** not reported **Trial registration:** C000000160 (UMIN Clinical Trials Registry)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated sequence stratified the groups based on gestational age, sex, and other factors to balance the groups.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not specified.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was placebo-controlled suggesting that the personnel were blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study was placebo controlled however there was no mention for how outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One infant in indomethacin group was excluded from all analyses following diagnosis with duodenal atresia. No incomplete outcomes were noted.
Selective reporting (reporting bias)	High risk	Protocol for original RCT was found registered prospectively at UMIN-CTR (University hospital Medical Information Network Center) Clinical Trial Registry (C000000160). Among the stated primary outcomes, PVL, ROP and developmental impairment were not reported.
Other bias	Unclear risk	Treatment groups not well matched for birth weight, possibly related to the small sample size

Ment 1985	
Study characteristics	
Methods	Single-center randomized controlled trial

Ment 1985		
Study characteristics		
Participants	**Inclusion criteria** 1. Birth weight of 600 g to 1250 g, parental consent, admitted to the newborn care unit by the 6th postnatal hour. **Exclusion criteria** 1. Congenital abnormalities 2. Ultrasound evidence of GMH/IVH before participation	
Interventions	**Active intervention (n = 24)** Blinded IV Indomethacin. First 10 infants randomized to indomethacin received 0.2mg/kg IV for the 1st dose and 0.1mg/kg IV every 12 hours thereafter for a total of 5 doses. Remaining infants in the study received 0.1mg/kg per dose every 12 hours for a total of 5 doses. **Control (n = 24)** Equal volume IV placebo as saline	
Outcomes	Relevant outcomes for this study included 1. Mortality 2. IVH 3. NEC 4. Oliguria	
Notes	**Primary study location:** Yale, New Haven Connecticut, USA **Study period:** 1 June 1983 to 28 Feb 1985 **Trial registration:** not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization by ordinal number of admission in blocks of 10
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment are not provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study personnel, physicians and nurses caring for study infants were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Ultrasound studies reviewed by blinded observers.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomized infants accounted for
Selective reporting (reporting bias)	Unclear risk	There is no protocol available for comparison

Ment 1985		
Study characteristics		
Other bias	Unclear risk	The study was terminated when statistical significance achieved, unclear if this was pre-specified.

Ment 1988		
Study characteristics		
Methods	Single-center randomized controlled trial	
Participants	**Inclusion criteria** 1. Birth weight of 600 g to 1250 g 2. Normal 6-hour echoencephalogram 3. No major congenital malformations **Exclusion criteria** 1. No documented urinary output in 1st 24 hours 2. IVH on pre-study ultrasound examination	
Interventions	**Active intervention (n = 19)** Blinded IV Indomethacin; initial dose of 0.1 mg/kg at 6 to 12 hours, followed by 2 doses of 0.1 mg/kg every 24 hours (3 total doses) **Control (n = 17)** Blinded IV placebo	
Outcomes	Relevant outcomes for this study included 1. Mortality 2. IVH 3. Oliguria	
Notes	**Primary study location:** Yale, New Haven Connecticut, USA **Study period:** 1 May 1985 to 31 March 1987 **Trial registration:** not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	By ordinal number of admissions in blocks of 10.
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment are not provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study personnel, physicians and nurses caring for study infants were blinded.
Blinding of outcome assessment (detection bias)	Low risk	ECHOs were reviewed by blinded observers.

Ment 1988		
Study characteristics		
All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Echocardiography data was only available for 33 infants on day 5 due to technical difficulties. Outcomes for all randomized infants accounted for.
Selective reporting (reporting bias)	Unclear risk	No protocol available for comparison
Other bias	Low risk	Appeared free of other bias

Ment 1994a		
Study characteristics		
Methods	Multi-center (3 centers) randomized controlled trial	
Participants	**Inclusion criteria** 1. Birth weight 600 g to 1250 g 2. Mild IVH (grade 1 or 2) at 6 to 11 hours 3. No major congenital malformations	
Interventions	**Active intervention (n = 27)** Blinded IV Indomethacin; initial dose of 0.1 mg/kg at 6 to 12 hours, followed by 2 doses of 0.1 mg/kg every 24 hours (3 total doses) **Control (n = 34)** Blinded IV placebo (as equal volume saline solution)	
Outcomes	Relevant outcomes for this study included 1. Mortality 2. IVH 3. NEC 4. Oliguria	
Notes	**Primary study location:** Yale New Haven Hospital, New Haven Connecticut; Women and Infants' Hospital, Providence, RI; and Maine Medical Center, Portland, USA **Study period:** 5 Sept 5 1989 to 31 Aug 1992 **Trial registration:** not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomization procedure used
Allocation concealment (selection bias)	Unclear risk	No information provided on allocation concealment.
Blinding of participants and personnel	Low risk	Equal volume placebo used suggesting that care providers were blinded to the allocation

Ment 1994a		
Study characteristics		
(performance bias) All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant is missing from analysis for oliguria without explanation. Otherwise all randomized infants accounted for.
Selective reporting (reporting bias)	Unclear risk	It was unclear if there were deviations from the original protocol.
Other bias	Low risk	Appears free of other bias.

Ment 1994b	
Study characteristics	
Methods	Multi-center (3 centers) randomized controlled trial
Participants	**Inclusion criteria** 1. Birth weight of 600 g to 1250 g 2. Admitted by 6 hours of age **Exclusion criteria** 1. Major congenital anomalies 2. Death within first 12 postnatal hours 3. Evidence of IVH
Interventions	**Active intervention (n = 209)** Blinded IV Indomethacin; initial dose of 0.1 mg/kg at 6 to 12 hours, followed by 2 doses of 0.1 mg/kg every 24 hours (3 total doses) **Control (n = 222)** Blinded IV placebo (as equal volume saline solution)
Outcomes	Relevant outcomes for this study included 1. Mortality 2. IVH 3. NEC 4. CLD 5. Oliguria 6. Neurodevelopmental outcome
Notes	**Primary study location:** Yale New Haven Hospital, New Haven Connecticut; Women and Infants' Hospital, Providence, RI; and Maine Medical Center, Portland, USA **Study period:** 5 Sept 1989- to 31 Aug 1992 **Trial registration:** not reported
Risk of bias	

Ment 1994b		
Study characteristics		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomization procedure used
Allocation concealment (selection bias)	Low risk	Central allocation concealment via telephone call to pharmacy.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Details of blinding not provided; however, placebo was used for control group suggesting care providers were blinded to the allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All radiologists were unaware of neonate clinical condition and randomization when evaluating ECHO.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomized infants were accounted for.
Selective reporting (reporting bias)	Unclear risk	It was unclear if there were any deviations from the original protocol.
Other bias	Low risk	Appears free of other bias

Morales-Suarez 1994	
Study characteristics	
Methods	Single-center randomized controlled trial
Participants	**Inclusion criteria** 1. GA between 28-36 weeks 2. Intubated in the delivery room and requiring ventilation in ICU **Exclusion criteria** 1. End-stage disease 2. Major congenital malformation 3. Thrombocytopenia (defined as platelet count < 50 000/mm3) 4. Clinical evidence of any bleeding 5. Oliguria (defined as urine output ≤ 0.5 mL/kg/hour) 6. Pneumothorax
Interventions	**Active intervention (n = 40)** Indomethacin Sodium Trihydrate (Indocid, *Merck Sharp and Domme), 1mg/ml solution for injection, 3 doses of 100 mcg/kg/dose every 12 hours **Control (n = 40)** Normal saline bolus following the same scheme as the active intervention

Morales-Suarez 1994		
Study characteristics		
Outcomes	Relevant outcomes for this study included 1. Mortality 2. IVH 3. Surgical PDA closure	
Notes	**Primary study location:** Unidad de Cuidados Intensivos Neonatales, Insituto Nacional de Perinatologia, Mexico DF, Mexico **Study period:** not reported **Trial registration:** not reported **Translation:** translated from Spanish	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Details of sequence generation not provided
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Authors report trial is double blinded however do not further specify blinding efforts.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors report study was double blinded, but do not explicitly state that outcome assessors are blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data noted
Selective reporting (reporting bias)	Unclear risk	Study protocol unavailable. Unclear if any deviations from protocol exist.
Other bias	Low risk	No additional sources of bias were noted

Rennie 1986	
Study characteristics	
Methods	Single-center randomized controlled trial
Participants	**Inclusion criteria** 1. Birth weight less than 1750 g 2. Admitted within 24 hours of life 3. No IVH 4. Must have passed urine
Interventions	**Active intervention (n =24)**

Rennie 1986		
Study characteristics		
	Blinded IV Indomethacin 0.2mg/kg IV. 3 doses were given at 24-hour intervals (unless treatment stopped by care team). **Control (n = 26)** Identical volume saline as placebo	
Outcomes	Relevant outcomes for this study included 1. Mortality 2. IVH 3. Treatment for symptomatic PDA 4. Surgical PDA closure 5. CLD 6. Oliguria	
Notes	**Primary study location:** Liverpool regional NICU, UK **Study period:** May 1984 to June 1985 **Trial registration:** not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors did not mention if allocation of treatment groups was randomized.
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study used placebo and all personnel involved in care were blinded to the group assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study used placebo and all personnel involved in care were blinded to the group assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcomes noted
Selective reporting (reporting bias)	Unclear risk	Could not judge if there were any deviations in protocol.
Other bias	Low risk	Appeared free of other bias.

Sangtawesin 2006	
Study characteristics	
Methods	Single-center randomized controlled trial
Participants	**Inclusion criteria** 1. GA between 28-32 weeks and birth weight $\leq$ 1500 g

Sangtawesin 2006		
Study characteristics		
	Exclusion criteria 1. Maternal prenatal infection 2. Illicit drug or NSAID use 3. Hydrops fetalis 4. Unstable clinical conditions 5. Congenital heart disease (other than PDA) 6. Other major congenital anomalies 7. Persistent pulmonary hypertension 8. Serum creatinine equal to or greater than 1.5 mg/dL 9. Platelet count equal to or less than 75,000/uL 10. Abnormal coagulogram	
Interventions	**Active intervention (n = 22)** Oral ibuprofen solution: 3 doses of ibuprofen dosed at 10mg/kg/dose via orogastric tube followed by 0.5mL distilled water. 2nd and 3rd dose were given at 24 and 48 hours after the first dose. **Control (n =20)** Oral placebo that was an orange starch solution that resembled ibuprofen	
Outcomes	Relevant outcomes for this study included 1. Mortality 2. IVH 3. Treatment for symptomatic PDA 4. NEC 5. CLD	
Notes	**Primary study location:** Queen Sirikit National Institute of Child Health, Thailand **Study period:** July 2003 to April 2004 **Trial registration:** not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomization method used
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not specified.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo prepared by pharmacist to look like treatment, personnel blinded of group assignment.
Blinding of outcome assessment	Low risk	Single assessor blinded to treatment condition

Sangtawesin 2006		
Study characteristics		
(detection bias) All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomized infants accounted for in analysis.
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable. Unclear if any deviations from protocol exist.
Other bias	Low risk	Appears free of other bias

Schmidt 2001	
Study characteristics	
Methods	Multi-center (32 centers) randomized double-blind control trial
Participants	**Inclusion criteria** 1. Infants with birth weight from 500 g to 999 g that survived to 2 hours of age. **Exclusion criteria** 1. Unable to administer study drug within 6 hours of birth 2. structural heart disease or renal disease, or both known or strongly suspected 3. Dysmorphic features or congenital abnormalities likely to affect life expectancy or neurologic development or to be associated with structural heart disease or renal disease 4. Maternal tocolytic therapy with indomethacin or another prostaglandin inhibitor within 72 hours before delivery 5. Overt clinical bleeding at more than one site 6. Platelet count <50,000/mm^3 7. Hydrops 8. Not considered viable 9. Unlikely to be available for follow-up.
Interventions	**Active intervention (n = 574)** Blinded IV Indomethacin at 0.1mg/kg/dose every 24 hours for a total of 3 doses **Control (n = 569)** Equal volume of blinded IV placebo
Outcomes	Relevant outcomes for this study included 1. Mortality 2. IVH 3. Treatment for symptomatic PDA 4. Surgical PDA ligation

Schmidt 2001		
Study characteristics		
	5. CLD 6. NEC 7. Gastrointestinal perforation 8. Neurodevelopmental outcome 9. Periventricular leukomalacia	
Notes	**Primary study location:** The primary study location was McMaster University, Hamilton, Canada. The study was conducted across 32 centers in Canada, Australia, New Zealand, Hong Kong and the USA **Study period:** January 1996 to March 1998 **Trial registration:** NCT00009646	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation by computer random-number generator.
Allocation concealment (selection bias)	Low risk	Allocation was completed by an offsite statistician, and known only to the onsite pharmacist
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All syringes were partially masked with tape to ensure indomethacin and placebo vials appeared identical. Except for data monitoring committee and study pharmacists, no one involved in the study or in care/follow-up of infants were aware of treatment group assignments.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Except for data monitoring committee and study pharmacists, no one involved in the study or in care/follow-up of infants were aware of treatment group assignments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 children were lost to follow-up in the indomethacin group (1%), and 7 children were lost to follow-up in the control group (1.2%). All randomized infants accounted for.
Selective reporting (reporting bias)	Unclear risk	Study was registered with ClinicalTrials.gov (NCT00009646) retrospectively. Study was completed from 1996 to 1998 and the study was registered in 2001. Unclear if any deviations from original protocol exist.
Other bias	Low risk	Appears free of other bias.

Setzer Bandstra 1988	
Study characteristics	
Methods	Single-center randomized controlled trial
Participants	**Inclusion criteria** 1. Inborn infants with birth weights of 500 g to 1300 g admitted to the NICU and requiring supplemental oxygen (if study entry was accomplished within 12 hours of birth)

Setzer Bandstra 1988		
Study characteristics		
	Exclusion criteria 1. Terminal condition 2. No parental informed consent 3. Supplemental oxygen not required 4. Grades 2 to 4 IVH on pre study echoencephalogram 5. Major congenital malformation 6. Inability to perform pre study echoencephalogram 7. Overt congenital infection 8. Hemostatic abnormalities 9. Maternal acquired immunodeficiency syndrome.	
Interventions	**Active intervention (n = 99)** IV Indomethacin reconstituted with distilled water to yield 1 mg/mL indomethacin. First dose (0.2mL/kg, i.e. 0.2 mg/kg) given over 15 seconds within 12 hours of birth. Second and third doses (0.1 mL/kg, i.e. 0.1 mg/kg each) given at 12-hour intervals thereafter. **Control (n = 100)** Blinded IV placebo	
Outcomes	Relevant outcomes for this study included 1. Mortality 2. IVH 3. Treatment for symptomatic PDA 4. Periventricular leukomalacia 5. CLD 6. NEC 7. Oliguria 8. Neurodevelopmental outcome	
Notes	**Primary study location:** University of Miami, USA **Study period:** February 1983 to June 1985 **Trial registration:** not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization was effected by drawing consecutive pre coded envelopes
Allocation concealment (selection bias)	Low risk	Patients allocated uses pre coded envelopes
Blinding of participants and personnel	Low risk	Identical vials of indomethacin and placebo were prepared by Merck Sharp and Dohme. Investigators unaware of group assignments.

Setzer Bandstra 1988		
Study characteristics		
(performance bias) All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Research personnel unaware of infant treatment assignment reviewed maternal and neonatal records.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all randomized infants
Selective reporting (reporting bias)	Unclear risk	It was unclear if there were deviations from the original protocol.
Other bias	Low risk	none noted

Supapannachart 1999	
Study characteristics	
Methods	Single-center randomized controlled trial
Participants	**Inclusion criteria** 1. Birth weight < 1250 g 2. Randomization within first 24 hours 3. Platelet count >60,000/*u*L 4. Plasma creatinine < 2mg/dL & BUN <30 mg/dL 5. No bleeding diathesis 6. Urine output during 8 hours prior to randomization >0.5 mL/kg/hour **Exclusion criteria** 1. Major congenital anomalies 2. Suspicion of NEC
Interventions	**Active intervention (n = 15)** IV Indomethacin 0.2mg/kg initial dose, followed by two doses of 0.1mg/kg every 12 hours **Control (n = 15)** IV placebo
Outcomes	Relevant outcomes for this study included 1. Mortality 2. IVH 3. Treatment for symptomatic PDA 4. Surgical PDA ligation 5. CLD 6. NEC
Notes	**Primary study location:** Ramathibodi Hospital, Bangkok, Thailand

Supapannachart 1999		
Study characteristics		
	Study period: 1 April 1994 to 31 May1 1995 **Trial registration:** not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation method unspecified.
Allocation concealment (selection bias)	Low risk	Sealed envelope technique used.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All personnel were blinded to group, identical placebo was administered to control
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All personnel were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomized infants accounted for.
Selective reporting (reporting bias)	Unclear risk	Study protocol unavailable. Unclear if any deviations to protocol exist.
Other bias	Low risk	Appears free of other bias.

Van Overmeire 2004	
Study characteristics	
Methods	Multi-center (7 centers) randomized controlled trial
Participants	**Inclusion criteria** 1. Gestational age of 24 to 30 weeks admitted within 6 hours of birth 2. Written informed consent from parents **Exclusion criteria** 1. major congenital malformation 2. Chromosomal anomaly 3. IVH higher than grade 1 already detected during baseline cranial ultrasonography 4. Apgar score at 5 minutes of less than 5 5. Signs of congenital infection or life-threatening septicemia 6. Uncontrolled hypotension 7. contraindications for administration of ibuprofen (serum creatinine

Van Overmeire 2004		
Study characteristics		
	>115 μmol/L, platelet count < $60x10^9$/L, tendency to bleed as revealed by hematuria, blood in endotracheal or gastric aspirate or stools or oozing from puncture sites)	
Interventions	**Active intervention (n = 205)** IV Ibuprofen lysine; initial dose of 10 mg/kg within the first 6 hours of life, followed by two doses of 5 mg/kg after 24 hours and 48 hours **Control (n = 210)** IV placebo (normal saline)	
Outcomes	Relevant outcomes for this study included 1. Mortality 2. IVH 3. Treatment for symptomatic PDA 4. Surgical PDA ligation 5. CLD 6. NEC 7. Oliguria 8. Periventricular leukomalacia	
Notes	**Primary study location:** the primary study location was Antwerp University Hospital, Edegem, Belgium. The study was conducted across 7 centers in Belgium **Study period:** 1 Feb 1 1999 to 30 Sept 2001 **Trial registration:** not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization was done independently by the chief pharmacist at each hospital in a one-to-one ratio between ibuprofen and placebo, in blocks of 10
Allocation concealment (selection bias)	Low risk	Details of allocation concealment not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Attending and consulting physicians, nurses, study collaborators, and parents were unaware of treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Attending and consulting physicians, nurses, study collaborators, and parents were unaware of treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All infants randomized accounted for in analysis.
Selective reporting (reporting bias)	Unclear risk	No protocol available for comparison

Van Overmeire 2004		
Study characteristics		
Other bias	Low risk	Appears free of other bias.

Vincer 1987		
Study characteristics		
Methods	Single-center randomized controlled trial	
Participants	**Inclusion criteria** 1. Infants weighing less than 1500 g at birth who required respiratory support by 12 hours of age	
Interventions	**Active intervention (n = 15)** IV Indomethacin 0.2mg/kg/dose; 3 doses given at 12, 24 and 36 hours after birth **Control (n = 15)** Identical volume of IV placebo	
Outcomes	Relevant outcomes for this study included 1. Mortality 2. IVH 3. Treatment for symptomatic PDA 4. Surgical PDA ligation 5. CLD 6. NEC 7. Neurodevelopmental outcome 8. Periventricular leukomalacia	
Notes	**Primary study location:** Dalhousie University, Halifax, Canada **Study period:** not reported **Trial registration:** not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The eligible infants were enrolled to each group in pairs, the first of each pair was randomly assigned to receive either indomethacin or placebo and the second infant in each pair received the alternate treatment
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Equal volume saline to indomethacin provided, all investigators were blinded until completion of study.
Blinding of outcome assessment	Low risk	All investigators were blinded to treatment allocation until study completion

Vincer 1987		
Study characteristics		
(detection bias) All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomized infants accounted for in the primary analysis
Selective reporting (reporting bias)	Unclear risk	Unable to judge as protocol was not available
Other bias	Low risk	Appeared free of other bias.

Vogtmann 1988	
Study characteristics	
Methods	Single-center randomized controlled trial
Participants	**Inclusion criteria** 1. Birthweight ≤ 1500 g, gestational age ≤ 30 weeks **Exclusion criteria** 1. Small for gestational age 2. Likely to die 3. Requiring mechanical ventilation 4. Twins 5. Congenital malformations 6. Congenital infections 7. Transfer to intermediate care before day 5 8. Death before day 7 9. Admission during evening/nights or on weekends when investigators were not on call
Interventions	**Active intervention (n = 19)** Oral Indomethacin 0.2 mg/kg/day from days 3 to 5 **Control (n = 22)** Standard of care
Outcomes	Relevant outcomes for this study included 1. Mortality 2. NEC 3. Treatment for symptomatic PDA 4. Surgical PDA ligation
Notes	**Primary study location:** German Democratic Republic University Hospital, East Germany **Study period:** not reported (duration 16 months) **Trial registration:** not reported **Translation:** article translated from German
Risk of bias	

Vogtmann 1988		
Study characteristics		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Assigned by random draw
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo was used, and personnel were not blinded to experimental group
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors were not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Infants who died before day 8 were removed from the study.
Selective reporting (reporting bias)	Unclear risk	No protocol available for comparison
Other bias	Low risk	No other obvious sources of bias identified

BUN: blood urea nitrogen**; BW:** birth weight; **CLD:** chronic lung disease; **ICU:** intensive care unit; **GA:** gestational age; **GMH:** germinal matrix hemorrhage; **IV:** intravenous; **IVH: i**ntraventricular hemorrhage; **NEC:** necrotizing enterocolitis; **NICU**: intensive care unit; **NSAID:** non-steroidal anti-inflammatory drugs ; **PDA:** patent ductus arteriosus; **PVH:** periventricular- intraventricular hemorrhage; **PVL:** periventricular leukomalacia; **RCT:** randomized controlled trial; **RDS:** respiratory distress syndrome; **ROP:** retinopathy of prematurity; **SD:** standard deviation.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Alfaleh 2008	Wrong outcomes
Barrington 1986	Commentary
Cotts 2009	Wrong patient population
Domanico 1994	Abstract only
Gregoire 2004	Wrong outcomes
Gutierrez 1987	Abstract only
Hammerman 1986	Wrong patient population
Hammerman 2005	Commentary
Harma 2018	Wrong outcomes
Kääpä 1985	Wrong patient population
Liebowitz 2017	Wrong study design
Mahony 1982	Wrong patient population
McGuire 2002	commentary
Meau-Petit 2005	Conference abstract of included study
Ment 1987	Conference abstract of included study
Ment 1998	Commentary
Ment 1999	Wrong outcomes
Morales-Suarez 1992	Conference abstract of included study
Naulaers 2005	Wrong outcomes
Pleacher 2004	Wrong outcomes
Puckett 1985	Abstract only
Roze 2003	Conference abstract of included study
Rubaltelli 1998	Wrong comparator
Schmidt 2002	commentary
Schmidt 2011	Wrong comparator
Tyson 2002	Commentary
Valls-i-Soler 1999	Wrong comparator
van Overmeire 2002	Conference abstract of included study
Varvarigou 1996	Wrong study design
Vohr 1999	Wrong outcomes
Zarkesh 2013	Abstract only

Characteristics of studies awaiting classification [ordered by study ID]

Akbari Asbagh 2015	
Methods	Single-center randomized controlled trial
Participants	**Inclusion criteria** 1. Birthweight < 1500 g, GA < 32 weeks
Interventions	**Active intervention (n = 16)** Oral acetaminophen for a period of two days starting during first 24 hours of life **Control (n = 16)** No placebo
Outcomes	Primary outcome: PDA closure
Notes	**Primary study location:** Vali-Asr Hospital, Tehran **Study Period:** March 2012 to March 2013 The article is in Persian. We contacted the primary author for further information on outcome data and we are awaiting a response

Kalani 2016	
Methods	Single-center 3-arm study
Participants	**Inclusion criteria** 1. Birthweight < 1500g, GA < 32 weeks 2. 6 to 12 hours old
Interventions	**Active intervention 1 (n = 31)** Oral ibuprofen 10, 5, 5 mg/kg every 24 hours **Active intervention 2 (n = 31)** Oral indomethacin 0.2 mL/kg daily for 3 days **Control (n = 31)** Standard of care
Outcomes	Relevant outcomes include 1. Mortality 2. IVH 3. PDA 4. NEC 5. GI bleeding
Notes	**Primary study location:** Akbar-Abadi Hospital (affiliated with Iran University of Medical Sciences, Theran, Iran) **Study period:** 2013 to 2014 The methods section suggests that it is a retrospective study, and we were unable to establish contact with the primary author to clarify this discrepancy

Seok 1988	
Methods	Single-center randomized controlled trial
Participants	**Inclusion criteria** 1. Birthweight < 1500 g
Interventions	**Active intervention (n = 23)** Indomethacin 0.2 mg/kg initial dose followed by 2 doses of 0.1 mg/kg at 24-hour intervals. 15 participants received IV formulation and 8 received oral formulation **Control (n = 23)** No placebo
Outcomes	Primary outcome: germinal matrix or intraventricular haemorrhage
Notes	**Primary study location:** Il Sin Christian Hospital, Pusan, Korea **Study Period:** August 1995 to June 1997 The article is in Korean. We are awaiting translation of the article from Korean to English

GA: gestational age; **GI:** gastrointestinal; **IVH:** intraventricular haemorrhage; **NEC:** necrotizing enterocolitis; **PDA:** patent ductus arteriosus.

Characteristics of ongoing studies [ordered by study ID]

NCT03641209	
Study name	Extremely low gestational age infants' Paracetamol Study (Paras)
Methods	Randomized, placebo-controlled, double-blind, phase 2, single-center clinical trial
Participants	**Inclusion criteria** 1. Premature infants born before 28 + 0 gestation weeks and/or birth weight less than 1000 g **Exclusion criteria** 1. Severe malformation or suspected chromosomal defect or other very severe life- threatening disease (e.g. very severe birth asphyxia or persistent pulmonary hypertension, etc.)
Interventions	1. Experimental: paracetamol 10 mg/mL infusion solution, intravenous loading dose 20 mg/kg, followed by maintenance dose 7.5 mg/kg every 6 hours up to 9 days 2. Placebo comparator: placebo 0.45% sodium chloride (NaCl) solution, equal amounts in mL as would have been given in the experimental drug
Outcomes	Primary outcome: postnatal age of the observed closure of ductus arteriosus
Starting date	3 September 2018
Contact information	Principal Investigator: Outi Aikio, MD, PhD; Department of Pediatrics, Oulu University Hospital, Oulu, Finland, 90014
Notes	Estimated enrolment: 40 infants Estimated primary completion date: 1 September 2022

NCT04459117	
Study name	Prophylactic treatment of the ductus arteriosus in preterm infants by acetaminophen (TREOCAPA)
Methods	Phase II/III European multicenter randomized controlled trial
Participants	**Inclusion criteria** 1. Birth between 23 to 26 weeks for Phase II, between 23 to 28 weeks for Phase III 2. Post natal age < 12 hours 3. Parental or Legal Authority Consent 4. Parents with a social security or health insurance (if applicable according to the local regulation) **Exclusion criteria** 1. Birth defect /congenital anomaly 2. Twin-to-twin transfusion syndrome 3. Suspicion of pulmonary hypoplasia 4. Suspicion of hepatic impairment (hemorrhagic syndrome and/or

NCT04459117	
	severe hypoglycemia) 5. Clinical instability that can lead to rapid death 6. Impossibility to start treatment before 12 hours of life 7. Parents placed under judicial protection 8. Participation in other clinical trial using acetaminophen during the first 5 days of life, indomethacin or ibuprofen during the first 3 days of life or using rescue treatment of PDA not recommended in the TREOCAPA trial
Interventions	**Intervention arm: acetaminophen** In the 27 to 28 weeks gestational age group, the dosage is 2 mL/kg loading dose within 12 hours after birth followed by 0.75 mL/kg/ 6 hours during 5 days (total = 20 doses). In the 23 to 26 weeks gestational age group, the dosage will be minimum effective dose of acetaminophen to close the ductus arteriosus before or at day 7, found during the phase II. **Control arm: placebo (0.9% NaCl)**
Outcomes	Primary outcome measure: closure of ductus arteriosus
Starting date	29 October, 2020
Contact information	Jean-Christophe Rozé, Institut National de la Santé Et de la Recherche Médicale, France (jean-christophe.roze@inserm.fr)
Notes	Estimated enrolment: 824 infants Estimated primary completion date: April 2023

NaCl: sodium chloride.

Figures and tables

Additional tables

Table 1 ***Network effect estimates and ranking statistics for severe intraventricular hemorrhage (grade 3 or 4)***

Acetaminophen Mean SUCRA, 0.39; median rank, 4 (95% CrI, 1-4)			
1.69 (0.05, 85.3)	**Ibuprofen** Mean SUCRA, 0.67; median rank, 2 (95% CrI, 1-4)		
1.76 (0.06, 82.9)	1.05 (0.59, 1.86)	**Indomethacin** Mean SUCRA, 0.74; median rank, 2 (95% CrI, 1-3)	
1.17 (0.04, 55.2)	0.69 (0.41, 1.14)	0.66 (0.49, 0.87)	**Placebo** Mean SUCRA, 0.20; median rank, 3 (95% CrI, 2-4)

The unlabeled data in the boxes are risk ratios (RRs) and 95% credible intervals (CrIs). A RR >1 suggests that the upper left treatment is associated with a higher risk of having the outcome of interest vs the corresponding lower right treatment and the opposite is true for an RR <1. SUCRA, surface under the cumulative ranking curve

Table 2 ***Network effect estimates and ranking statistics for mortality***

Acetaminophen Mean SUCRA, 0.87; median rank, 1 (95% CrI, 1-4)			
0.58 (0.19, 1.76)	**Ibuprofen** Mean SUCRA, 0.51; median rank, 2 (95% CrI, 1-4)		
0.58 (0.19, 1.69)	0.99 (0.66, 1.53)	**Indomethacin** Mean SUCRA, 0.52; median rank, 2 (95% CrI, 1-4)	
0.49 (0.16, 1.36)	0.83 (0.57, 1.18)	0.85 (0.64, 1.05)	**Placebo** Mean SUCRA, 0.095; median rank, 4 (95% CrI, 3-4)

The unlabeled data in the boxes are risk ratios (RRs) and 95% credible intervals (CrIs). A RR >1 suggests that the upper left treatment is associated with a higher risk of having the

outcome of interest vs the corresponding lower right treatment and the opposite is true for an RR <1. SUCRA, surface under the cumulative ranking curve

Table 3 ***Network effect estimates and ranking statistics for receipt of pharmacotherapy for symptomatic PDA***

Acetaminophen Mean SUCRA, 0.52; median rank, 3 (95% CrI, 1-4)			
1.66 (0.57, 7.10)	**Ibuprofen** Mean SUCRA, 0.90; median rank, 1 (95% CrI, 1-3)		
1.10 (0.40, 4.53)	0.66 (0.32, 1.43)	**Indomethacin** Mean SUCRA, 0.56; median rank, 2 (95% CrI, 1-3)	
0.32 (0.13, 1.12)	0.20 (0.098, 0.33)	0.30 (0.17, 0.43)	**Placebo** Mean SUCRA, 0.01; median rank, 4 (95% CrI, 3-4)

The unlabeled data in the boxes are risk ratios (RRs) and 95% credible intervals (CrIs). A RR >1 suggests that the upper left treatment is associated with a higher risk of having the outcome of interest vs the corresponding lower right treatment and the opposite is true for an RR <1. SUCRA, surface under the cumulative ranking curve

Table 4 ***Network effect estimates and ranking statistics for surgical or interventional PDA closure***

Ibuprofen Mean SUCRA, 0.88; median rank, 1 (95% CrI, 1-2)		
0.64 (0.17, 2.39)	**Indomethacin** Mean SUCRA, 0.61; median rank, 2 (95% CrI, 1-2)	
0.24 (0.06, 0.64)	0.40 (0.14, 0.66)	**Placebo** Mean SUCRA, 0.002; median rank, 3 (95% CrI, 3-3)

The unlabeled data in the boxes are risk ratios (RRs) and 95% credible intervals (CrIs). A RR >1 suggests that the upper left treatment is associated with a higher risk of having the outcome of interest vs the corresponding lower right treatment and the opposite is true for an RR <1. SUCRA, surface under the cumulative ranking curve

Table 5 ***Network effect estimates and ranking statistics for necrotizing enterocolitis***

Ibuprofen Mean SUCRA, 0.69; median rank, 1 (95% CrI, 1-3)		
0.96 (0.40, 2.55)	**Indomethacin** Mean SUCRA, 0.66; median rank, 2 (95% CrI, 1-3)	
0.73 (0.31, 1.4)	0.76 (0.35, 1.2)	**Placebo** Mean SUCRA, 0.15; median rank, 3 (95% CrI, 2-3)

The unlabeled data in the boxes are risk ratios (RRs) and 95% credible intervals (CrIs). A RR >1 suggests that the upper left treatment is associated with a higher risk of having the outcome of interest vs the corresponding lower right treatment and the opposite is true for an RR <1. SUCRA, surface under the cumulative ranking curve

Table 6 ***Network effect estimates and ranking statistics for gastrointestinal perforation***

Ibuprofen Mean SUCRA, 0.15; median rank, 3 (95% CrI, 1-3)		
2.98 (0.30, 55.5)	**Indomethacin** Mean SUCRA, 0.70; median rank, 1 (95% CrI, 1-3)	
2.6 (0.42, 20)	0.92 (0.11, 3.9)	**Placebo** Mean SUCRA, 0.65; median rank, 2 (95% CrI, 1-3)

The unlabeled data in the boxes are risk ratios (RRs) and 95% credible intervals (CrIs). A RR >1 suggests that the upper left treatment is associated with a higher risk of having the outcome of interest vs the corresponding lower right treatment and the opposite is true for an RR <1. SUCRA, surface under the cumulative ranking curve

Table 7 ***Network effect estimates and ranking statistics for chronic lung disease***

Ibuprofen Mean SUCRA, 0.47; median rank, 2 (95% CrI, 1-3)		
0.96 (0.72, 1.26)	**Indomethacin** Mean SUCRA, 0.25; median rank, 3 (95% CrI, 1-3)	
1.05 (0.83, 1.32)	1.10 (0.93, 1.29)	**Placebo** Mean SUCRA, 0.77; median rank, 1 (95% CrI, 1-3)

The unlabeled data in the boxes are risk ratios (RRs) and 95% credible intervals (CrIs). A RR >1 suggests that the upper left treatment is associated with a higher risk of having the outcome of interest vs the corresponding lower right treatment and the opposite is true for an RR <1. SUCRA, surface under the cumulative ranking curve

Table 8 ***Network effect estimates and ranking statistics for oliguria***

Acetaminophen Mean SUCRA, 0.86; median rank, 1 (95% CrI, 1-4)			
0.52 (0.14, 1.62)	**Ibuprofen** Mean SUCRA, 0.35; median rank, 3 (95% CrI, 1-4)		
0.40 (0.12, 1.23)	0.78 (0.46, 1.34)	**Indomethacin** Mean SUCRA, 0.08; median rank, 4 (95% CrI, 3-4)	
0.68 (0.20, 1.97)	1.32 (0.85, 2.02)	1.69 (1.20, 2.29)	**Placebo** Mean SUCRA, 0.71; median rank, 2 (95% CrI, 1-3)

The unlabeled data in the boxes are risk ratios (RRs) and 95% credible intervals (CrIs). A RR >1 suggests that the upper left treatment is associated with a higher risk of having the outcome of interest vs the corresponding lower right treatment and the opposite is true for an RR <1. SUCRA, surface under the cumulative ranking curve

Table 9 ***Network effect estimates and ranking statistics for intraventricular hemorrhage (any grade)***

Acetaminophen Mean SUCRA, 0.78; median rank, 1 (95% CrI, 1-4)			
0.64 (0.21, 1.81)	**Ibuprofen** Mean SUCRA, 0.33; median rank, 3 (95% CrI, 1-4)		
0.79 (0.26, 2.14)	1.22 (0.84, 1.83)	**Indomethacin** Mean SUCRA, 0.73; median rank, 2 (95% CrI, 1-3)	
0.60 (0.20, 1.59)	0.94 (0.66, 1.31)	0.77 (0.62, 0.90)	**Placebo** Mean SUCRA, 0.16; median rank, 4 (95% CrI, 2-4)

The unlabeled data in the boxes are risk ratios (RRs) and 95% credible intervals (CrIs). A RR >1 suggests that the upper left treatment is associated with a higher risk of having the outcome of interest vs the corresponding lower right treatment and the opposite is true for an RR <1. SUCRA, surface under the cumulative ranking curve

Table 10 ***Network effect estimates and ranking statistics for periventricular leukomalacia (any grade)***

Ibuprofen Mean SUCRA, 0.43; median rank, 2 (95% CrI, 1-3)		
1.30 (0.46, 4.16)	**Indomethacin** Mean SUCRA, 0.80; median rank, 1 (95% CrI, 1-3)	
0.94 (0.40, 2.02)	0.74 (0.30, 1.35)	**Placebo** Mean SUCRA, 0.28; median rank, 2 (95% CrI, 1-3)

The unlabeled data in the boxes are risk ratios (RRs) and 95% credible intervals (CrIs). A RR >1 suggests that the upper left treatment is associated with a higher risk of having the outcome of interest vs the corresponding lower right treatment and the opposite is true for an RR <1. SUCRA, surface under the cumulative ranking curve

Table 11 ***Network effect estimates and ranking statistics for cerebral palsy***

Acetaminophen Mean SUCRA, 0.76; median rank, 1 (95% CrI, 1-3)		
0.38 (0.01, 6.97)	**Indomethacin** Mean SUCRA, 0.39; median rank, 2 (95% CrI, 1-3)	
0.36 (0.01, 6.31)	0.97 (0.44, 2.11)	**Placebo** Mean SUCRA, 0.35; median rank, 2 (95% CrI, 1-3)

The unlabeled data in the boxes are risk ratios (RRs) and 95% credible intervals (CrIs). A RR >1 suggests that the upper left treatment is associated with a higher risk of having the outcome of interest vs the corresponding lower right treatment and the opposite is true for an RR <1. SUCRA, surface under the cumulative ranking curve

Table 12 ***Heterogeneity priors for outcomes***

Outcome	**Heterogeneity Prior**
Severe intraventricular haemorrhage (IVH)	standard deviation ~ uniform (0, 2.0513)
Mortality	standard deviation ~ uniform (0, 1.203973)
Receipt of pharmacotherapy for symptomatic patent ductus arteriosus (PDA)	standard deviation ~ uniform (0, 2.944439)
Surgical or interventional PDA closure	standard deviation ~ uniform (0, 2.549911)
Necrotizing enterocolitis (NEC)	standard deviation ~ uniform (0, 1.669502)
Gastrointestinal perforation	standard deviation ~ uniform (0, 1.609438)
Chronic lung disease (CLD)	standard deviation ~ uniform (0, 1.532477)
Oliguria	standard deviation ~ uniform (0, 1.803594)
IVH of any grade	standard deviation ~ uniform (0, 1.329136)
Periventricular leukomalacia (PL)	standard deviation ~ uniform (0, 1.149906)
Cerebral palsy (CP)	standard deviation ~ uniform (0, 1.299283)

Prior distributions for the relative effects were determined heuristically based on the following: $N(0, (15 \cdot S)^2)$, where N denotes normal distribution and S denotes the outcome scale. The outcome scale is meant to represent an unreasonably large deviation on the scale of measurement which was determined heuristically based on available data

Figure 1 ***Study flow diagram***

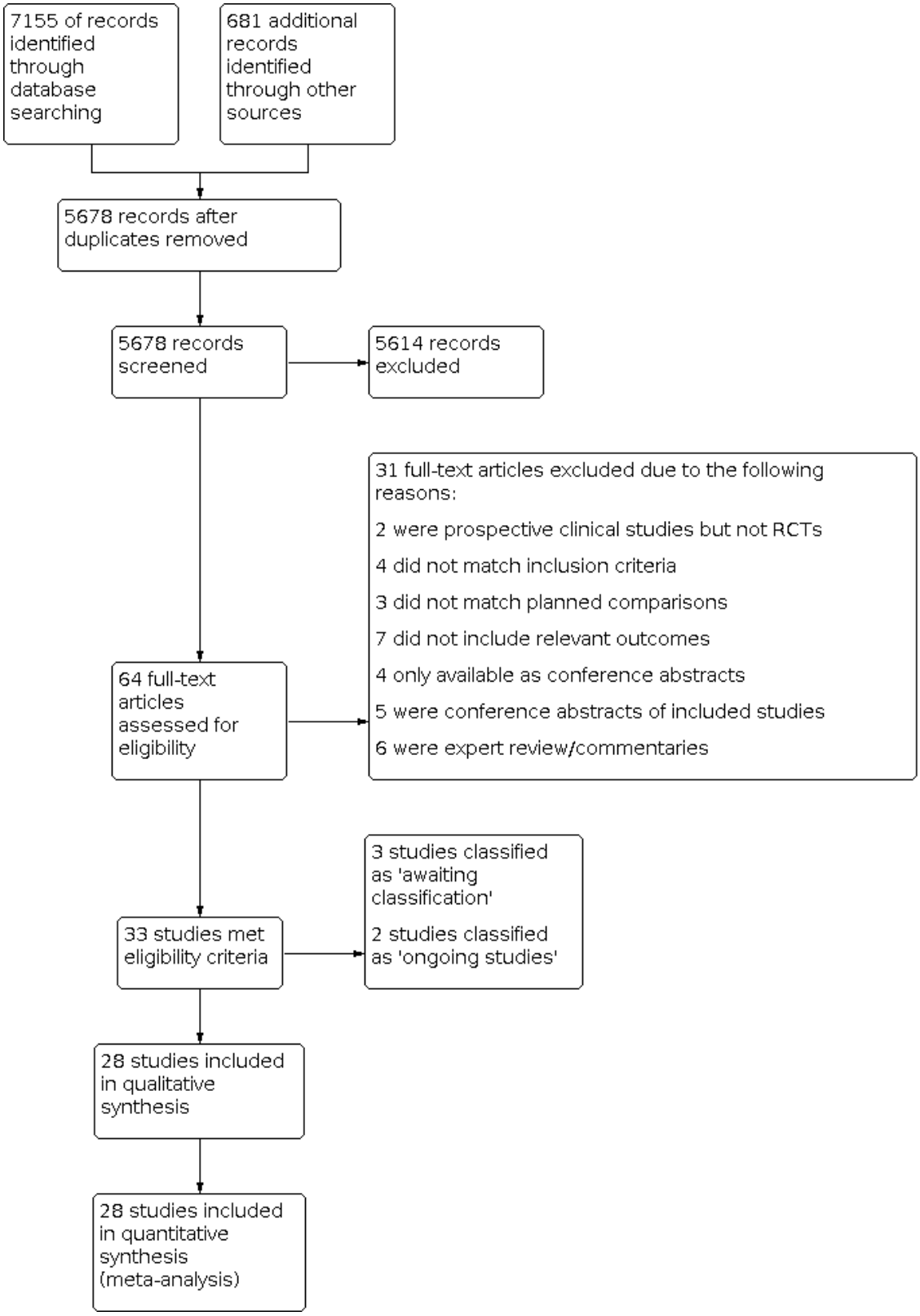


Figure 2 ***Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies***

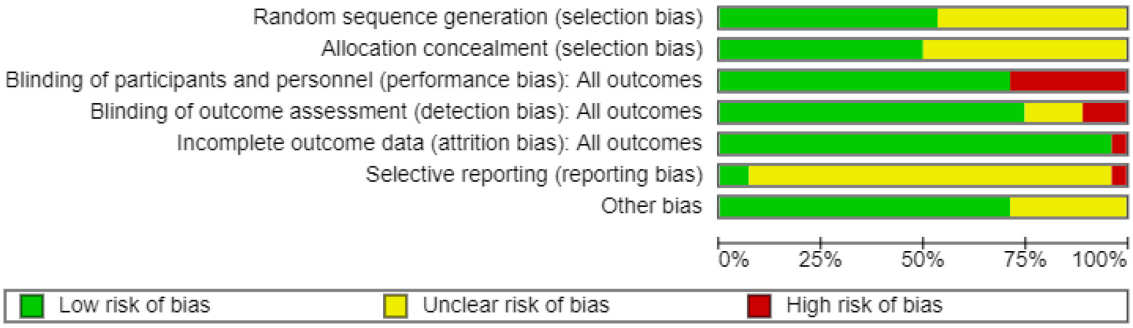


Figure 3 ***Risk of bias summary: review authors' judgements about each risk of bias item for each included study***

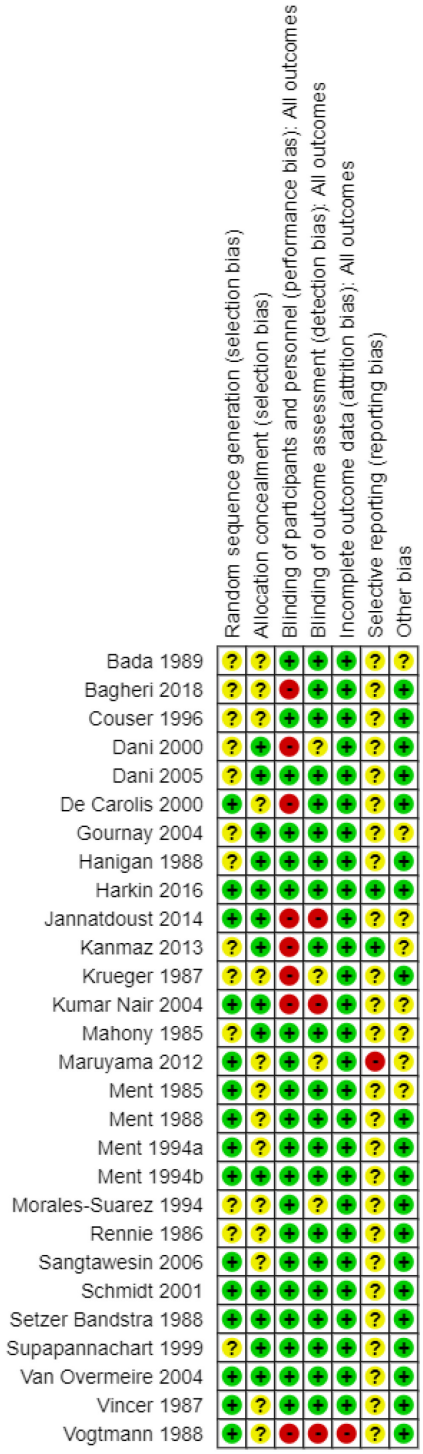


Figure 4 ***Network plot for severe intraventricular hemorrhage***

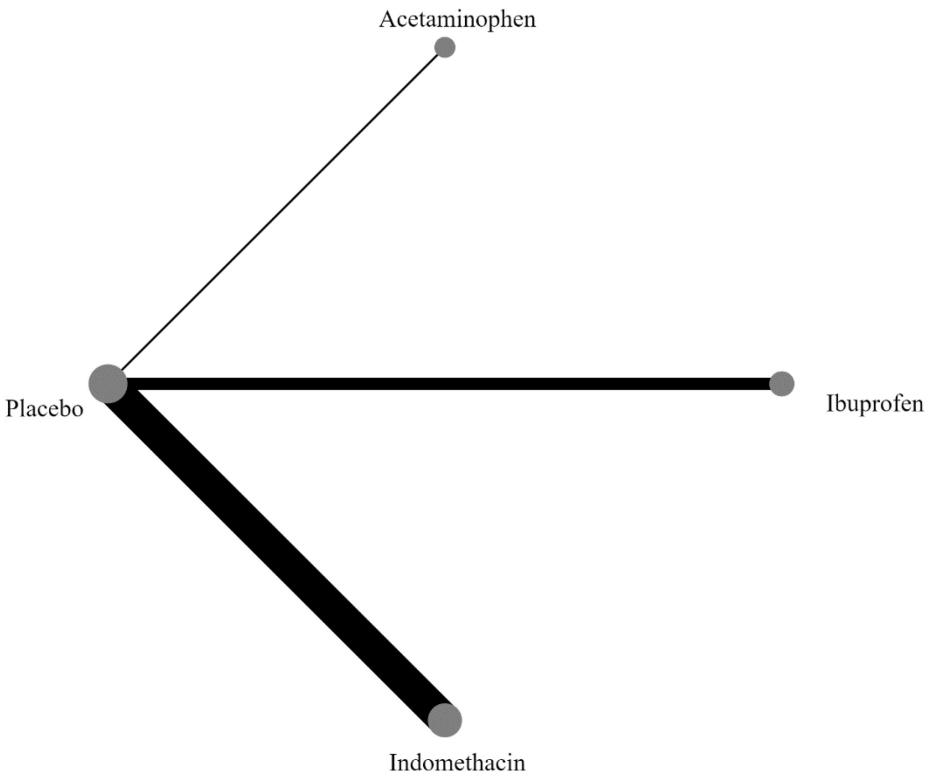


Figure 5 ***Forest plot of pairwise meta-analysis between indomethacin and placebo (conducted using Bayesian random-effects model) for severe intraventricular hemorrhage***

A RR<1 favors the intervention. CrI, Credible intervals

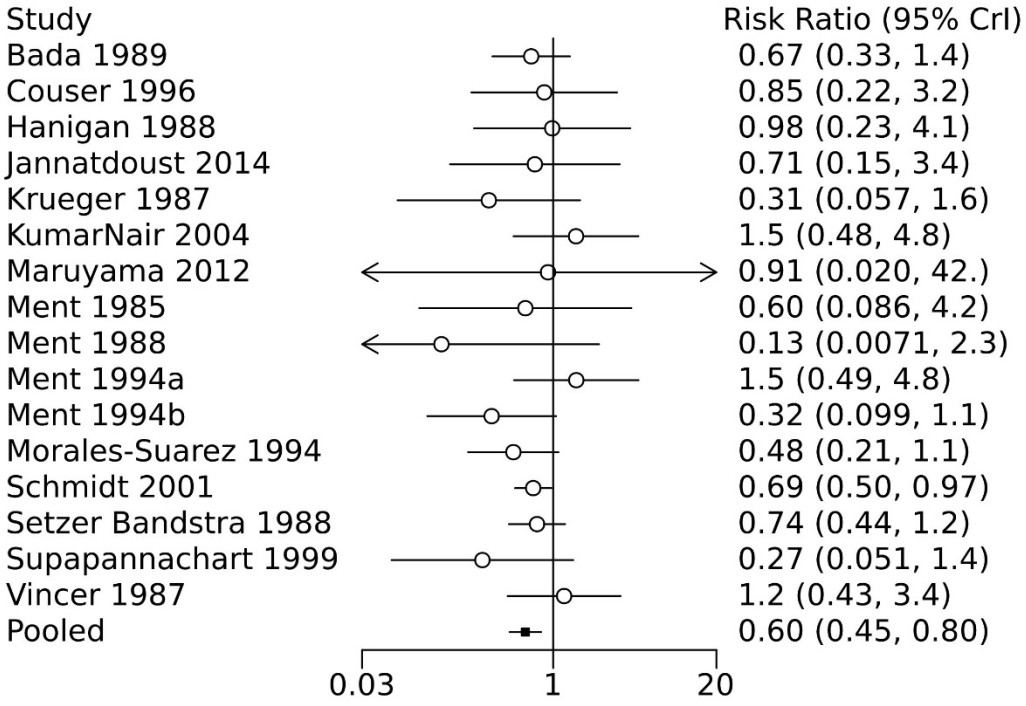


Figure 6 ***Forest plot of pairwise meta-analysis between ibuprofen and placebo (conducted using Bayesian random-effects model) for severe intraventricular hemorrhage***

A RR<1 favors the intervention. CrI, Credible intervals

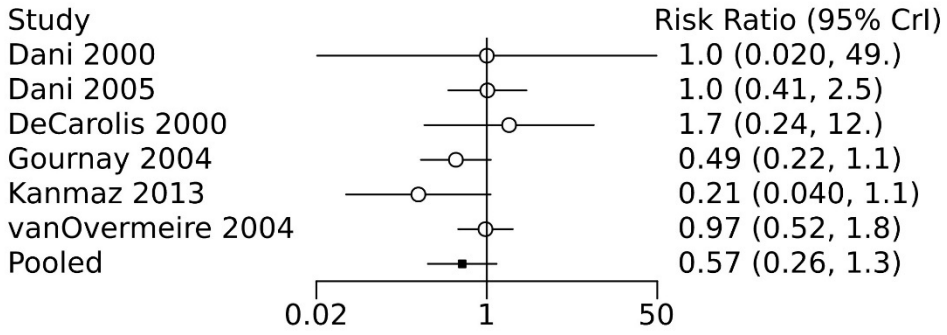


Figure 7 ***Forest plot of the relative network effect estimates with placebo as the comparator (conducted using Bayesian random-effects model) for severe intraventricular hemorrhage***

A RR<1 favors the intervention. CrI, Credible intervals

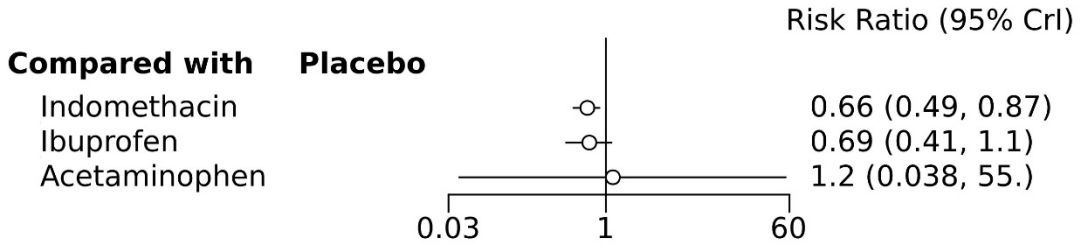


Figure 8 ***Comparison-adjusted funnel plot for severe intraventricular hemorrhage***

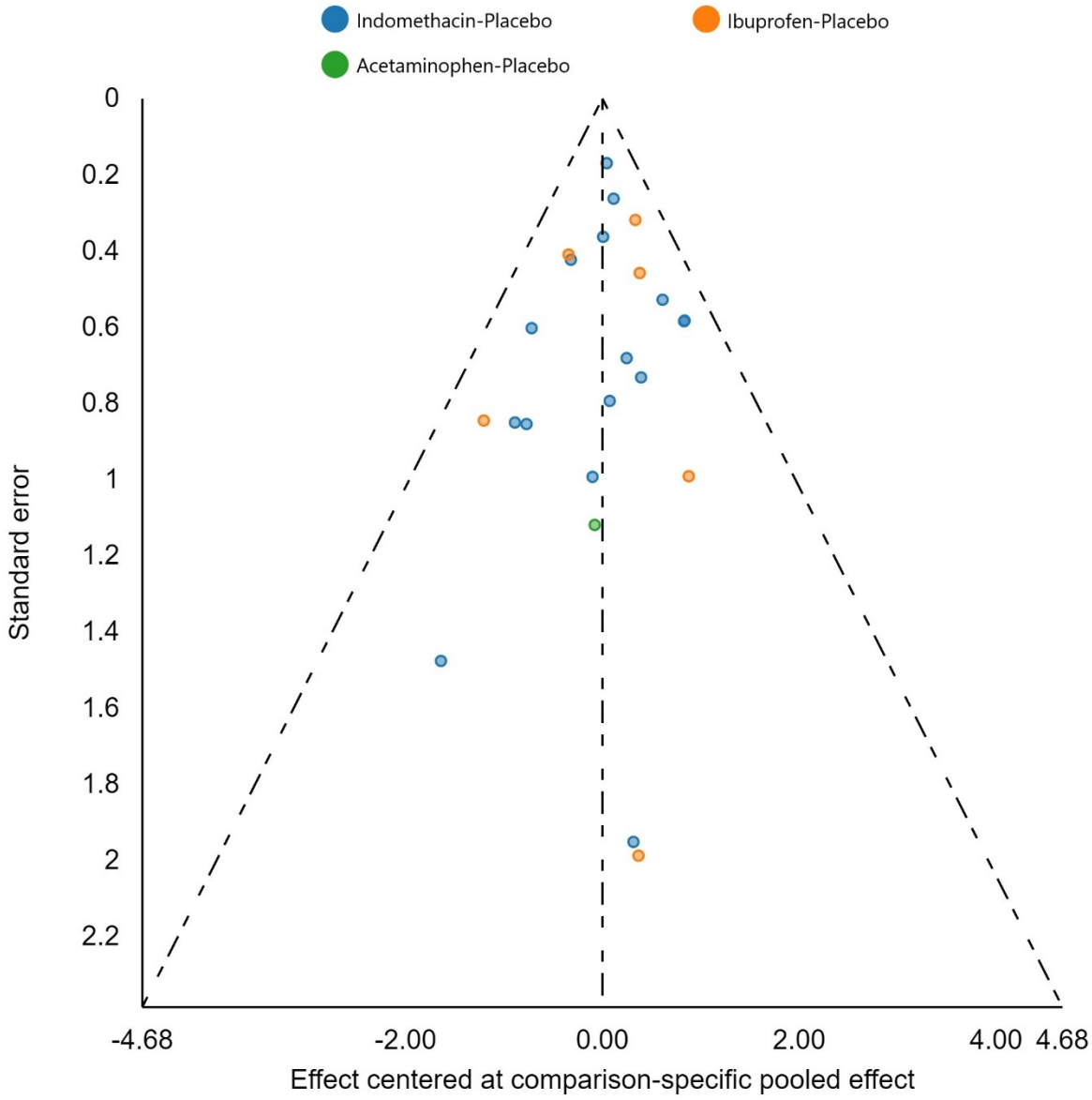


Figure 9 ***Ranking probability (rankogram) of each treatment modality for severe intraventricular hemorrhage***

Each rank is represented by a color. The height of each colored bar corresponds to the probability of an intervention being ranked in that specific ranking position

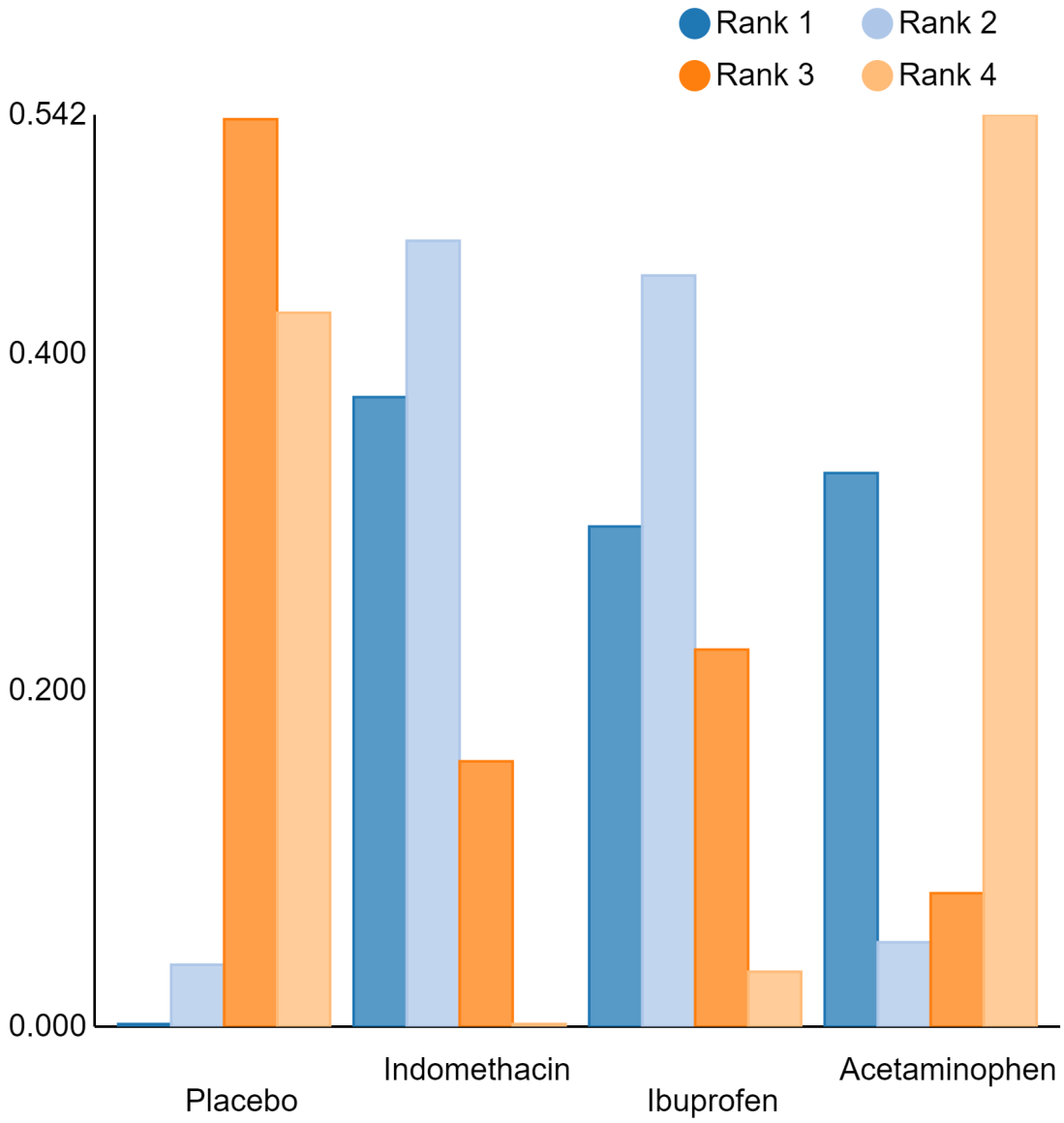


Figure 10 ***Network plot for mortality***

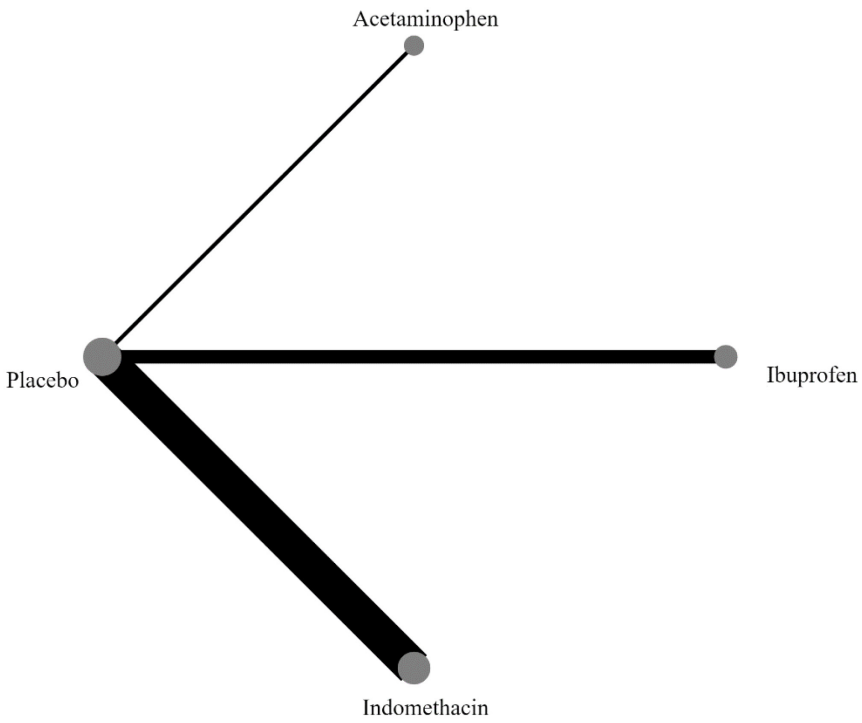


Figure 11 ***Forest plot of pairwise meta-analysis between indomethacin and placebo (conducted using Bayesian random-effects model) for mortality***

A RR<1 favors the intervention. CrI, Credible intervals

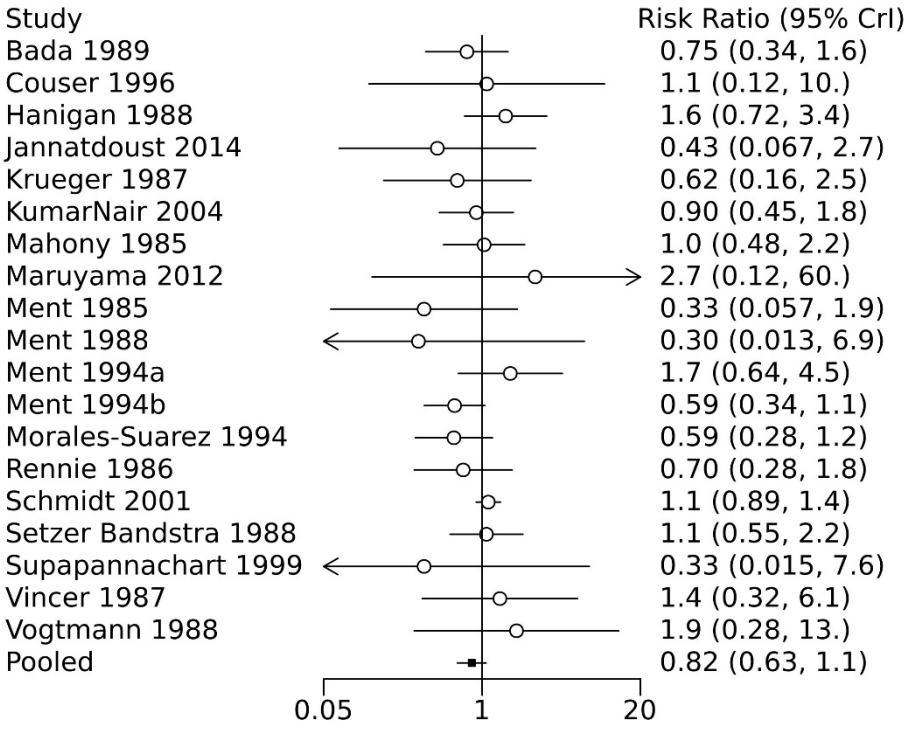


Figure 12 ***Forest plot of pairwise meta-analysis between ibuprofen and placebo (conducted using Bayesian random-effects model) for mortality***

A RR<1 favors the intervention. CrI, Credible intervals

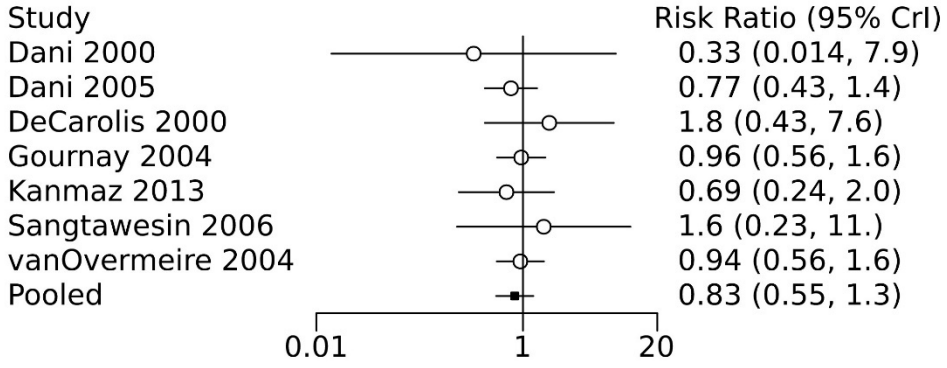


Figure 13 ***Forest plot of pairwise meta-analysis between acetaminophen and placebo (conducted using Bayesian random-effects model) for mortality***

A RR<1 favors the intervention. CrI, Credible intervals

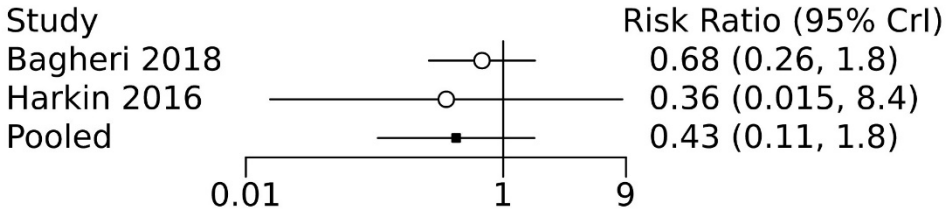


Figure 14 ***Forest plot of the relative network effect estimates with placebo as the comparator (conducted using Bayesian random-effects model) for mortality***

A RR<1 favors the intervention. CrI, Credible intervals

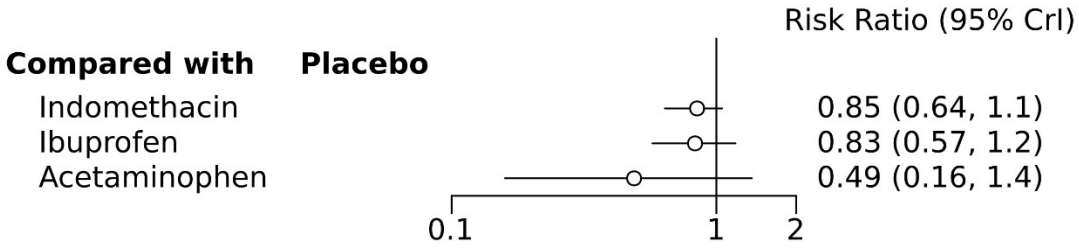


Figure 15 ***Comparison-adjusted funnel plot for mortality***

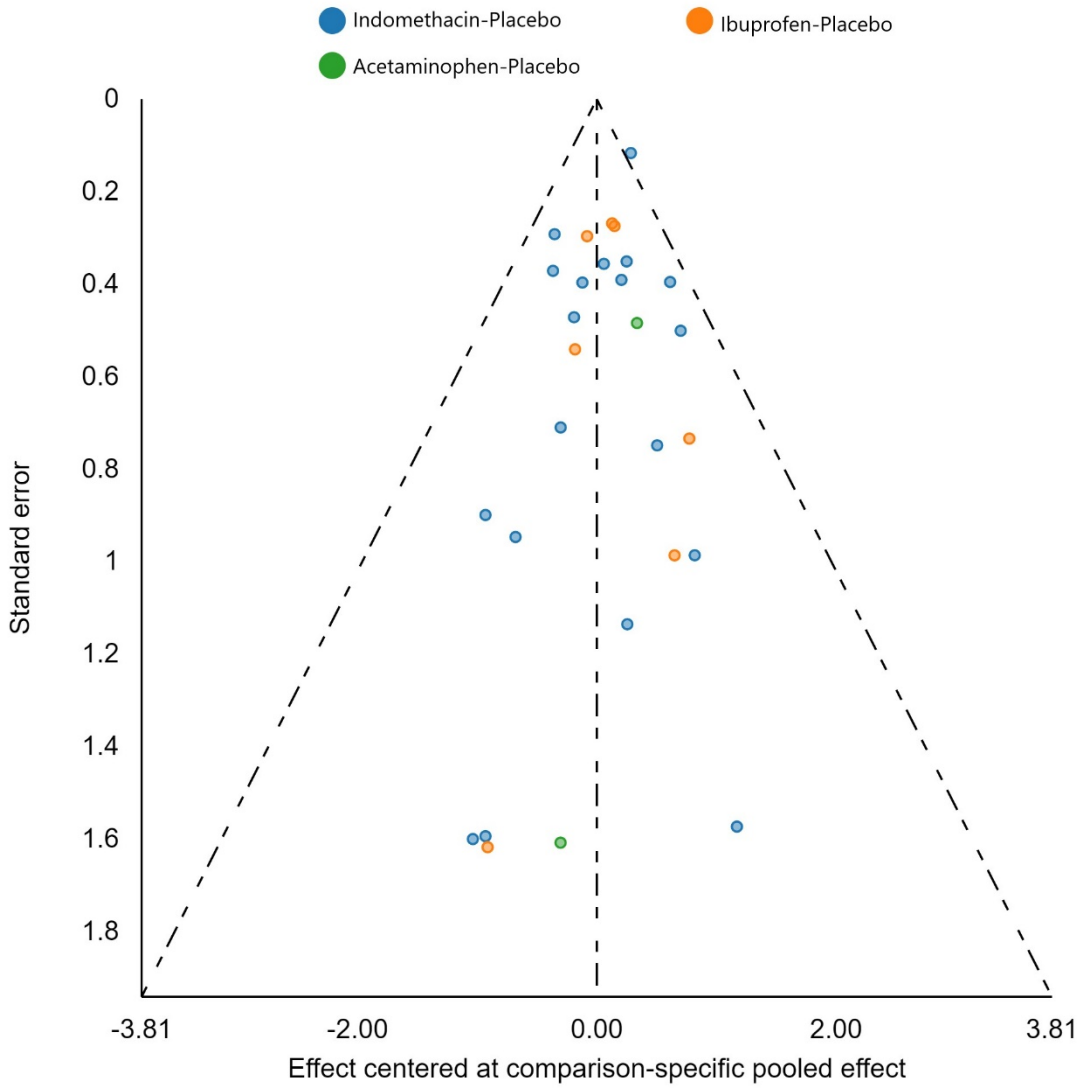


Figure 16 ***Ranking probability (rankogram) of each treatment modality for mortality***

Each rank is represented by a color. The height of each colored bar corresponds to the probability of an intervention being ranked in that specific ranking position

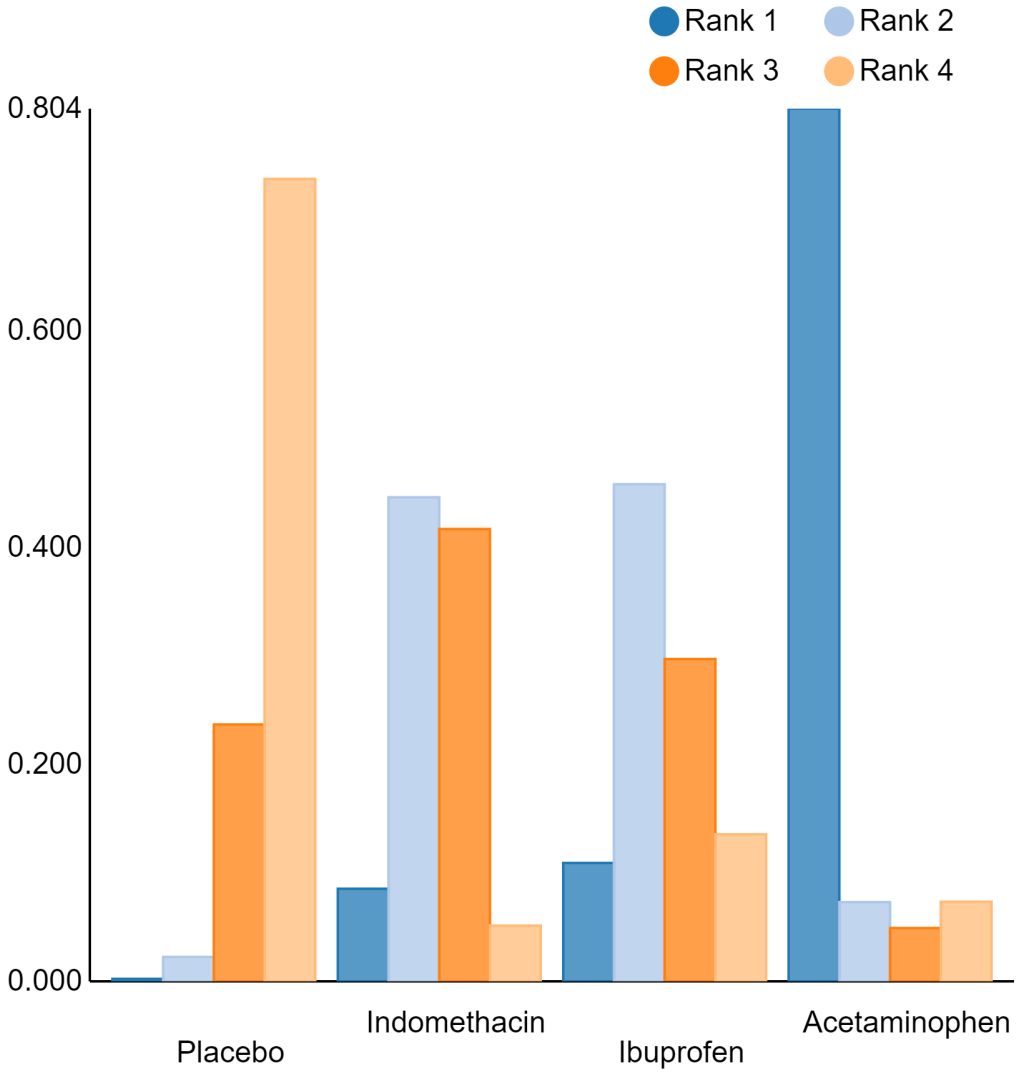


Figure 17 ***Network plot for pharmacotherapy for symptomatic PDA***

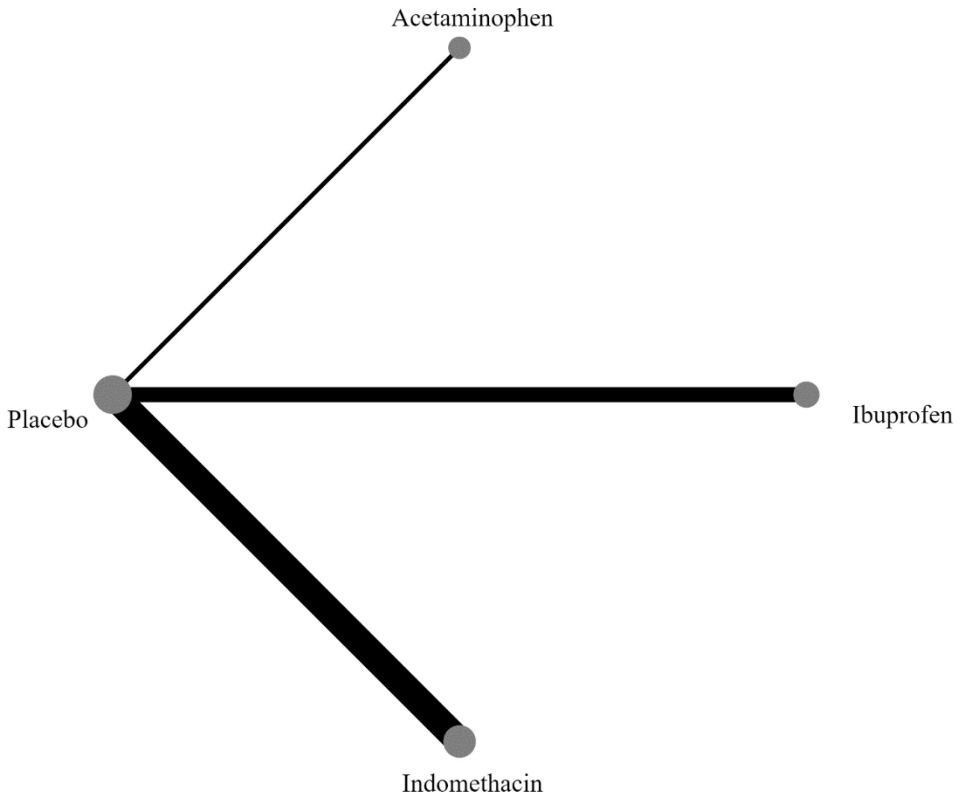


Figure 18 ***Forest plot of pairwise meta-analysis between indomethacin and placebo (conducted using Bayesian random-effects model) for pharmacotherapy for symptomatic PDA***

A RR<1 favors the intervention. CrI, Credible intervals

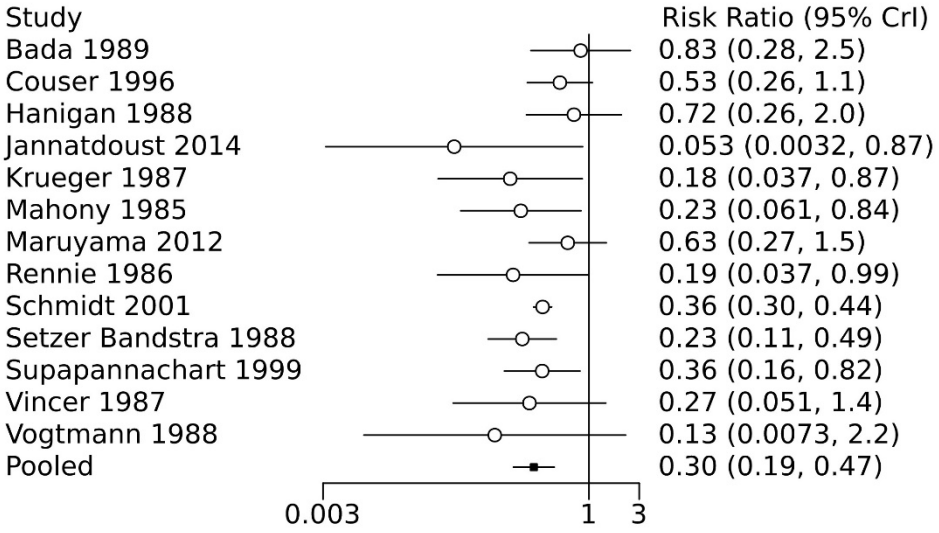


Figure 19 ***Forest plot of pairwise meta-analysis between ibuprofen and placebo (conducted using Bayesian random-effects model) for pharmacotherapy for symptomatic PDA***

A RR<1 favors the intervention. CrI, Credible intervals

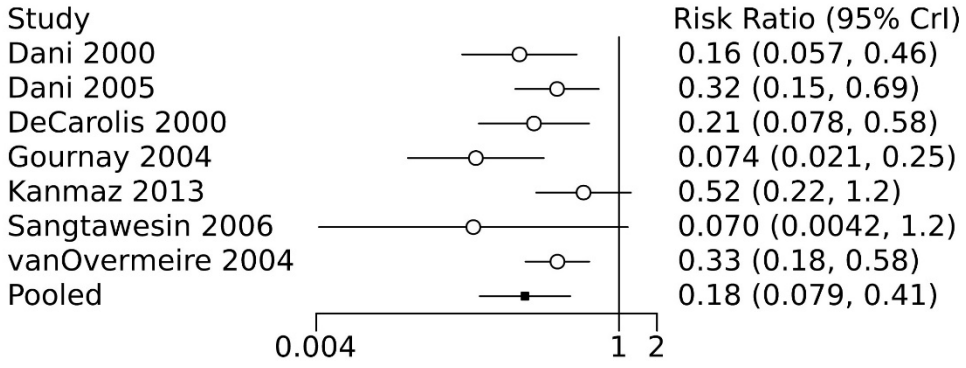


Figure 20 ***Forest plot of pairwise meta-analysis between acetaminophen and placebo (conducted using Bayesian random-effects model) for pharmacotherapy for symptomatic PDA***

A RR<1 favors the intervention. CrI, Credible intervals

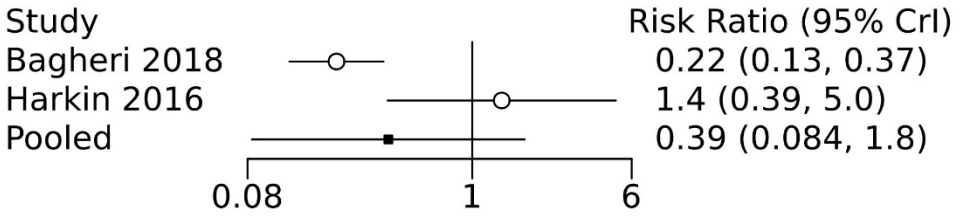


Figure 21 ***Forest plot of the relative network effect estimates with placebo as the comparator (conducted using Bayesian random-effects model) for pharmacotherapy for symptomatic PDA***

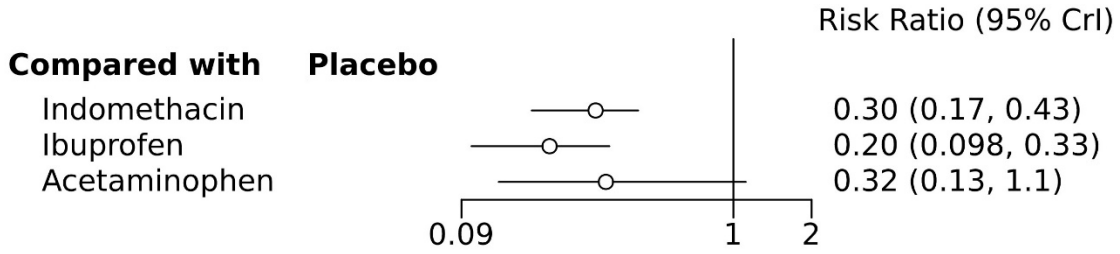


Figure 22 ***Comparison-adjusted funnel plot for pharmacotherapy for symptomatic PDA***

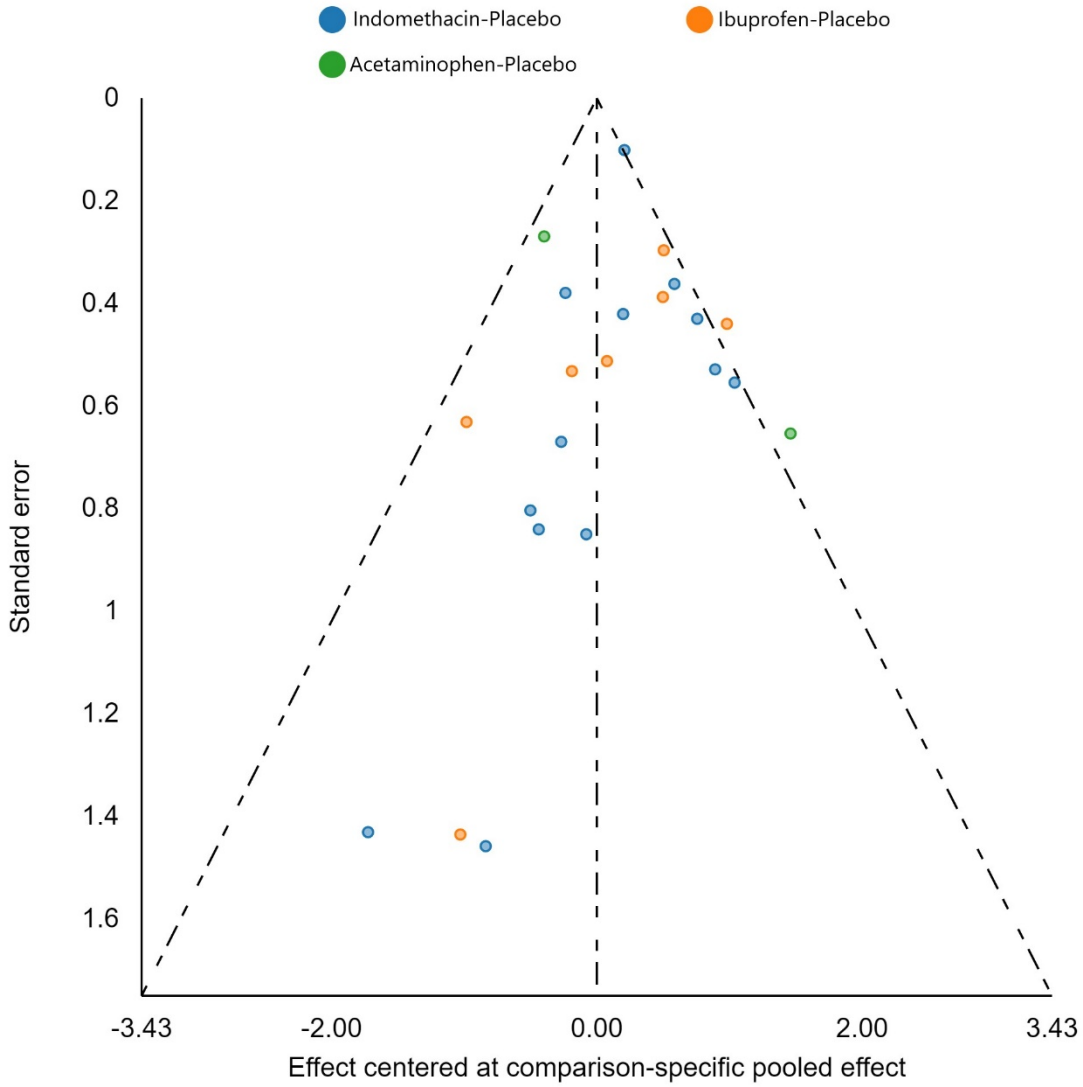


Figure 23 ***Ranking probability (rankogram) of each treatment modality for pharmacotherapy for symptomatic PDA***

Each rank is represented by a color. The height of each colored bar corresponds to the probability of an intervention being ranked in that specific ranking position

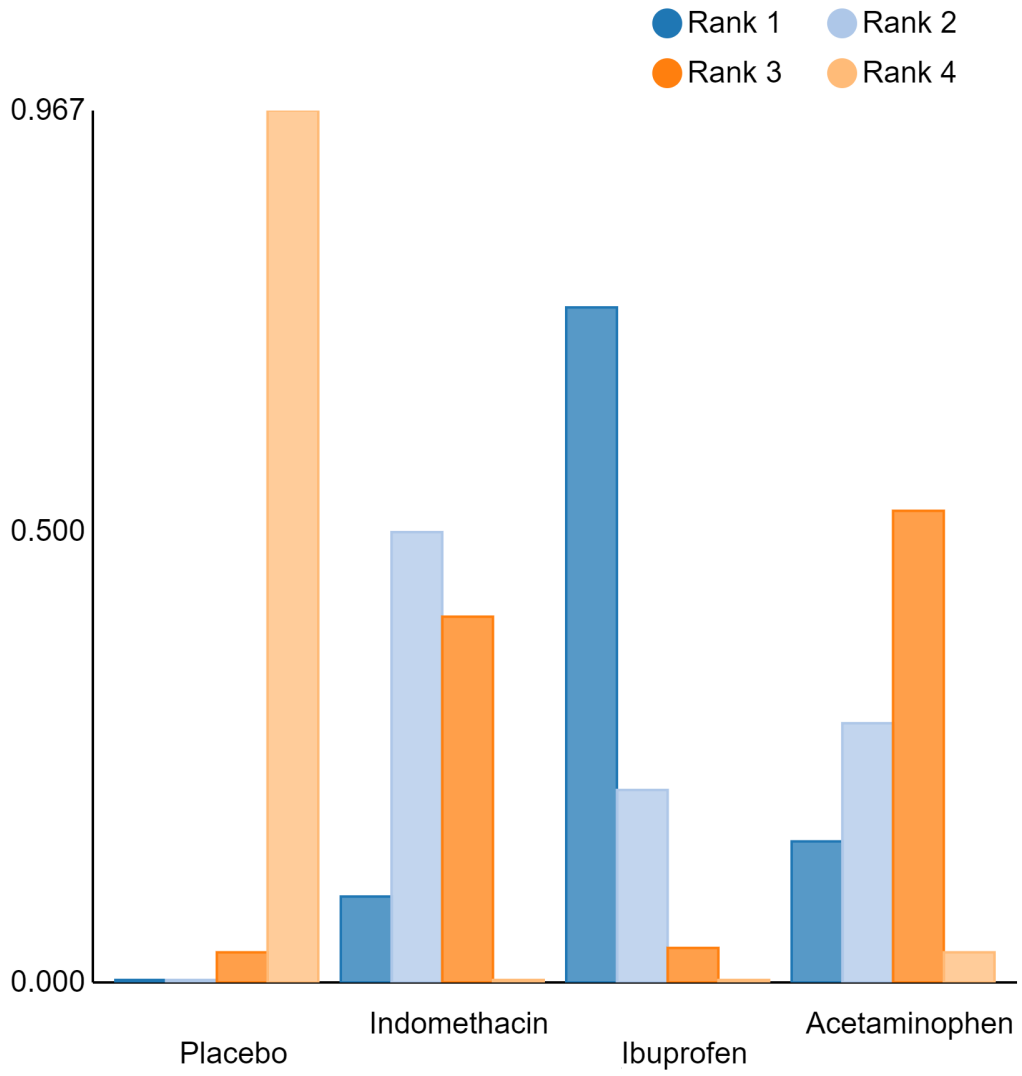


Figure 24 ***Network plot for surgical PDA closure***

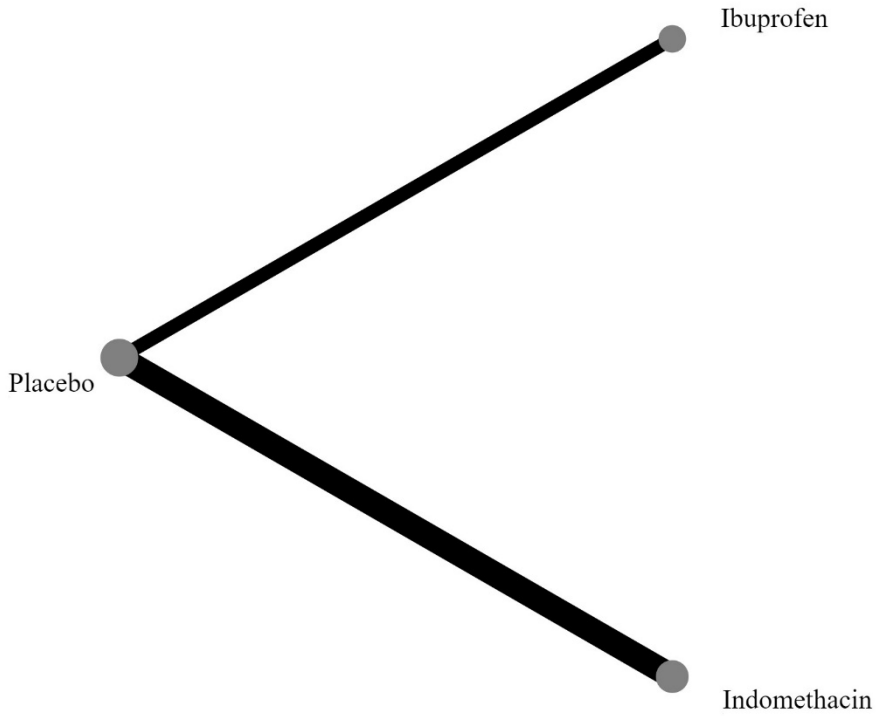


Figure 25 ***Forest plot of pairwise meta-analysis between indomethacin and placebo (conducted using Bayesian random-effects model) for surgical PDA closure***

A RR<1 favors the intervention. CrI, Credible intervals

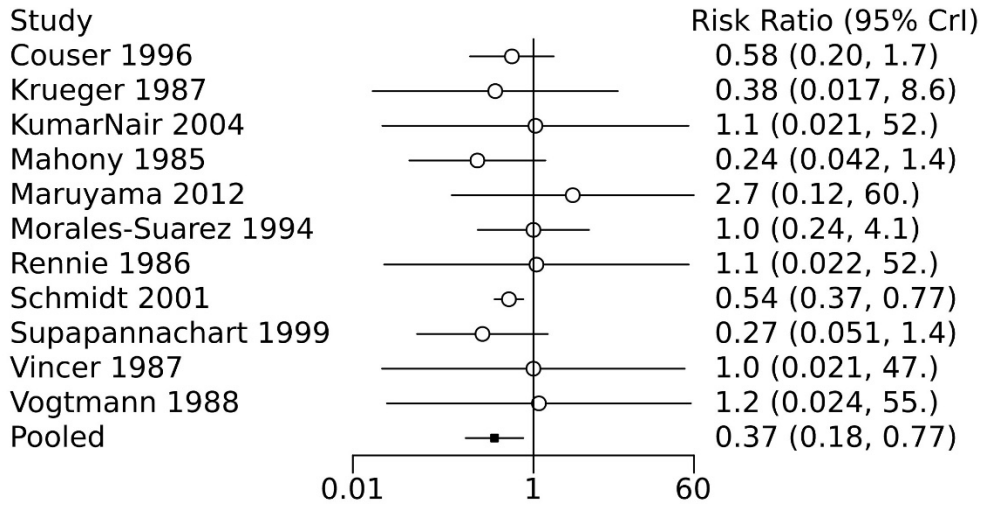


Figure 26 ***Forest plot of pairwise meta-analysis between ibuprofen and placebo (conducted using Bayesian random-effects model) for surgical PDA closure***

A RR<1 favors the intervention. CrI, Credible intervals

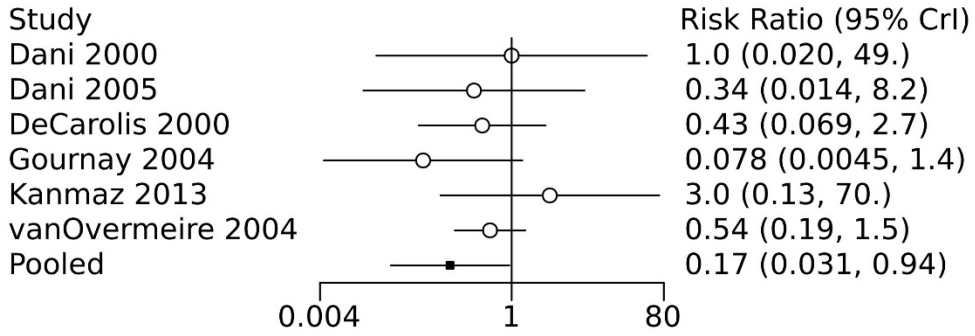


Figure 27 ***Forest plot of the relative network effect estimates with placebo as the comparator (conducted using Bayesian random-effects model) for surgical PDA closure***

A RR<1 favors the intervention. CrI, Credible intervals

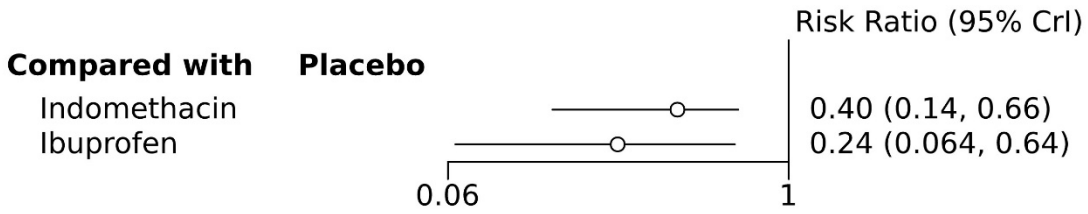


Figure 28 ***Comparison-adjusted funnel plot for surgical PDA closure***

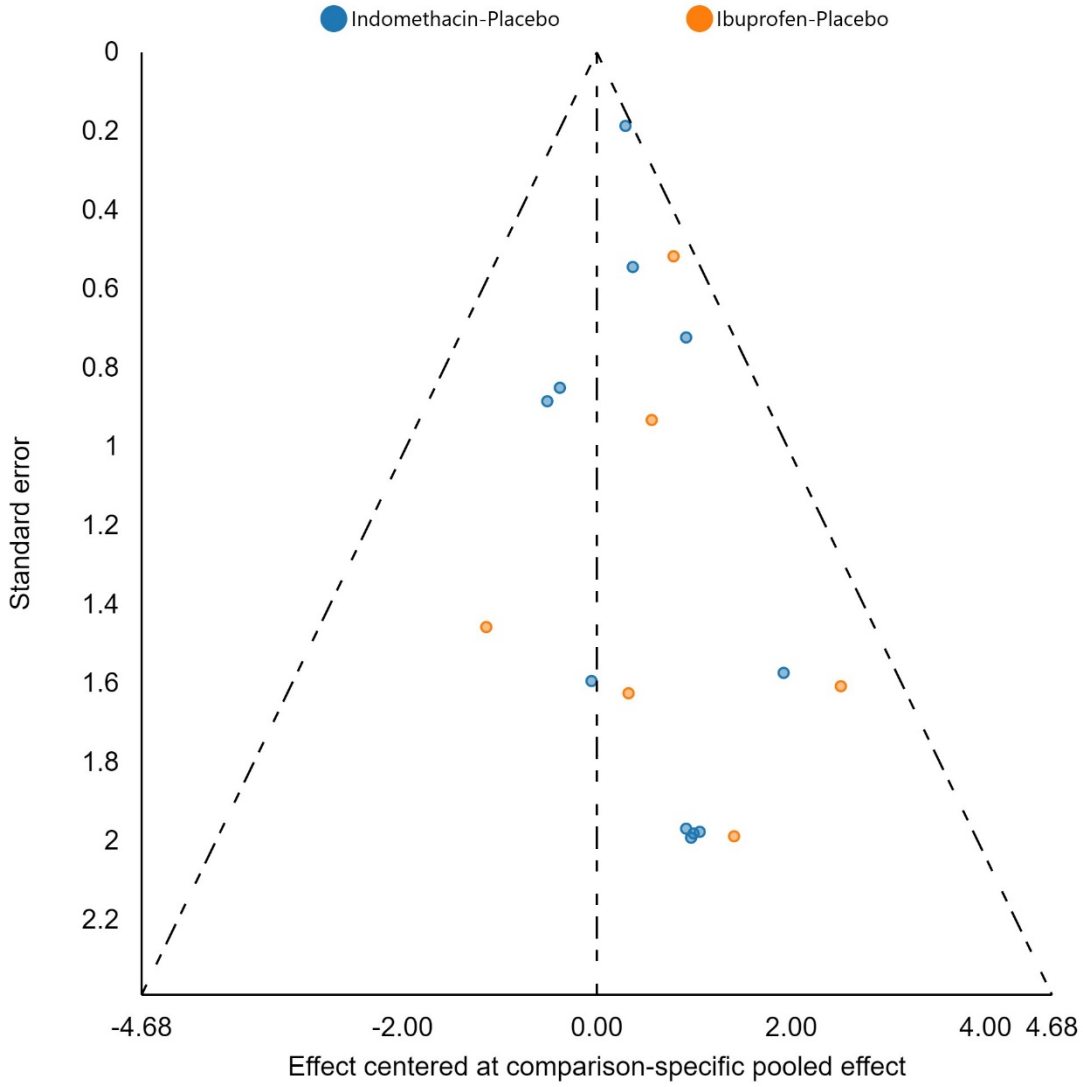


Figure 29 ***Ranking probability (rankogram) of each treatment modality for surgical PDA closure***

Each rank is represented by a color. The height of each colored bar corresponds to the probability of an intervention being ranked in that specific ranking position

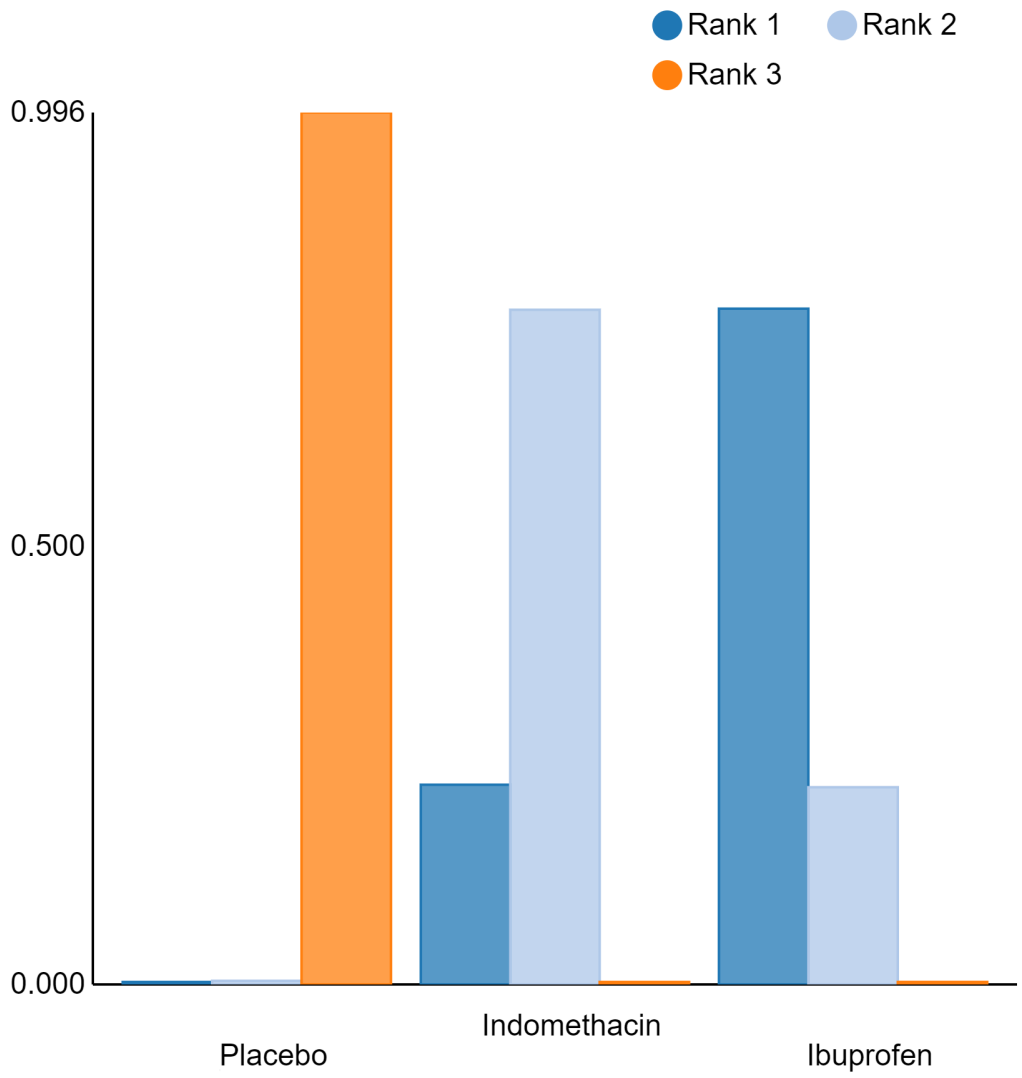


Figure 30 ***Network plot for necrotizing enterocolitis***

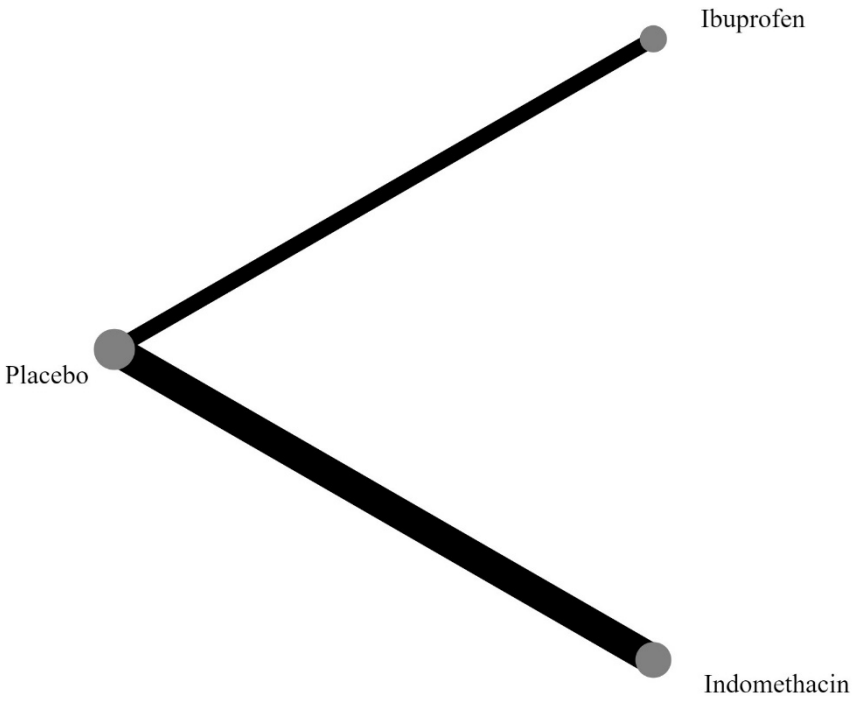


Figure 31 ***Forest plot of pairwise meta-analysis between indomethacin and placebo (conducted using Bayesian random-effects model) for necrotizing enterocolitis***

A RR<1 favors the intervention. CrI, Credible intervals

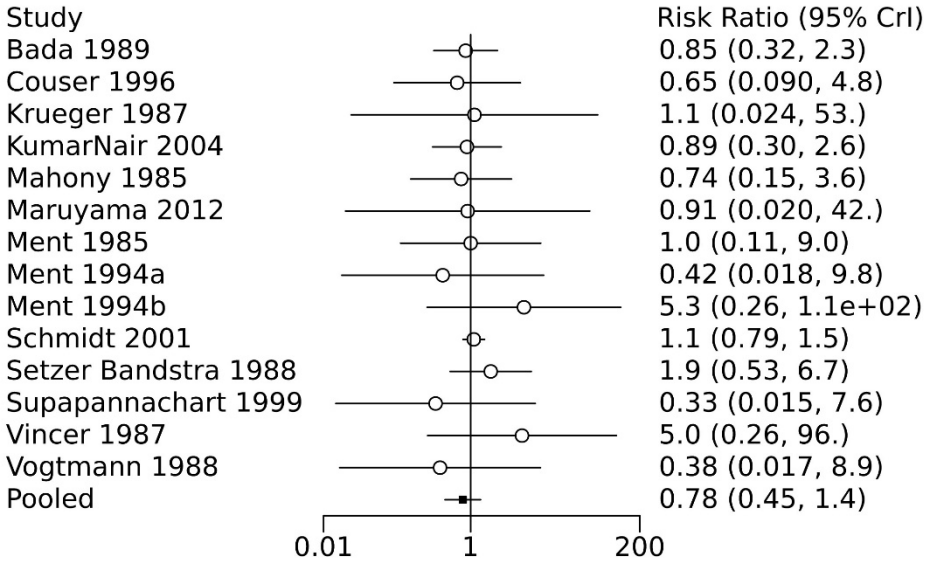


Figure 32 ***Forest plot of pairwise meta-analysis between ibuprofen and placebo (conducted using Bayesian random-effects model) for necrotizing enterocolitis***

A RR<1 favors the intervention. CrI, Credible intervals

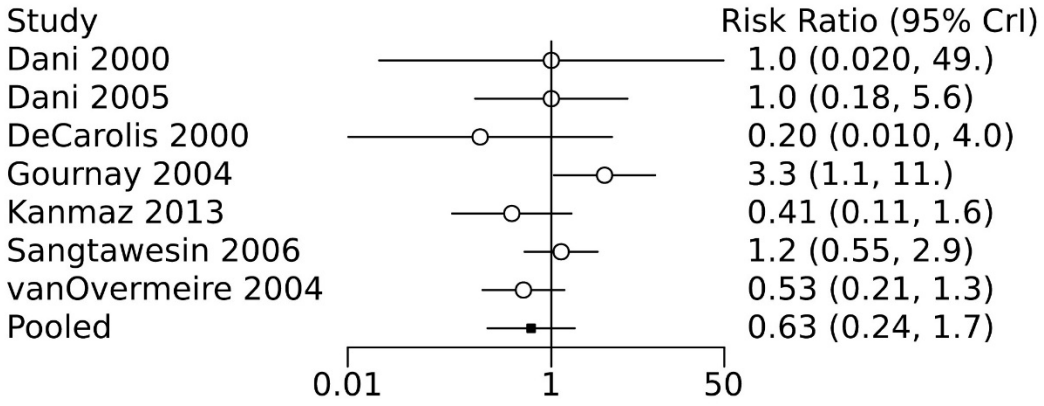


Figure 33 ***Forest plot of the relative network effect estimates with placebo as the comparator (conducted using Bayesian random-effects model) for necrotizing enterocolitis***

A RR<1 favors the intervention. CrI, Credible intervals

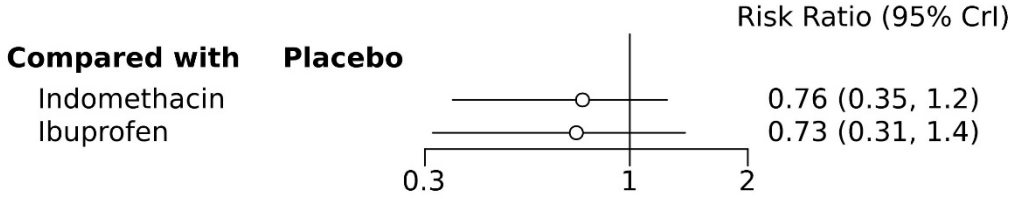


Figure 34 ***Comparison-adjusted funnel plot for necrotizing enterocolitis***

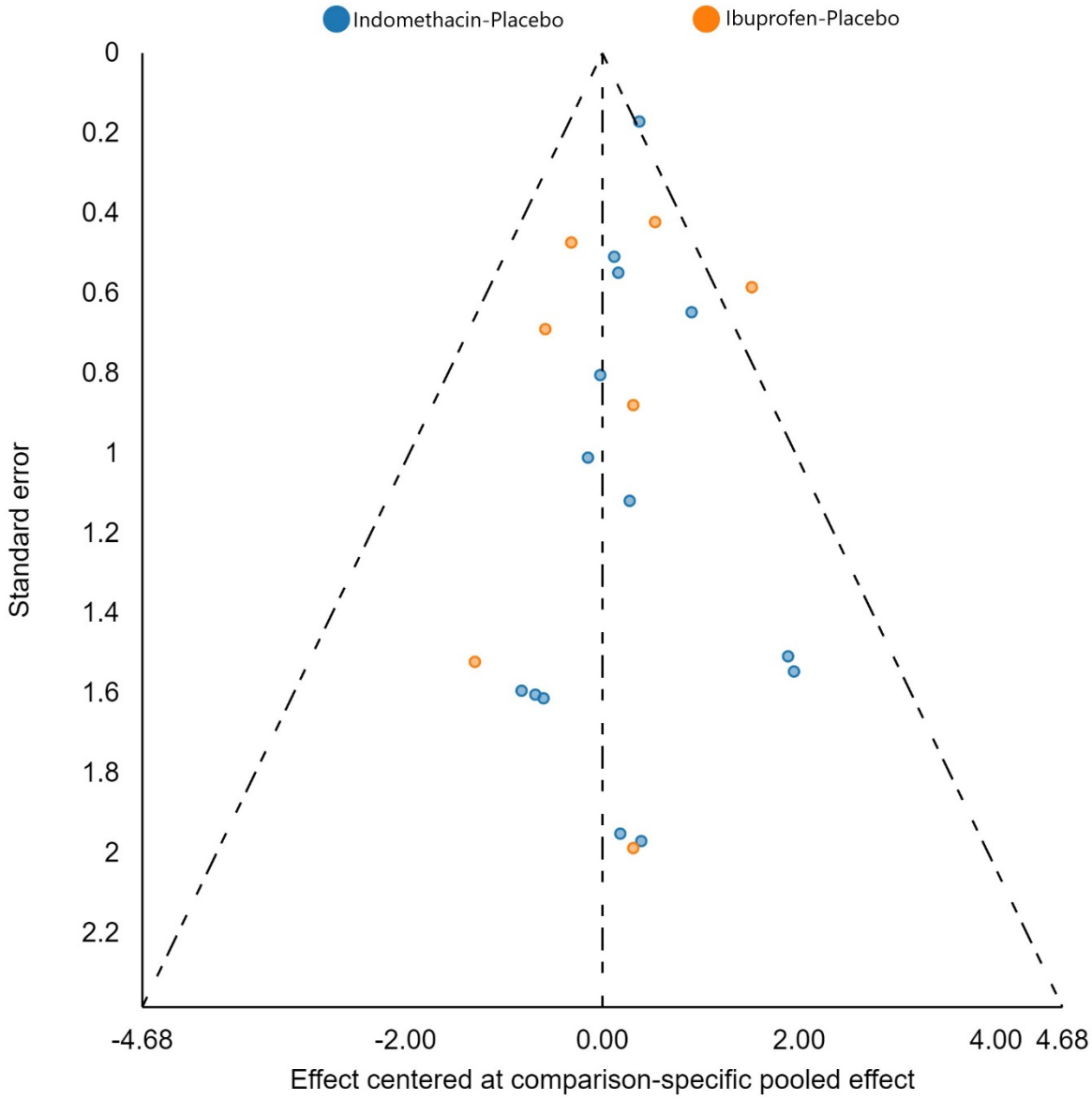


Figure 35 ***Ranking probability (rankogram) of each treatment modality for necrotizing enterocolitis***

Each rank is represented by a color. The height of each colored bar corresponds to the probability of an intervention being ranked in that specific ranking position

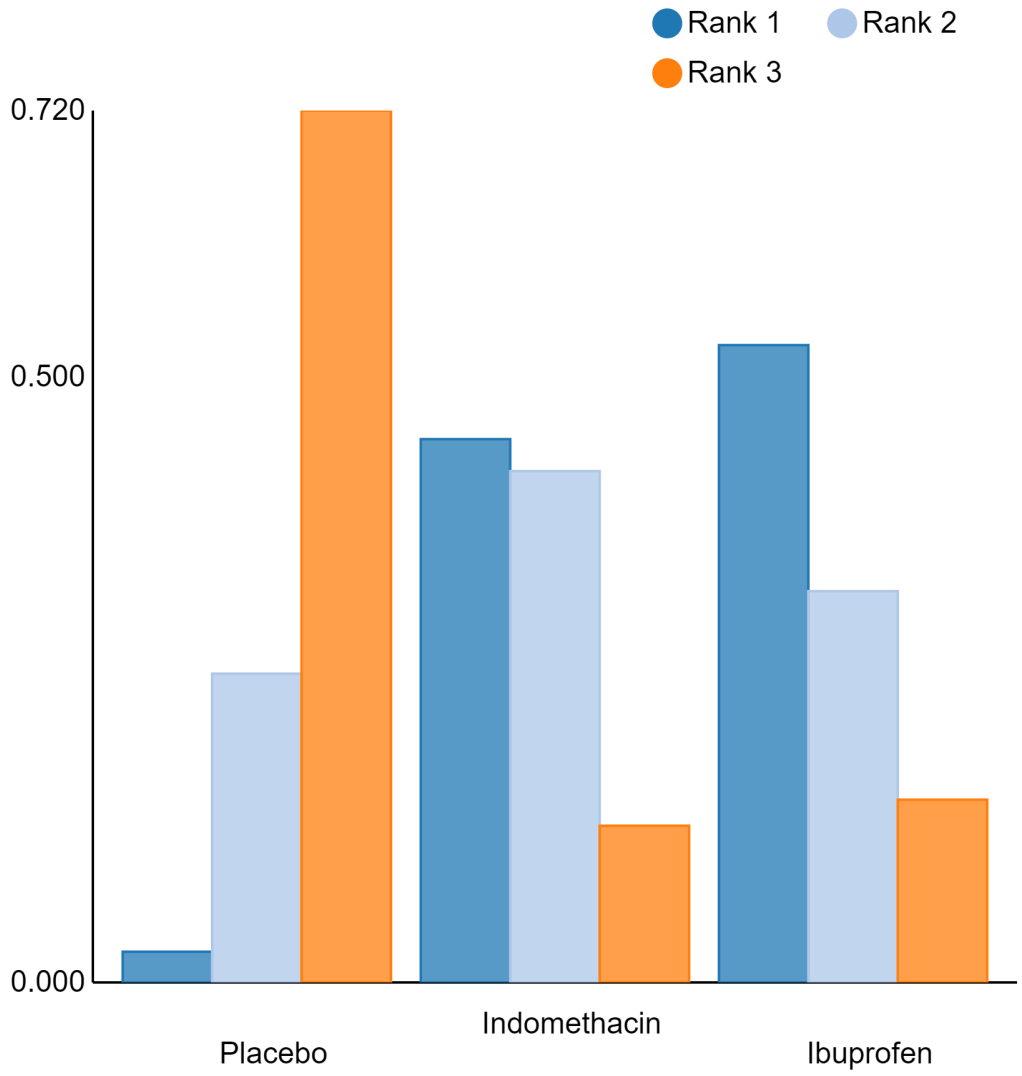


Figure 36 ***Network plot for gastrointestinal perforation***

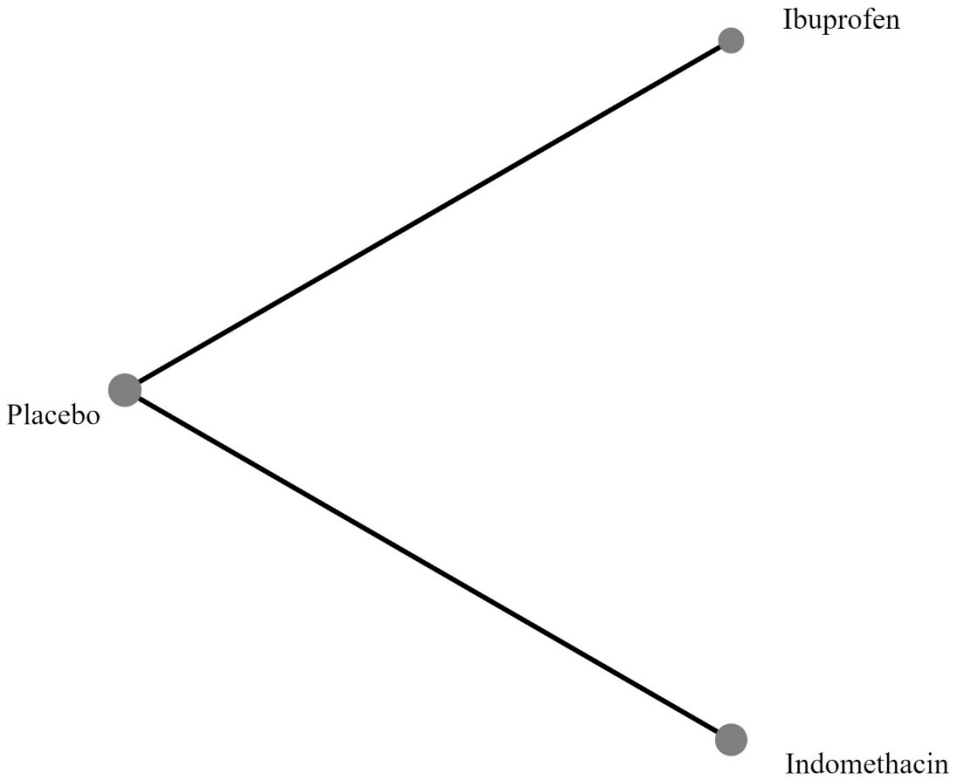


Figure 37 ***Forest plot of pairwise meta-analysis between indomethacin and placebo (conducted using Bayesian random-effects model) for gastrointestinal perforation***

A RR<1 favors the intervention. CrI, Credible intervals

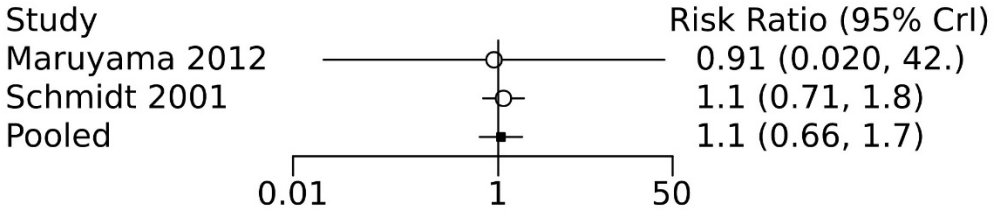


Figure 38 ***Forest plot of pairwise meta-analysis between ibuprofen and placebo (conducted using Bayesian random-effects model) for gastrointestinal perforation***

A RR<1 favors the intervention. CrI, Credible intervals

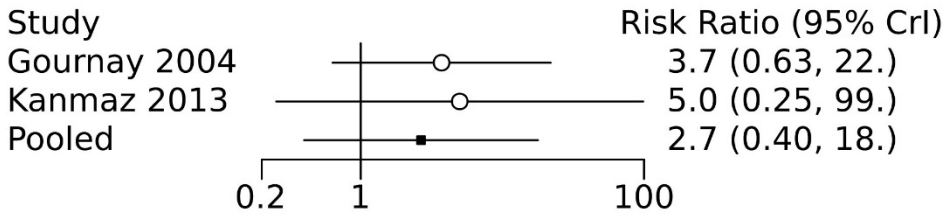


Figure 39 ***Forest plot of the relative network effect estimates with placebo as the comparator (conducted using Bayesian random-effects model) for gastrointestinal perforation***

A RR<1 favors the intervention. CrI, Credible intervals

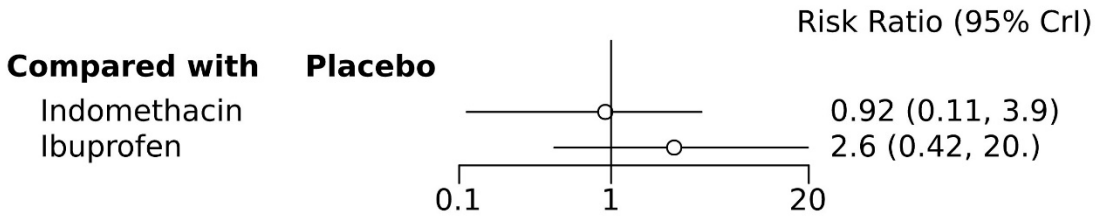


Figure 40 ***Ranking probability (rankogram) of each treatment modality for gastrointestinal perforation***

Each rank is represented by a color. The height of each colored bar corresponds to the probability of an intervention being ranked in that specific ranking position

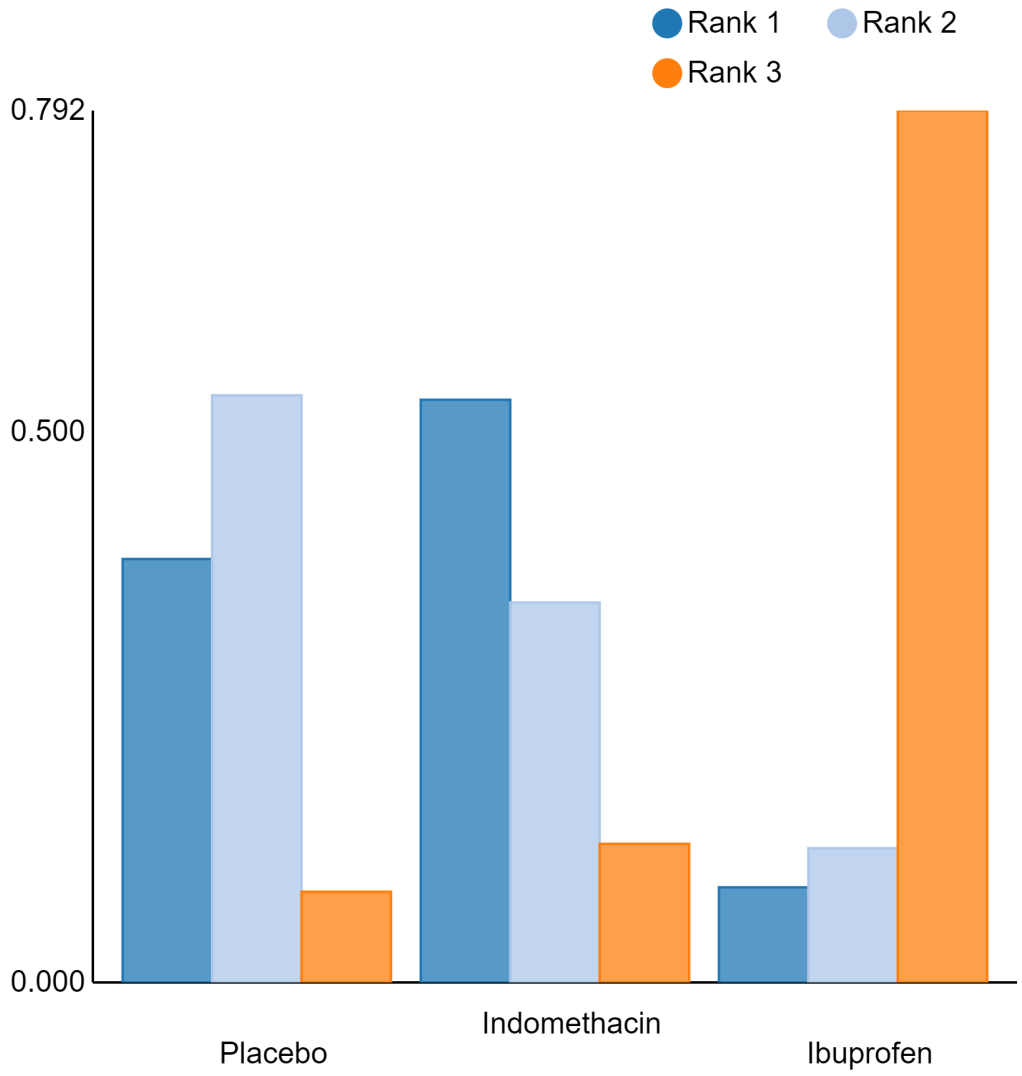


Figure 41 ***Network plot for chronic lung disease***

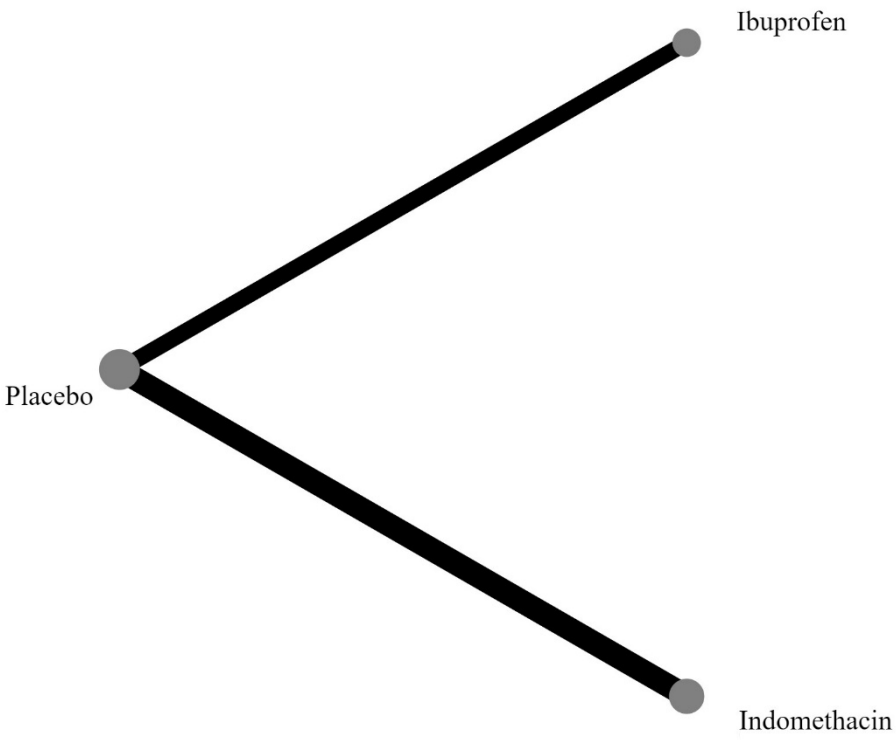


Figure 42 ***Forest plot of pairwise meta-analysis between indomethacin and placebo (conducted using Bayesian random-effects model) for chronic lung disease***

A RR<1 favors the intervention. CrI, Credible intervals

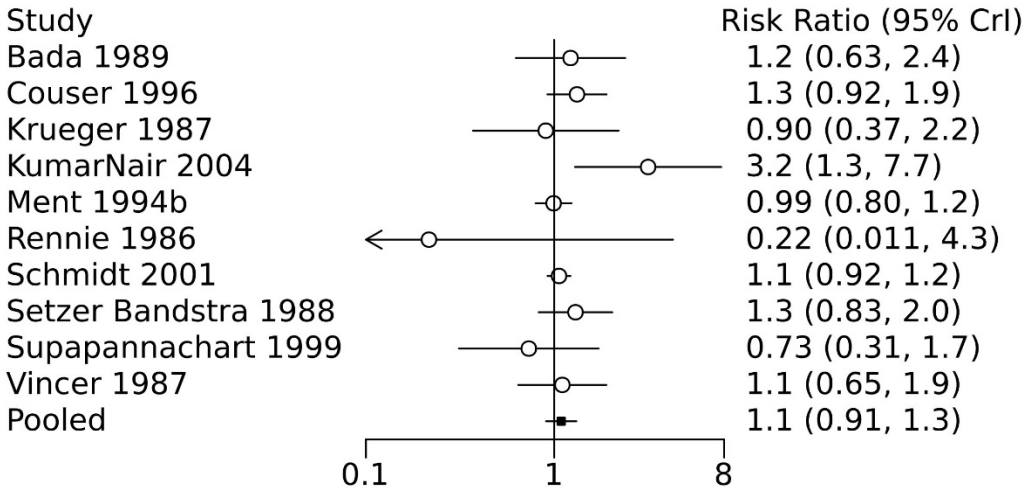


Figure 43 ***Forest plot of pairwise meta-analysis between ibuprofen and placebo (conducted using Bayesian random-effects model) for chronic lung disease***

A RR<1 favors the intervention. CrI, Credible intervals

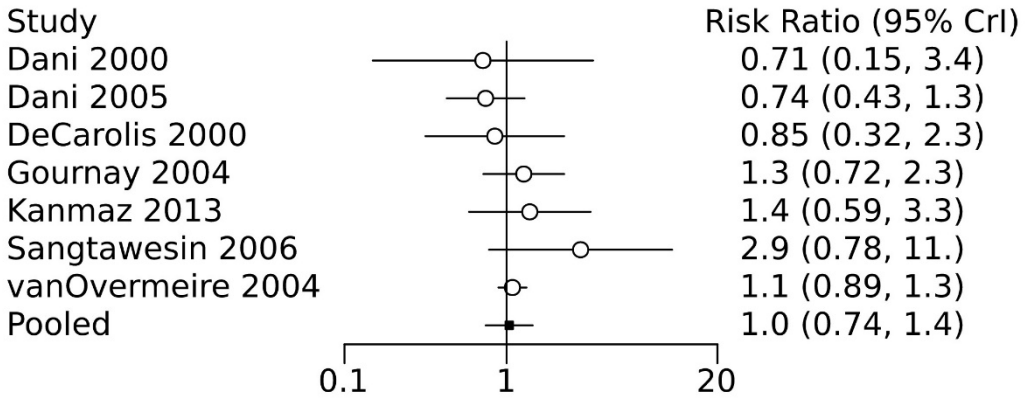


Figure 44 ***Forest plot of the relative network effect estimates with placebo as the comparator (conducted using Bayesian random-effects model) for chronic lung disease***

A RR<1 favors the intervention. CrI, Credible intervals

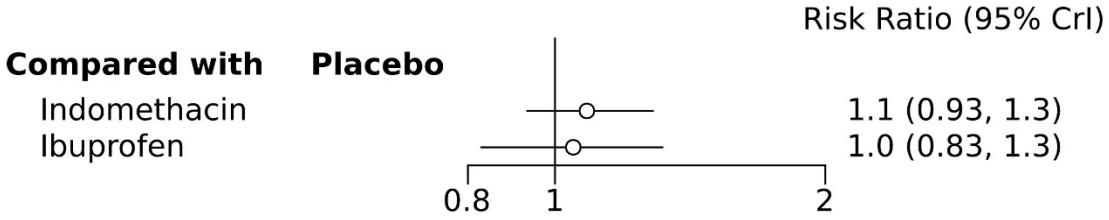


Figure 45 ***Comparison-adjusted funnel plot for chronic lung disease***

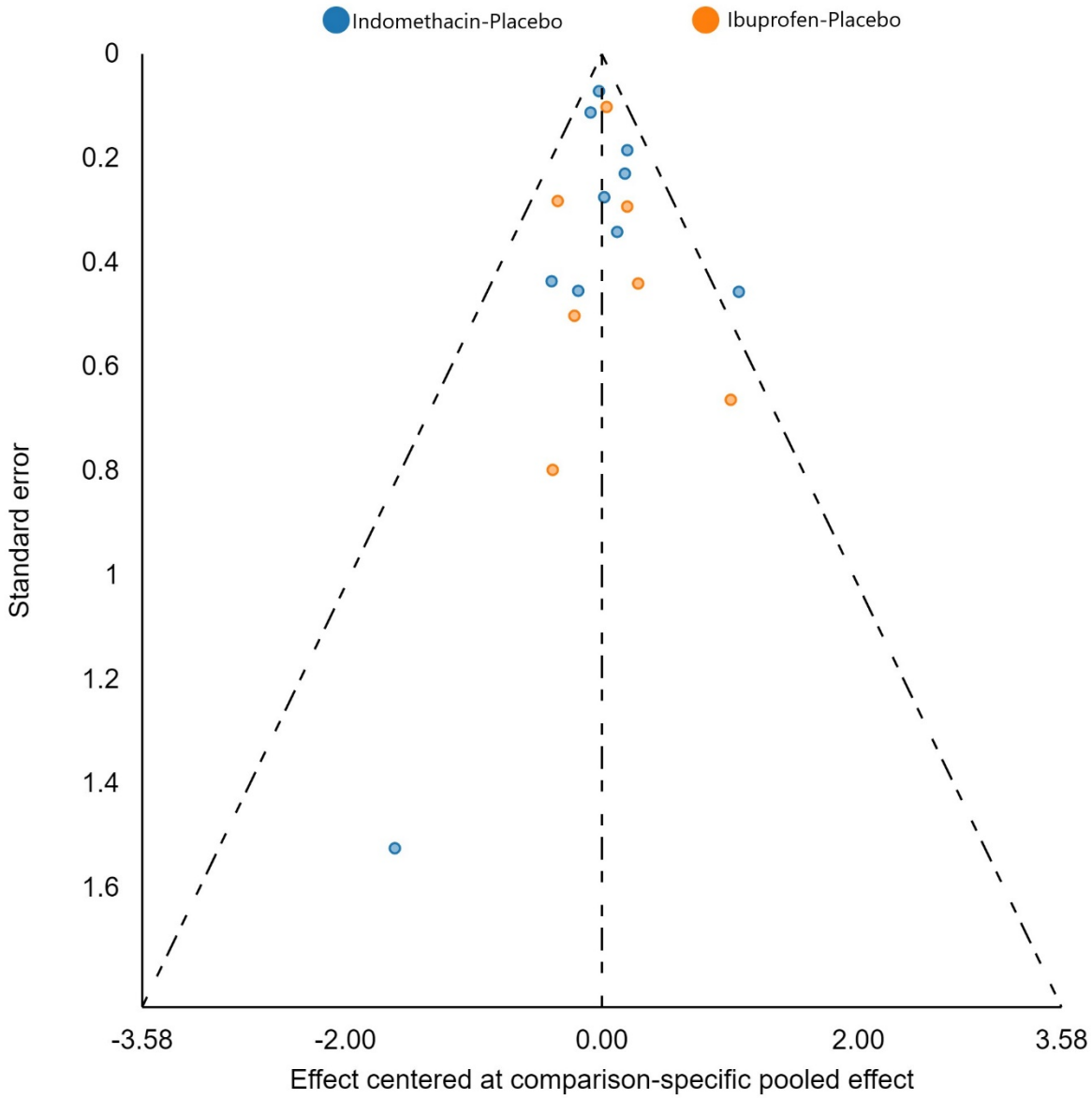


Figure 46 ***Ranking probability (rankogram) of each treatment modality for chronic lung disease***

Each rank is represented by a color. The height of each colored bar corresponds to the probability of an intervention being ranked in that specific ranking position

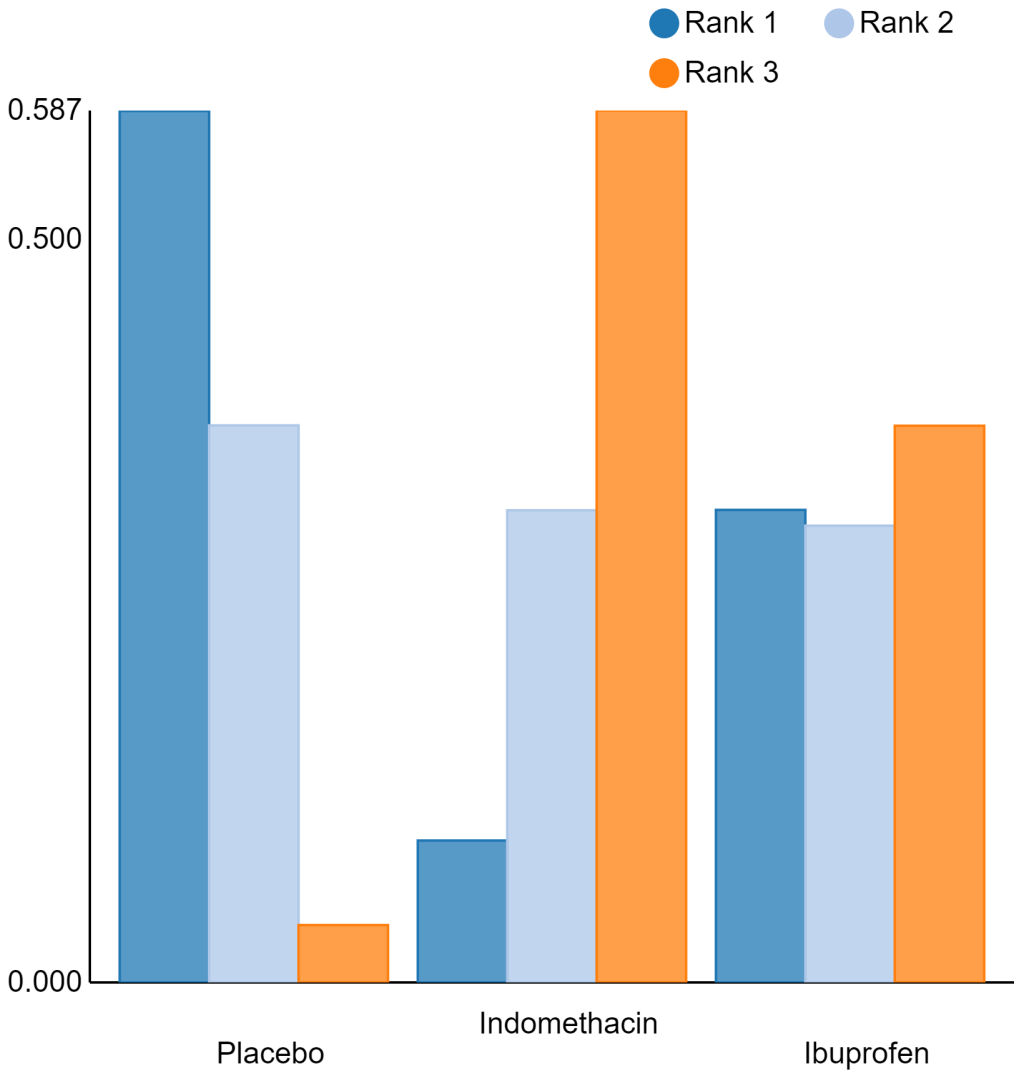


Figure 47 ***Network plot for oliguria***

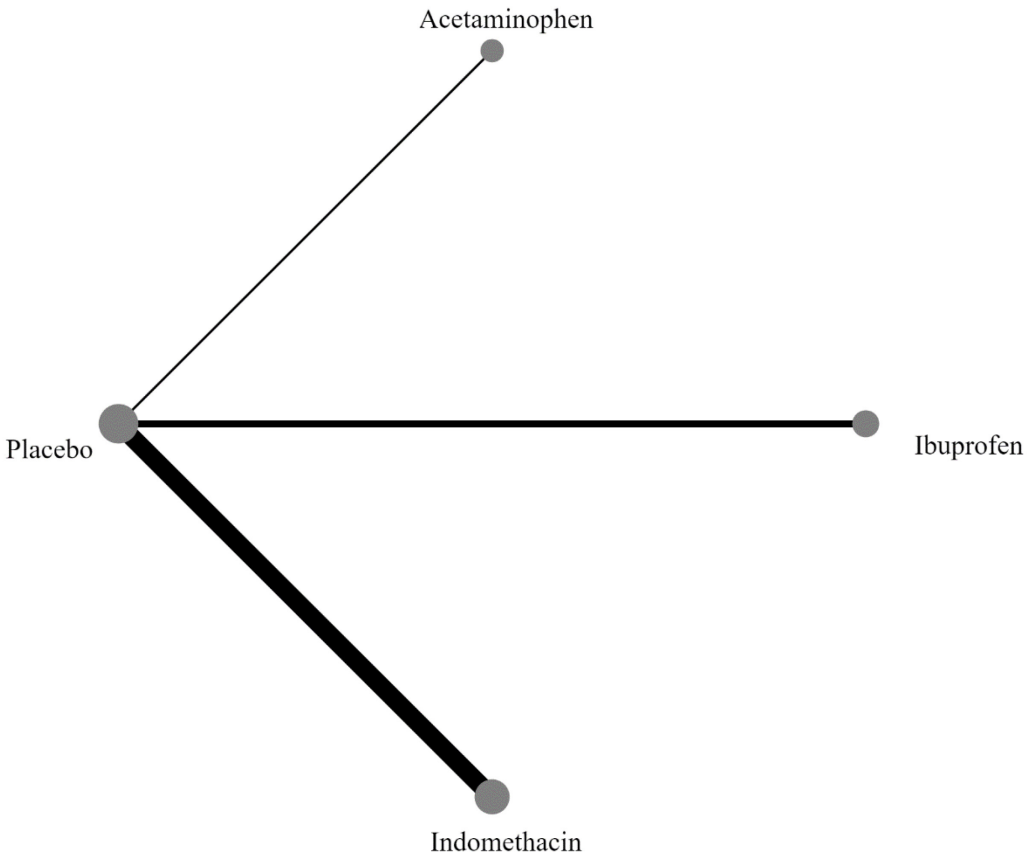


Figure 48 ***Forest plot of pairwise meta-analysis between indomethacin and placebo (conducted using Bayesian random-effects model) for oliguria***

A RR<1 favors the intervention. CrI, Credible intervals

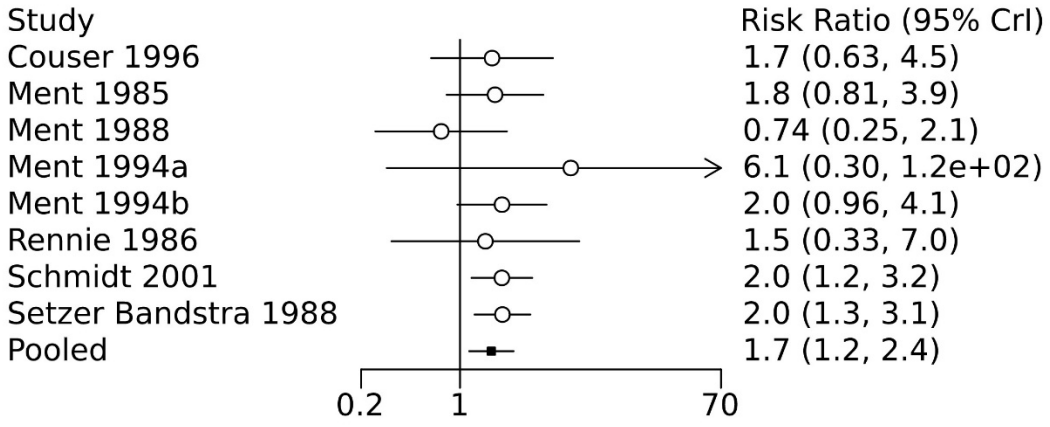


Figure 49 ***Forest plot of pairwise meta-analysis between ibuprofen and placebo (conducted using Bayesian random-effects model) for oliguria***

A RR<1 favors the intervention. CrI, Credible intervals

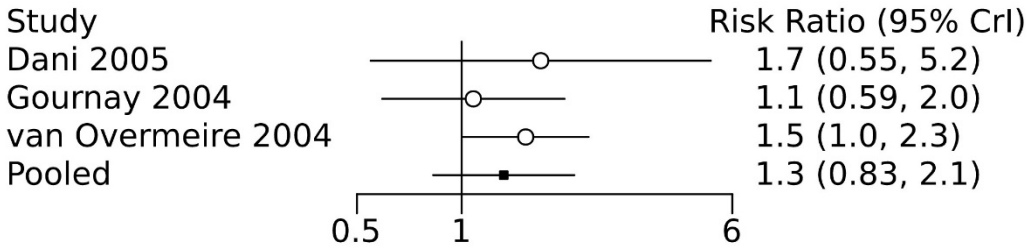


Figure 50 ***Forest plot of the relative network effect estimates with placebo as the comparator (conducted using Bayesian random-effects model) for oliguria***

A RR<1 favors the intervention. CrI, Credible intervals

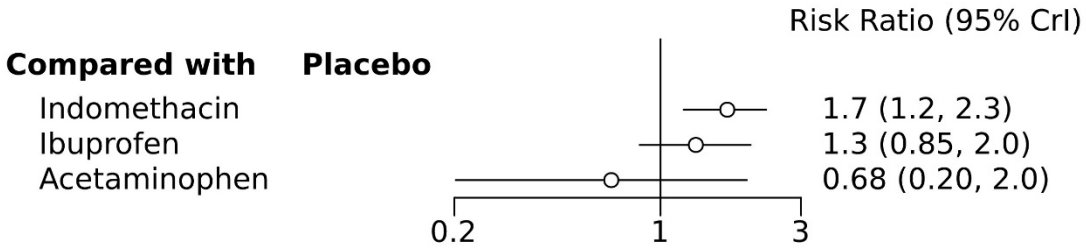


Figure 51 ***Comparison-adjusted funnel plot for oliguria***

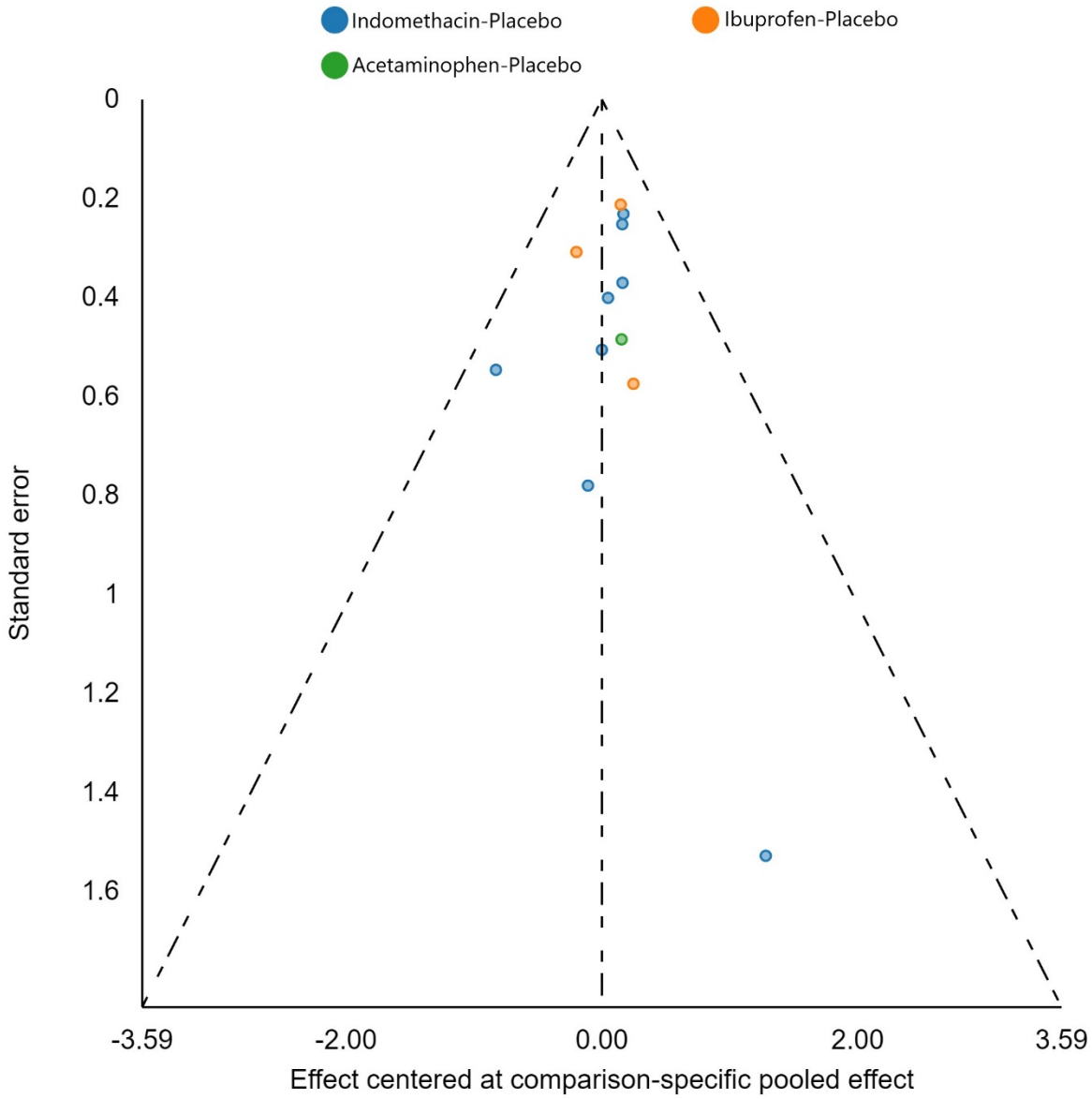


Figure 52 ***Ranking probability (rankogram) of each treatment modality for oliguria***
Each rank is represented by a color. The height of each colored bar corresponds to the probability of an intervention being ranked in that specific ranking position

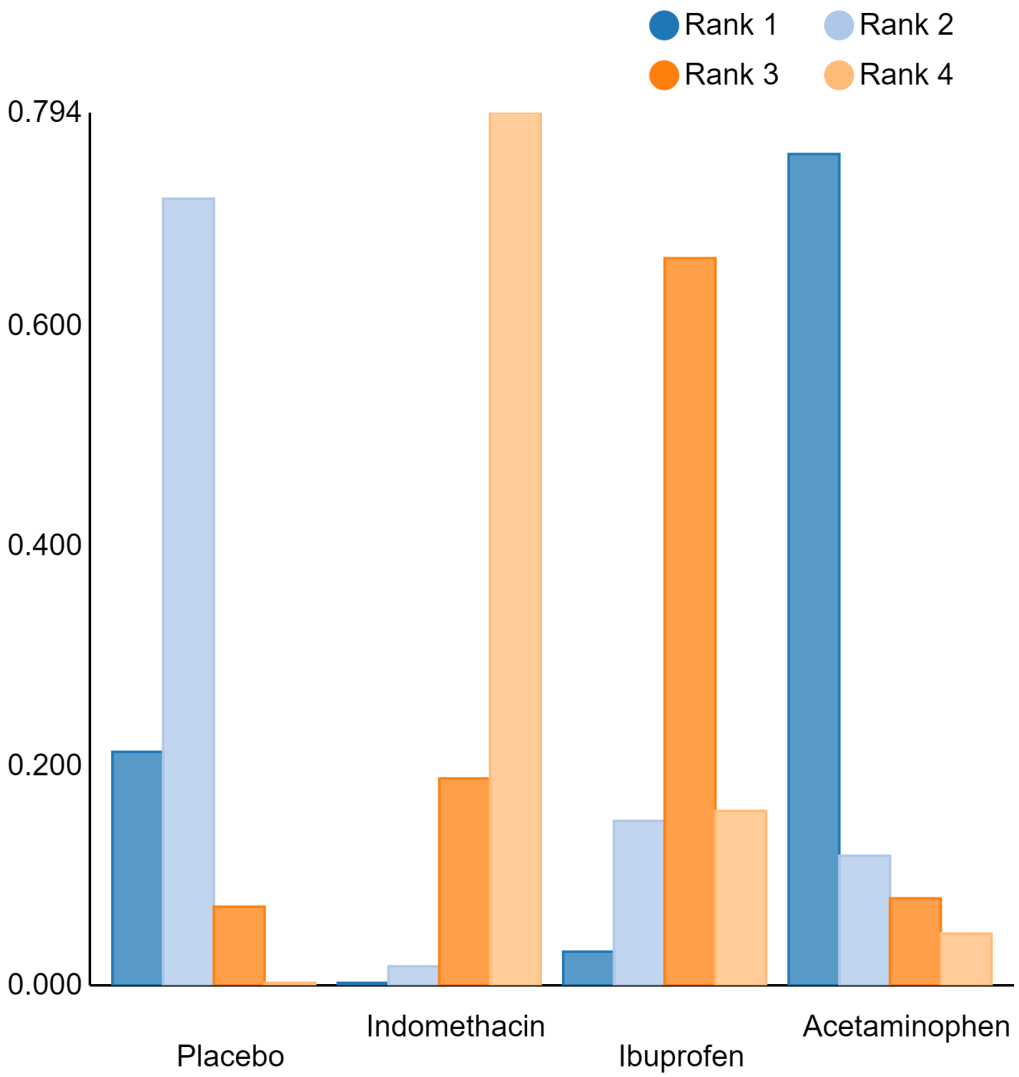


Figure 53 ***Network plot for intraventricular hemorrhage (any grade)***

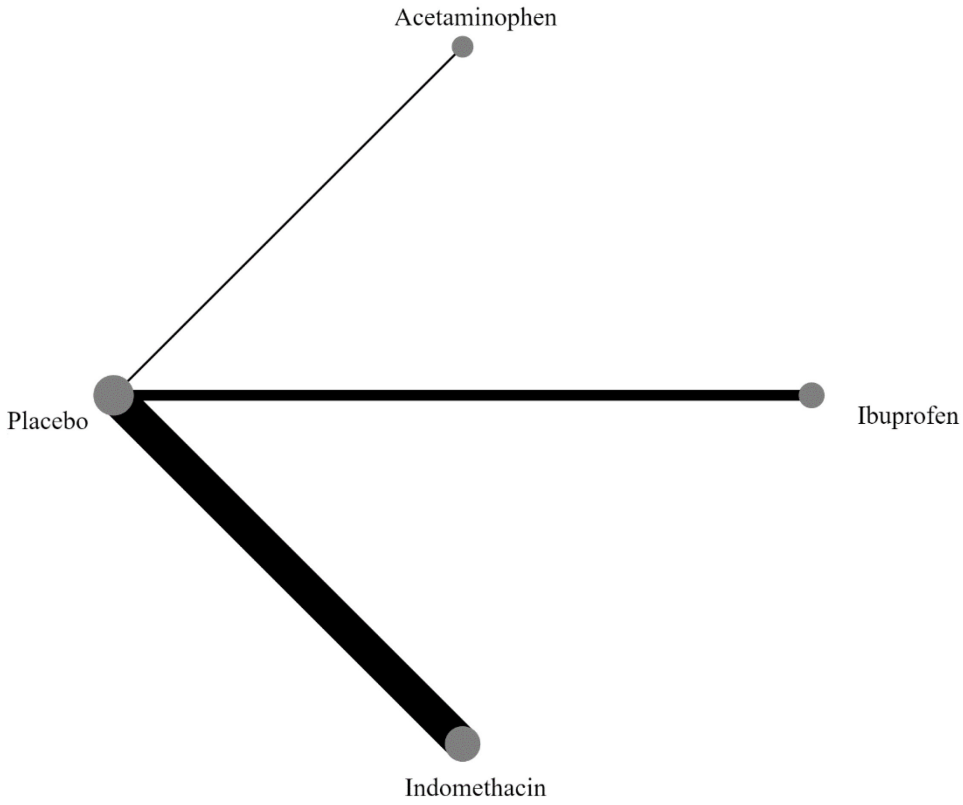


Figure 54 ***Forest plot of pairwise meta-analysis between indomethacin and placebo (conducted using Bayesian random-effects model) for intraventricular hemorrhage (any grade)***

A RR<1 favors the intervention. CrI, Credible intervals

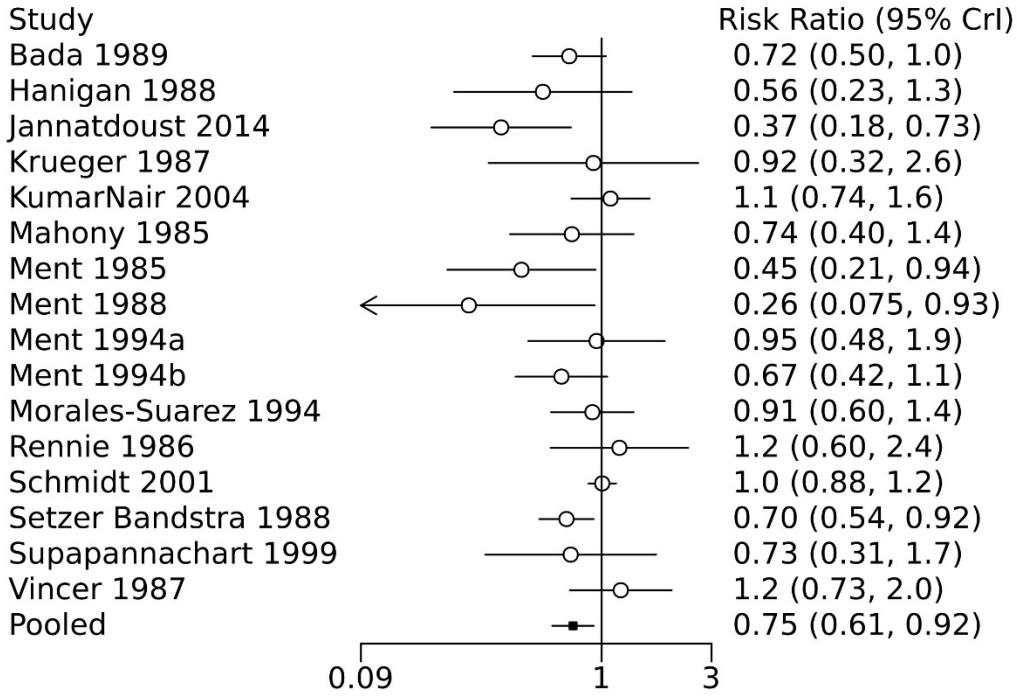


Figure 55 ***Forest plot of pairwise meta-analysis between ibuprofen and placebo (conducted using Bayesian random-effects model) for intraventricular hemorrhage (any grade)***

A RR<1 favors the intervention. CrI, Credible intervals

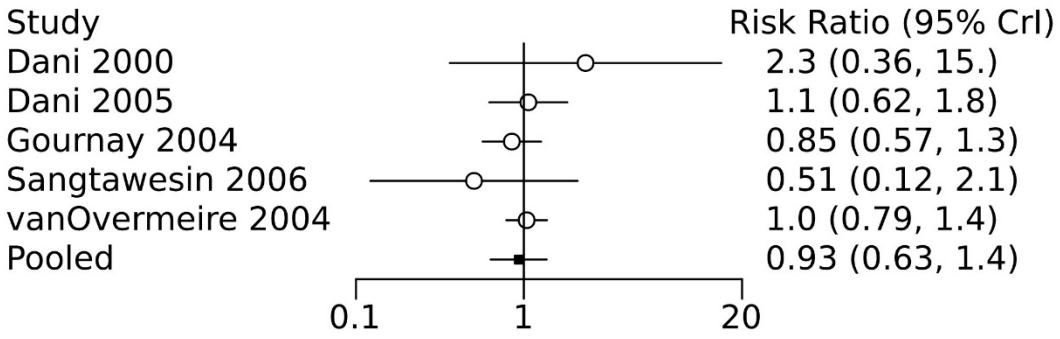


Figure 56 ***Forest plot of the relative network effect estimates with placebo as the comparator (conducted using Bayesian random-effects model) for intraventricular hemorrhage (any grade)***

A RR<1 favors the intervention. CrI, Credible intervals

Figure 57 ***Comparison-adjusted funnel plot for intraventricular hemorrhage (any grade)***

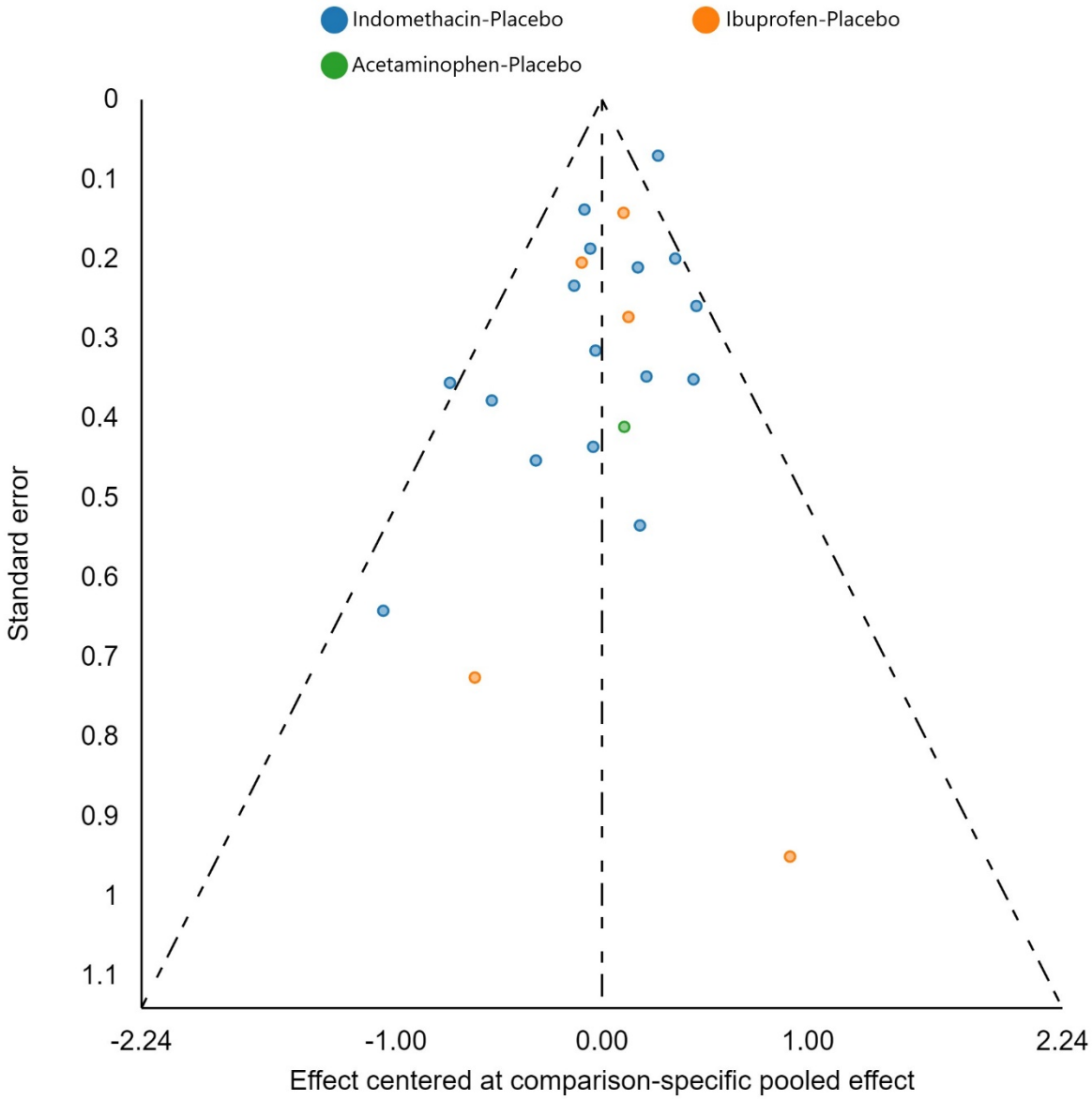


Figure 58 ***Ranking probability (rankogram) of each treatment modality for intraventricular hemorrhage (any grade)***

Each rank is represented by a color. The height of each colored bar corresponds to the probability of an intervention being ranked in that specific ranking position

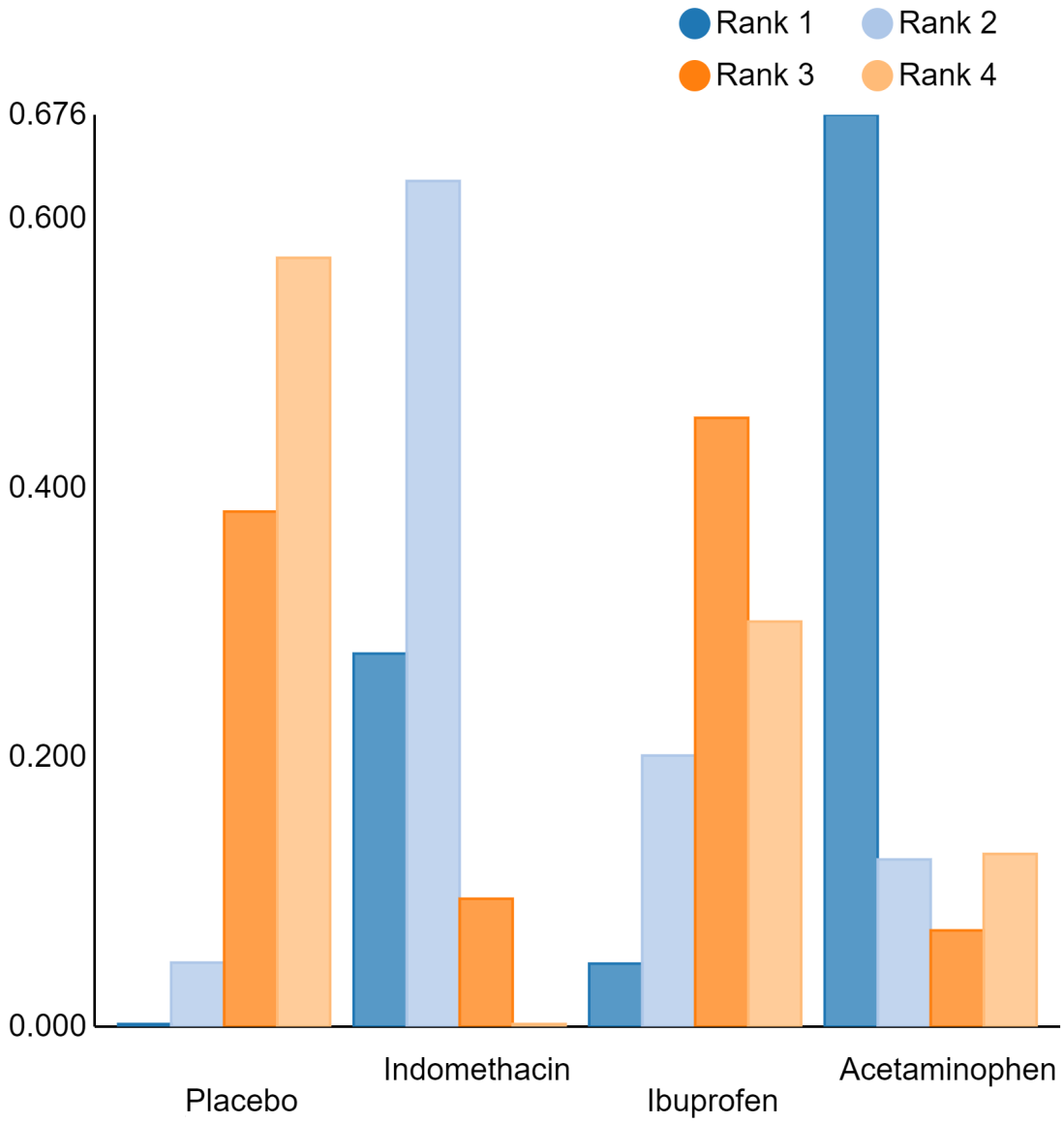


Figure 59 *Network plot for periventricular leukomalacia*

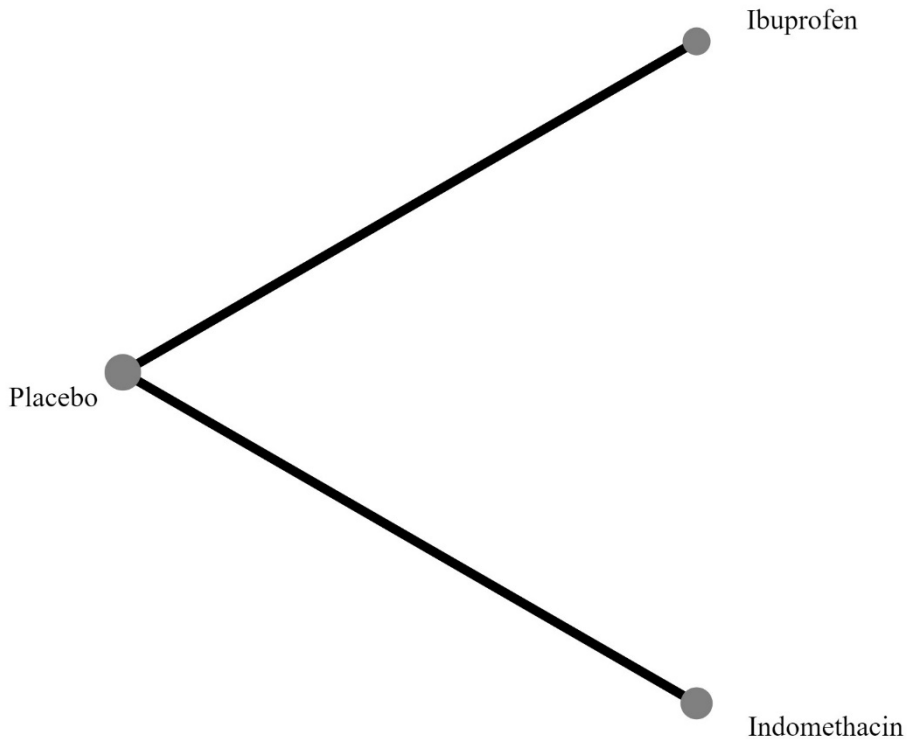


Figure 60 ***Forest plot of pairwise meta-analysis between indomethacin and placebo (conducted using Bayesian random-effects model) for periventricular leukomalacia***

A RR<1 favors the intervention. CrI, Credible intervals

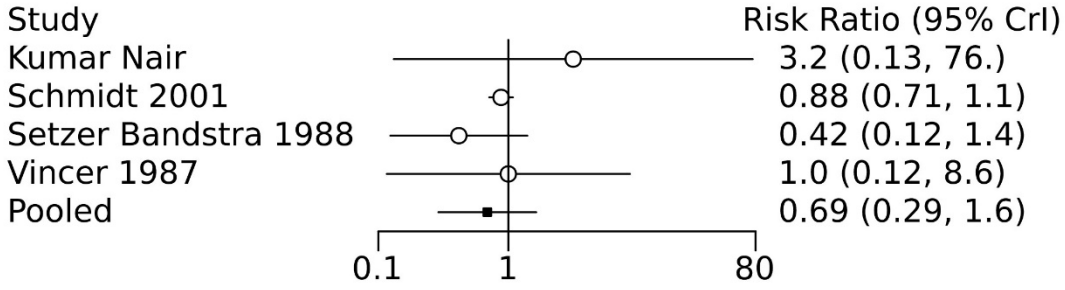


Figure 61 ***Forest plot of pairwise meta-analysis between ibuprofen and placebo (conducted using Bayesian random-effects model) for periventricular leukomalacia***

A RR<1 favors the intervention. CrI, Credible intervals

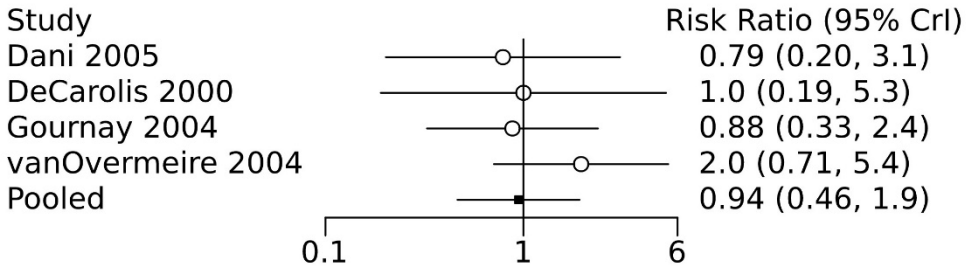


Figure 62 ***Forest plot of the relative network effect estimates with placebo as the comparator (conducted using Bayesian random-effects model) for periventricular leukomalacia***

A RR<1 favors the intervention. CrI, Credible intervals

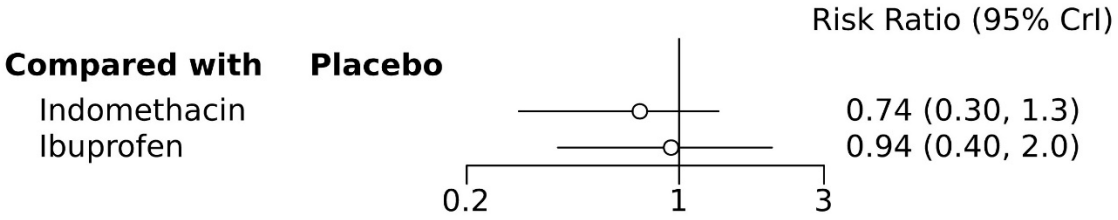


Figure 63 ***Ranking probability (rankogram) of each treatment modality for periventricular leukomalacia***

Each rank is represented by a color. The height of each colored bar corresponds to the probability of an intervention being ranked in that specific ranking position

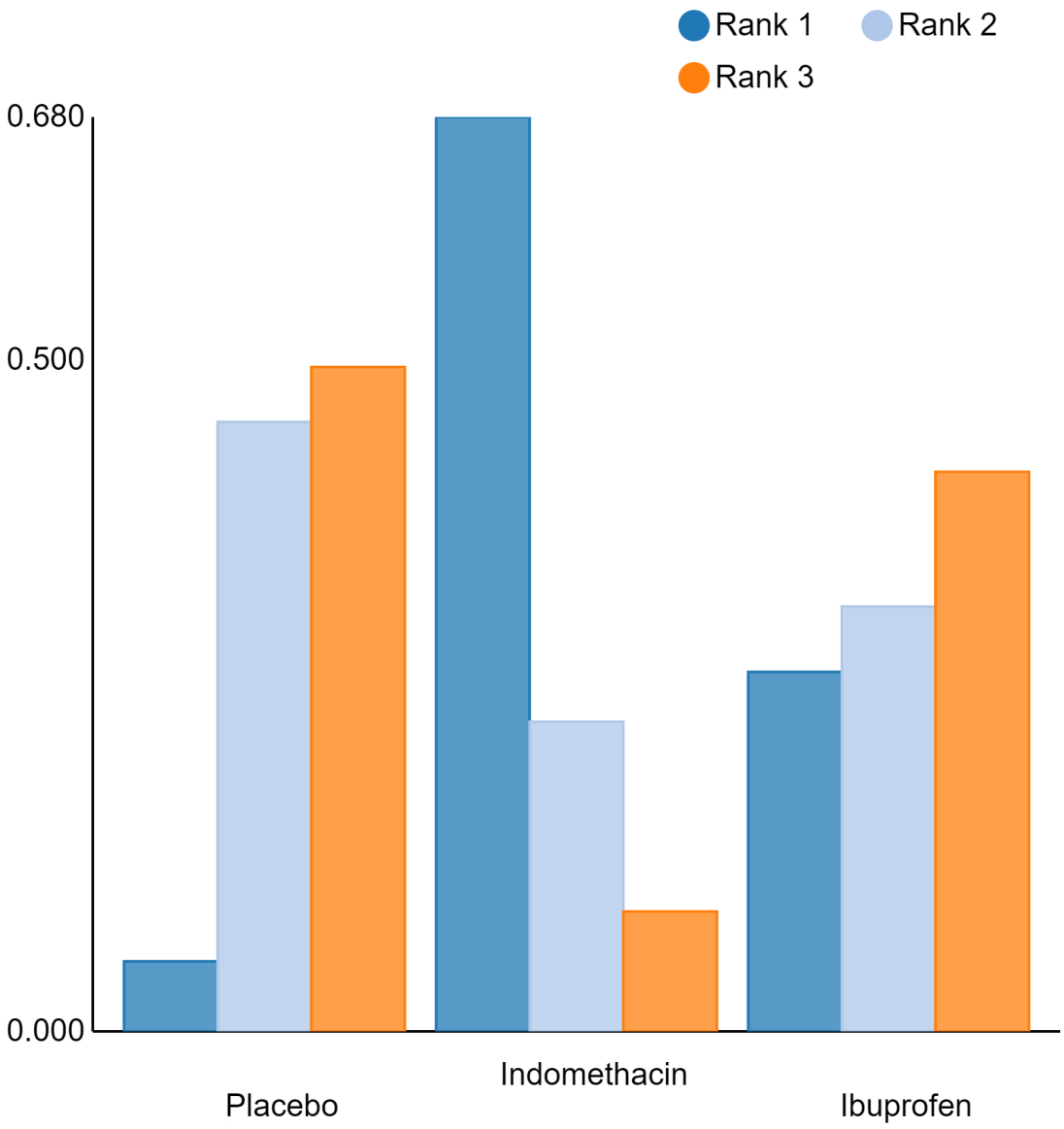


Figure 64 ***Network plot for cerebral palsy***

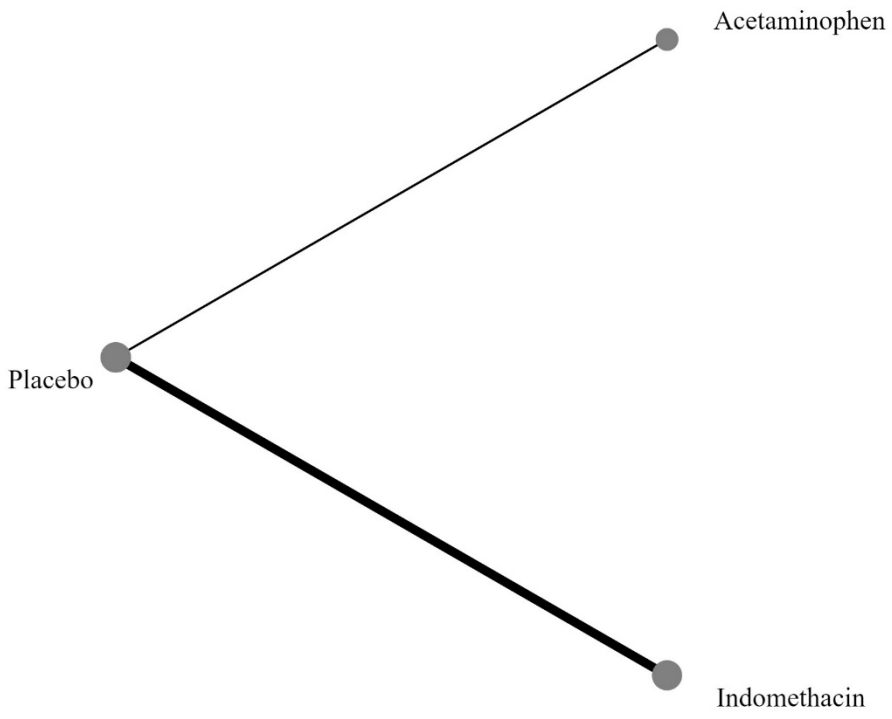


Figure 65 ***Forest plot of pairwise meta-analysis between indomethacin and placebo (conducted using Bayesian random-effects model) for cerebral palsy***

A RR<1 favors the intervention. CrI, Credible intervals

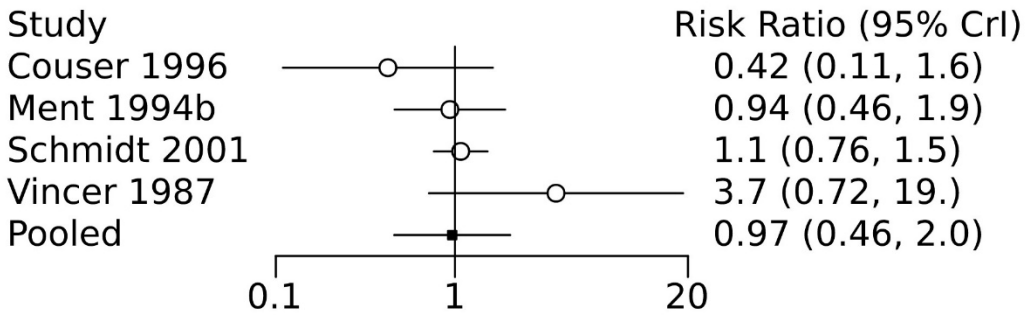


Figure 66 ***Forest plot of the relative network effect estimates with placebo as the comparator (conducted using Bayesian random-effects model) for cerebral palsy***

A RR<1 favors the intervention. CrI, Credible intervals

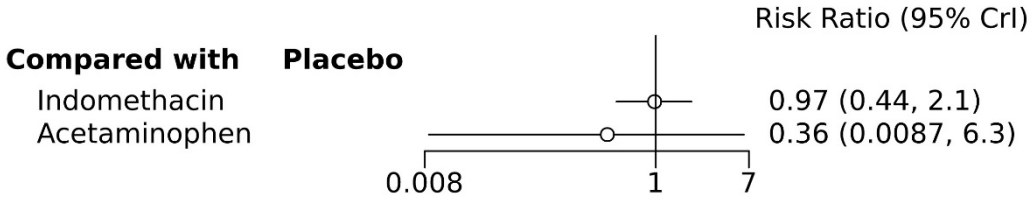
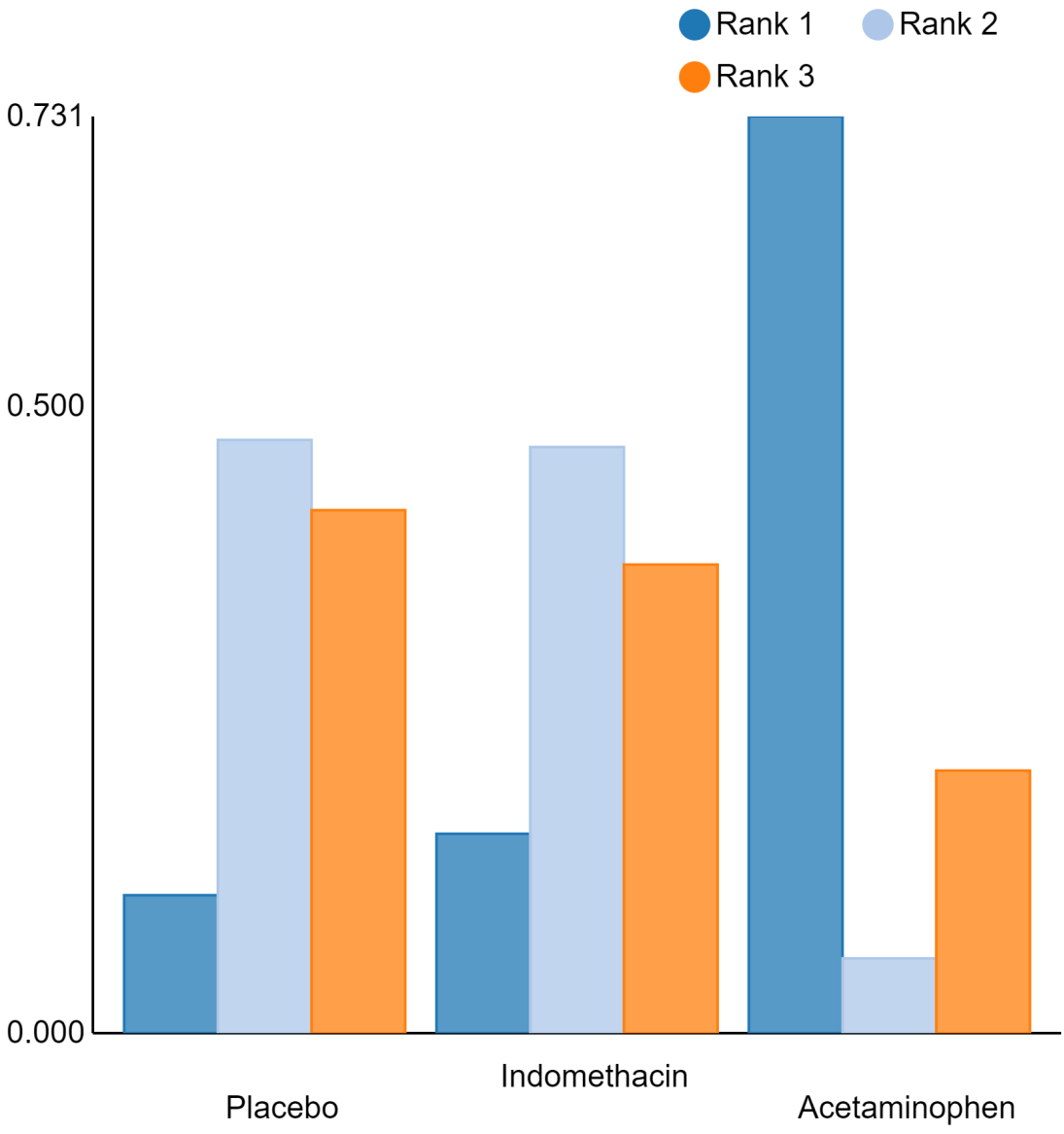


Figure 67 ***Ranking probability (rankogram) of each treatment modality for cerebral palsy***

Each rank is represented by a color. The height of each colored bar corresponds to the probability of an intervention being ranked in that specific ranking position



References

1. Santesso N, Glenton C, Dahm P, Garner P, Akl EA, Alper B, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. Journal of Clinical Epidemiology. 2020;119:126–35.

2. Clyman RI, Couto J, Murphy GM. Patent ductus arteriosus: are current neonatal treatment options better or worse than no treatment at all? Semin Perinatol. 2012 Apr;36(2):123–9.

3. The Canadian Neonatal Network™ [Internet]. [cited 2019 Dec 4]. Available from: http://www.canadianneonatalnetwork.org/portal/CNNHome.aspx

4. Gournay V. The ductus arteriosus: physiology, regulation, and functional and congenital anomalies. Arch Cardiovasc Dis. 2011 Nov;104(11):578–85.

5. Benitz WE, Committee on Fetus and Newborn, American Academy of Pediatrics. Patent Ductus Arteriosus in Preterm Infants. Pediatrics. 2016 Jan;137(1).

6. Ballabh P. Intraventricular hemorrhage in premature infants: mechanism of disease. Pediatr Res. 2010 Jan;67(1):1–8.

7. Brown ER. Increased risk of bronchopulmonary dysplasia in infants with patent ductus arteriosus. J Pediatr. 1979 Nov;95(5 Pt 2):865–6.

8. Chung MY, Fang PC, Chung CH, Huang CB, Ou Yang MH, Chen CC. Risk factors for hemodynamically-unrelated cystic periventricular leukomalacia in very low birth weight premature infants. J Formos Med Assoc. 2005 Aug;104(8):571–7.

9. Dice JE, Bhatia J. Patent Ductus Arteriosus: An Overview. J Pediatr Pharmacol Ther. 2007;12(3):138–46.

10. Dollberg S, Lusky A, Reichman B. Patent ductus arteriosus, indomethacin and necrotizing enterocolitis in very low birth weight infants: a population-based study. J Pediatr Gastroenterol Nutr. 2005 Feb;40(2):184–8.

11. Drougia A, Giapros V, Krallis N, Theocharis P, Nikaki A, Tzoufi M, et al. Incidence and risk factors for cerebral palsy in infants with perinatal problems: a 15-year review. Early Hum Dev. 2007 Aug;83(8):541–7.

12. Mitra S, Florez ID, Tamayo ME, Mbuagbaw L, Vanniyasingam T, Veroniki AA, et al. Association of Placebo, Indomethacin, Ibuprofen, and Acetaminophen With Closure of Hemodynamically Significant Patent Ductus Arteriosus in Preterm Infants. JAMA. 2018 Mar 27;319(12):1221–38.

13. Jain A, Shah PS. Diagnosis, Evaluation, and Management of Patent Ductus Arteriosus in Preterm Neonates. JAMA Pediatr. 2015 Sep;169(9):863–72.

14. Le J, Gales MA, Gales BJ. Acetaminophen for patent ductus arteriosus. Annals of Pharmacotherapy. 2015;49(2):241–6.

15. Grèen K, Drvota V, Vesterqvist O. Pronounced reduction of in vivo prostacyclin synthesis in humans by acetaminophen (paracetamol). Prostaglandins. 1989;37(3):311–5.

16. Seyberth HW, Rascher W, Hackenthal R, Wille L. Effect of prolonged indomethacin therapy on renal function and selected vasoactive hormones in very-low-birth-weight infants with symptomatic patent ductus arteriosus. J Pediatr. 1983 Dec;103(6):979–84.

17. Coombs RC, Morgan ME, Durbin GM, Booth IW, McNeish AS. Gut blood flow velocities in the newborn: effects of patent ductus arteriosus and parenteral indomethacin. Arch Dis Child. 1991 Oct;66(10):1261.

18. Wolf WM, Snover DC, Leonard AS. Localized intestinal perforation following intravenous indomethacin in premature infants. J Pediatr Surg. 1989 Apr;24(4):409–10.

19. Friedman WF, Hirschklau MJ, Printz MP, Pitlick PT, Kirkpatrick SE. Pharmacologic closure of patent ductus arteriosus in the premature infant. N Engl J Med. 1976 Sep 2;295(10):526–9.

20. Ohlsson A, Bottu J, Govan J, Ryan ML, Fong K, Myhr T. Effect of indomethacin on cerebral blood flow velocities in very low birth weight neonates with a patent ductus arteriosus. Dev Pharmacol Ther. 1993;20(1–2):100–6.

21. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. Cochrane Database Syst Rev. 2020 11;2:CD003481.

22. Bauer AZ, Kriebel D. Prenatal and perinatal analgesic exposure and autism: an ecological link. Environ Health. 2013 May 9;12:41.

23. Ji Y, Azuine RE, Zhang Y, Hou W, Hong X, Wang G, et al. Association of cord plasma biomarkers of In utero acetaminophen exposure with risk of attention-deficit/hyperactivity disorder and autism spectrum disorder in childhood. JAMA Psychiatry. 2020;77(2):180–9.

24. Ystrom E, Gustavson K, Brandlistuen RE, Knudsen GP, Magnus P, Susser E, et al. Prenatal exposure to acetaminophen and risk of ADHD. Pediatrics. 2017;140(5):e20163840–e20163840.

25. Ohlsson A, Shah PS. Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants. Cochrane Database Syst Rev. 2020 27;1:CD010061.

26. Ment LR, Stewart WB, Ardito TA, Huang E, Madri JA. Indomethacin promotes germinal matrix microvessel maturation in the newborn beagle pup. Stroke. 1992;23(8):1132–7.

27. Fowlie PW, Davis PG, McGuire W. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. Cochrane Database Syst Rev. 2010 Jul 7;(7):CD000174.

28. Ohlsson A, Shah SS. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database of Systematic Reviews. 2020;(1).

29. Härmä A, Aikio O, Härkin P, Leskinen M, Valkama M, Saarela T, et al. Subgroup analysis of the early paracetamol trial to preterm infants found hemodynamic changes and improved oxygenation. Early Human Development. 2020;145:105042–105042.

30. Harkin P, Harma A, Aikio O, Valkama M, Leskinen M, Saarela T, et al. Paracetamol accelerates closure of the ductus arteriosus after premature birth: a randomized trial. Journal of Pediatrics. 2016;177:72-7.e2.

31. Bisaglia M, Venezia V, Piccioli P, Stanzione S, Porcile C, Russo C, et al. Acetaminophen protects hippocampal neurons and PC12 cultures from amyloid beta-peptides induced oxidative stress and reduces NF-kappaB activation. Neurochemistry International. 2002;41(1):43–54.

32. Vergeade A, Bertram CC, Bikineyeva AT, Zackert WE, Zinkel SS, May JM, et al. Cardiolipin fatty acid remodeling regulates mitochondrial function by modifying the electron entry point in the respiratory chain. Mitochondrion. 2016;28:88–95.

33. Baik N, Urlesberger B, Schwaberger B, Schmölzer GM, Avian A, Pichler G. Cerebral haemorrhage in preterm neonates: does cerebral regional oxygen saturation during the immediate transition matter? Archives of Disease in Childhood: Fetal and Neonatal Edition. 2015;100(5):F422–7.

34. Cimatti AG, Martini S, Galletti S, Vitali F, Aceti A, Frabboni G, et al. Cerebral Oxygenation and Autoregulation in Very Preterm Infants Developing IVH During the Transitional Period: A Pilot Study. Front Pediatr [Internet]. 2020 Jul 15 [cited 2020 Oct 21];8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7373744/

35. Reese J, Shelton EL, Slaughter JC, McNamara PJ. Prophylactic Indomethacin Revisited. J Pediatr. 2017 Jul;186:11-14.e1.

36. Stavel M, Wong J, Cieslak Z, Sherlock R, Claveau M, Shah PS. Effect of prophylactic indomethacin administration and early feeding on spontaneous intestinal perforation in extremely low-birth-weight infants. J Perinatol. 2017;37(2):188–93.

37. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr. 1978 Apr;92(4):529–34.

38. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg. 1978 Jan;187(1):1–7.

39. Meyer CL, Payne NR, Roback SA. Spontaneous, isolated intestinal perforations in neonates with birth weight less than 1,000 g not associated with necrotizing enterocolitis. J Pediatr Surg. 1991 Jun;26(6):714–7.

40. Pumberger W, Mayr M, Kohlhauser C, Weninger M. Spontaneous localized intestinal perforation in very-low-birth-weight infants: a distinct clinical entity different from necrotizing enterocolitis. J Am Coll Surg. 2002 Dec;195(6):796–803.

41. Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA, et al. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics. 2005;116(6):1353–60.

42. de Vries LS, Eken P, Dubowitz LM. The spectrum of leukomalacia using cranial ultrasound. Behavioural Brain Research. 1992;49(1):1–6.

43. Steiner S. Bayley Scales of Infant Development. San Antonio, TX: The Psychological Corporation; 1993.

44. Bayley N. Bayley Scales of Infant and Toddler Development. San Antonio, TX: The Psychological Corporation; 2005.

45. Griffiths R. The Abilities of Babies: a Study of Mental Measurement. London: University of London Press; 1954.

46. Griffiths R. The Abilities of Young Children: a Comprehensive System of Mental Measurement for the First Eight Years. London: Child Development Research Center; 1970.

47. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database of Systematic Reviews. 2013;(1).

48. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA G r. o. u. p. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Journal of Clinical Epidemiology. 2009;62(10):1006–12.

49. van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades AE, Welton NJ. Automating network meta-analysis. Res Synth Methods. 2012 Dec;3(4):285–99.

50. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane Handbook for Systematic Reviews of Interventions. 2nd Edition. Chichester (UK): John Wiley & Sons; 2019.

51. Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 2011 Feb;64(2):163–71.

52. Costantini I, Paul E, Caldwell DM, López-López JA, Pearson RM. Protocol for a systematic review and network meta-analysis of randomized controlled trials examining the effectiveness of early parenting interventions in preventing internalising problems in children and adolescents. Systematic Reviews. 2020;9(1):244–244.

53. Baker SG, Kramer BS. The transitive fallacy for randomized trials: if A bests B and B bests C in separate trials, is A better than C? BMC Medical Research Methodology. 2002;2:13–13.

54. Cipriani A, Higgins JPT, Geddes JR, Salanti G. Conceptual and technical challenges in network meta-analysis. Ann Intern Med. 2013 Jul 16;159(2):130–7.

55. Donegan S, Williamson P, Gamble C, Tudur-Smith C. Indirect comparisons: a review of reporting and methodological quality. PLOS One. 2010;5(11):e11054–e11054.

56. White IR, Barrett JK, Jackson D, Higgins JPT. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. Res Synth Methods. 2012 Jun;3(2):111–25.

57. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Stat Med. 2010 Mar 30;29(7–8):932–44.

58. Veroniki AA, Vasiliadis HS, Higgins JPT, Salanti G. Evaluation of inconsistency in networks of interventions. Int J Epidemiol. 2013 Feb;42(1):332–45.

59. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Medical Decision Making: an International Journal of the Society for Medical Decision Making. 2013;33(5):607–17.

60. Lambert PC, Sutton AJ, Burton PR, Abrams KR, Jones DR. How vague is vague? A simulation study of the impact of the use of vague prior distributions in MCMC using WinBUGS. Statistics in Medicine. 2005;24(15):2401–28.

61. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med. 2004 Oct 30;23(20):3105–24.

62. Gelman A, Rubin DB. Inference from Iterative Simulation Using Multiple Sequences. Statist Sci. 1992 Nov;7(4):457–72.

63. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2020.

64. Owen RK, Bradbury N, Xin Y, Cooper N, Sutton A. MetaInsight: an interactive web-based tool for analyzing, interrogating, and visualizing network meta-analyses using R-shiny and netmeta. Research Synthesis Methods. 2019;10(4):569–81.

65. Palmer T, Sterne J, editors. Meta-Analysis in Stata. In: An Updated Collection From the Stata Journal. College Station (TX): Stata Press; 2016.

66. Brignardello-Petersen R, Bonner A, Alexander PE, Siemieniuk RA, Furukawa TA, Rochwerg B, et al. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. Journal of Clinical Epidemiology. 2018;93:36–44.

67. Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ. 2014 Sep 24;349:g5630.

68. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008 Apr 26;336(7650):924–6.

69. Schünemann H, Brozek J, Guyatt G, Oxman A, editors. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. Available from gdt.guidelinedevelopment.org/app/handbook/handbook.html.

70. Yepes-Nuñez JJ, Li SA, Guyatt G, Jack SM, Brozek JL, Beyene J, et al. Development of the summary of findings table for network meta-analysis. J Clin Epidemiol. 2019 Nov;115:1–13.

71. Seok EJ, Kim EJ, Jeon SS, Seo SS. Effect of indomethacin therapy on prevention of intraventricular hemorrhage in very low birth weight infant. Journal of the Korean Society of Neonatal Science. 1998;5(1):27–34.

72. Akbari Asbagh P, Zarkesh MR, Nili F, Nayeri FS, Tofighi Naeem A. Prophylactic teatment with oral paracetamol for patent ductus arteriosus in preterm infants: a randomized clinical trial. Tehran University Medical Journal. 2015;73(2):86–92.

73. Kalani M, Shariat M, Khalesi N, Farahani Z, Ahmadi S. A comparison of early ibuprofen and indomethacin administration to prevent intraventricular hemorrhage among preterm infants. Acta Medica Iranica. 2016;54(12):788–92.

74. Aikio O. Extremely low gestatonal age infants' paracetamol study (Paras). https://clinicaltrials.gov/ct2/show/NCT03641209 (first received 21 August 2018).

75. Rozé JC. Prophylactic treatment of the ductus arteriosus in preterm Infants by acetaminophen (TREOCAPA). https://clinicaltrials.gov/ct2/show/NCT04459117 (first received 7 July 2020)

76. Bada HS, Green RS, Pourcyrous M, Leffler CW, Korones SB, Magill HL, et al. Indomethacin reduces the risks of severe intraventricular hemorrhage. Journal of Pediatrics. 1989;115(4):631–7.

77. Couser R J, Ferrara TB, Wright GB, Cabalka AK, Schilling CG, Hoekstra RE, et al. Prophylactic indomethacin therapy in the first twenty-four hours of life for the prevention of patent ductus arteriosus in preterm infants treated prophylactically with surfactant in the delivery room. Journal of Pediatrics. 1996;128(5 Pt 1):631–7.

78. Couser RJ, Hoekstra RE, Ferrara B, Wright GB, Cabalka AK, Connet JE. Neurodevelopmental follow-up at 36months' corrected age of preterm infants treated withprophylactic indomethacin. Archives of Pediatric and Adolescent Medicine. 2000;154(6):598–602.

79. Hanigan WC, Kennedy G, Roemisch F, Anderson R, Cusack T, Powers W. Administration of indomethacin for the prevention of periventricular-intraventricular hemorrhage in high-risk neonates. Journal of Pediatrics. 1988;112(6):941–7.

80. Jannatdoust A, Samadi M, Yeganehdoust S, Heydarzadeh M, Alikhah H, Piri R, et al. Effects of intravenous indomethacin on reduction of symptomatic patent ductus arteriosus cases and decreasing the need for prolonged mechanical ventilation. Journal of Cardiovascular and Thoracic Research. 2014;6(4):257–9.

81. Krueger E, Mellander M, Bratton D, Cotton R. Prevention of symptomatic patent ductus arteriosus with a single dose of indomethacin. Journal of Pediatrics. 1987;111(5):749–54.

82. Kumar Nair PA, Pai MG, Gazal HA, Da Costa DE, Al Khusaiby SM. Indomethacin prophylaxis for intraventricular hemorrhage in very low birth weight babies. Indian Pediatrics. 2004;41(6):551–8.

83. Mahony L, Caldwell RL, Girod D A, Hurwitz RA, Jansen RD, Lemons JA, et al. Indomethacin therapy on the first day of life in infants with very low birth weight. Journal of Pediatrics. 1985;106(5):801–5.

84. Maruyama K, Fujiu T. Effects of prophylactic indomethacin on renal and intestinal blood flows in premature infants. Pediatrics International. 2012;54(4):480–5.

85. Ment L R, Duncan CC, Ehrenkranz RA, Kleinman CS, Pitt BR, Taylor KJ, et al. Randomized indomethacin trial for prevention of intraventricular hemorrhage in very low birth weight infants. Journal of Pediatrics. 1985;107(6):937–43.

86. Ment LR, Duncan CC, Ehrenkranz RA, Kleinman CS, Taylor K J, Scott DT, et al. Randomized low-dose indomethacin trial for prevention of intraventricular hemorrhage in very low birth weight neonates. Journal of Pediatrics. 1988;112(6):948–55.

87. Ment LR, Oh W, Ehrenkranz RA, Phillip AG, Vohr B, Allan W, et al. Low-dose indomethacin therapy and extension of intraventricular hemorrhage: a multicenter randomized trial. Journal of Pediatrics. 1994;124(6):951–5.

88. Ment LR, Oh W, Ehrenkranz RA, Philip AG, Vohr B, Allan W, et al. Low-dose indomethacin and prevention of intraventricular hemorrhage: a multicenter randomized trial. Pediatrics. 1994;93(4):543–50.

89. Ment LR, Vohr B, Oh W, Scott DT, Allan WC, Westerveld M, et al. Neurodevelopmental outcome at 36 months' corrected age of preterm infants in the Multicenter Indomethacin Intraventricular Hemorrhage Prevention Trial. Pediatrics. 1996;98:714–8.

90. Ment LR, Vohr B, Allan W, Westerveld M, SparrowSS, Schneider KC, et al. Outcome of children in theindomethacin intraventricular hemorrhage prevention trial. Pediatrics. 2000;105:485–91.

91. Vohr BR, Allan WC, Westerveld M, Schneider KC, Katz KH, Makuch RW, et al. School-age outcomes of very low birth weight infants in the indomethacin intraventricular hemorrhage prevention trial. Pediatrics. 2003;111(4 Pt 1):e340–6.

92. Ment LR, Vohr BR, Makuch RW, Westerveld M, Katz KH, Schneider KC, et al. Prevention of intraventricular hemorrhage by indomethacin in male preterm infants. Journal of Pediatrics. 2004;145(6):832–4.

93. Luu TM, Ment LR, Schneider KC, Katz KH, Allan WC, Vohr BR. Lasting effects of preterm birth and neonatal brain hemorrhage at 12 years of age. Pediatrics. 2009;123(3):1037–44.

94. Morales-Suarez M, De Jesus Sanchez-Gil T, Lemus-Varela L, Udaeta-Mora E. Low doses indomethacin for prevention of intraventricular hemorrhage in the preterm newborn infant with mechanical ventilation: final report of a randomized study. Boletin Medico del Hospital Infantil de Mexico. 1994;51(6):389–94.

95. Rennie J M, Doyle J, Cooke RW. Early administration of indomethacin to preterm infants. Archives of Disease in Childhood. 1986;61(3):233–8.

96. Schmidt B, Davis P, Moddemann D, Ohlsson A, Roberts RS, Saigal S, et al. Long-Term Effects of Indomethacin Prophylaxis in Extremely-Low-Birth-Weight Infants. New England Journal of Medicine. 2001 Jun 28;344(26):1966–72.

97. Ohlsson A, Roberts RS, Schmidt B, Davis P, ModdemanD, Saigal S, et al. Male/female differences in indomethacin effects in preterm infants. Journal of Pediatrics. 2005;147:860–2.

98. Schmidt B, Roberts RS, Fanaroff A, Davis P, Kirpalani HM N C, et a. l. Indomethacin prophylaxis, patent ductusarteriosus, and the risk of bronchopulmonary dysplasia:further analyses from the Trial of Indomethacin Prophylaxisin Preterms (TIPP). Journal of Pediatrics. 2006;148:730–4.

99. Zupancic JAF, Richardson DK, O'Brien BJ, Cronin CG, Schmidt B, Roberts R, et al. Retrospective economic evaluation of a controlled trial of indomethacin prophylaxis for patent ductus arteriosus in premature infants. Early Hum Dev. 2006 Feb;82(2):97–103.

100. Bandstra ES, Montalvo BM, Goldberg RN, Pacheco I, Ferrer PL, Flynn J, et al. Prophylactic indomethacin for prevention of intraventricular hemorrhage in premature infants. Pediatrics. 1988;82(4):533–42.

101. Setzer ES M BM, Goldberg RN, Smith M, Bancalari E. Prophylactic indomethacin and intraventricular hemorrhagein the premature. In 1984. p. 345A-345A.

102. Setzer ES, Torres-Arraut E, Gomez-del-Rio M, Young ML P I, Ferrer PL, et a. l. Cardiopulmonary effects of prophylactic indomethacin in the very low birth weight infant. In 1984. p. 346A-346A.

103. Supapannachart S, Khowsathit P, Patchakapati B. Indomethacin prophylaxis for patent ductus arteriosus (PDA) in infants with a birth weight of less than 1250 grams. Journal of the Medical Association of Thailand = Chotmaihet Thangphaet. 1999;82 Suppl 1:S87–92.

104. Vincer M, Allen A, Evans J, Nwaesei C, Stinson D, Rees E, et al. Early intravenous indomethacin prolongs respiratory support in very low birth weight infants. Acta Paediatrica. 1987;76(6):894–7.

105. Vincer M, Allen A. Does prophylactic indomethacin inVLBW (<1500 grams birth weight) infants cause cerebral palsy (CP)? Pediatric Research. 1998;43:232–232.

106. Vogtmann C, Grubbe G, Ruckhäberle KE, Böttcher H, Ockert C. Effects of early therapy with indomethacin on the manifestation of a persistent ductus arteriosus in extremely underweight premature infants. Monatsschrift Kinderheilkund. 1988;136(9):636–9.

107. Dani C, Bertini G, Reali M F, Murru P, Fabris C, Vangi V, et al. Prophylaxis of patent ductus arteriosus with ibuprofen in preterm infants. Acta Paediatrica. 2000;89(11):1369–74.

108. Dani C, Bertini G, Pezzati M, Poggi C, Guerrini P, Martano C, et al. Prophylactic ibuprofen for the prevention of intraventricular hemorrhage among preterm infants: a multicenter, randomized study. Pediatrics. 2005;115(6):1529–35.

109. De Carolis M P, Romagnoli C, Polimeni V, Piersigilli F, Zecca E, Papacci P, et al. Prophylactic ibuprofen therapy of patent ductus arteriosus in preterm infants. European Journal of Pediatrics. 2000;159(5):364–8.

110. Gournay V, Roze J C, Kuster A, Daoud P, Cambonie G, Hascoet J M, et al. Prophylactic ibuprofen versus placebo in very premature infants: a randomized, double-blind, placebo-controlled trial. Lancet. 2004;364(9449):1939–44.

111. Kanmaz G, Erdeve O, Canpolat FE, Oğuz SS, Uras N, Altug N, et al. Serum ibuprofen levels of extremely preterm infants treated prophylactically with oral ibuprofen to prevent patent ductus arteriosus. European Journal of Clinical Pharmacology. 2013;69(5):1075–81.

112. Sangtawesin V, Sangtawesin C, Raksasinborisut C, Sathirakul K, Kanjanapattanakul W, Khorana M, et al. Oral ibuprofen prophylaxis for symptomatic patent ductus arteriosus of prematurity. Journal of the Medical Association of Thailand. 2006;89(3):314–21.

113. Van Overmeire B, Allegaert K, Casaer A, Debauche C, Decaluwé W, Jespers A, et al. Prophylactic ibuprofen in premature infants: a multicenter, randomized, double-blind, placebo-controlled trial. Lancet. 2004;364(9449):1945–9.

114. van Overmeire B, Casaer A, Allegaert K, Debauche C, Decaluwe W, Jespers A, et al. Multicenter randomized double-blind placebo-controlled trial of ibuprofen prophylaxis in very preterm infants. Pediatric Research. 2002;51(4):379A-379A.

115. Bagheri M. M, Bahman-Bijari B, Torabi-Nejad M. H, Niknafs P, Mousavi H, Sabzevari F, et al. Is prophylactic parenteral paracetamol effective to diminish incidence of PDA in preterm neonates? A randomized trial. Iranian Journal of Pediatrics. 2018;28(4):e11735–e11735.

116. Juujärvi S, Kallankari H, Pätsi P, Leskinen M, Saarela T, Hallman M, et al. Follow-up study of the early, randomized paracetamol trial to preterm infants, found no adverse reactions at the two-years corrected age. Acta Paediatrica. 2019;108(3):452–8.

117. Liebowitz M, Clyman RI. Prophylactic indomethacin compared with delayed conservative management of the patent ductus arteriosus in extremely preterm infants: effects on neonatal outcomes. Journal of Pediatrics. 2017;187:119–26.

118. Varvarigou A, Bardin CL, Beharry K, Chemtob S, Papageorgiou A, Aranda JV. Early ibuprofen administration to prevent patent ductus arteriosus in premature newborn infants. JAMA. 1996 Feb 21;275(7):539–44.

119. Cotts T. Escalating dose indomethacin for prophylactic closure of patent ductus arteriosus does not improve closure rates and is associated with increased complications. Journal of Pediatrics. 2009;154(1):153–153.

120. Hammerman C, Strates E, Valaitis S. The silent ductus: its precursors and its aftermath. Pediatric Cardiology. 1986;7(3):121–7.

121. Kääpä P. Early closure of ductus arteriosus with indomethacin. Klinische Pädiatrie. 1985;197(2):172–172.

122. Rubaltelli F, Bertini G, Reali MF, Vangi V, Dani C. Does early closure of PDA with ibuprofen reduce the severity of RDS in premature infants? Pediatric Research. 1998;43:296A-296A.

123. Schmidt B, Seshia M, Shankaran S, Mildenhall L, Tyson J, Lui K, et al. Effects of prophylactic indomethacin in extremely low-birth-weight infants with and without adequate exposure to antenatal corticosteroids. Archives of Pediatrics and Adolescent Medicine. 2011;165(7):642–6.

124. Valls-i-Soler A, Lopez-de-Heredia J, Roman L, Fernandez-Ruanova MB. Prophylactic indomethacin (INDO) in very low birth weight (VLBW) infants with RDS. A pilot study on the effects of a slow infusion rate. Pediatric Research. 1999;45(6):901–901.

125. Alfaleh K, Smyth JA, Roberts RS, Solimano A, Asztalos EV, Schmidt B; Trial of Indomethacin Prophylaxis in Preterms I n. v. e. s. t. i. g. a. t. o. r. s. Prevention and 18-month outcomes of serious pulmonary hemorrhage in extremely low birth weight infants: results from the trial of indomethacin prophylaxis in preterms. Pediatrics. 2008;121(2):e233–8.

126. Gregoire N, Gualano V, Geneteau A, Millerioux L, Brault M, Mignot A, et al. Population pharmacokinetics of ibuprofen enantiomers in very premature neonates. Journal of Clinical Pharmacology. 2004;44(10):1114–24.

127. Harma A, Harkin P, Leskinen M, Valkama M, Saarela T, Aikio O, et al. Does intravenous paracetamol offer neonatal brain protection? Study of hemodynamics and cerebral oxygenation in very premature infants. Neonatology. 2018;113(4):417–8.

128. Ment LR, Vohr B, Allan W, Westerveld M, Katz KH, Schneider KC, et al. The etiology and outcome of cerebral ventriculomegaly at term in very low birth weight preterm infants. Pediatrics. 1999;104(2 Pt 1):243–8.

129. Naulaers G, Delanghe G, Allegaert K, Debeer A, Cossey V, Vanhole C, et al. Ibuprofen and cerebral oxygenation and circulation. Archives of Disease in Childhood Fetal Neonatal Edition. 2005;90(1):F75–6.

130. Pleacher MD, Vohr BR, Katz KH, Ment LR, Allan WC. An evidence-based approach to predicting low IQ in very preterm infants from the neurological examination: outcome data from the indomethacin Indomethacin Intraventricular Hemorrhage Prevention Trial. Pediatrics. 2004;113(2):416–9.

131. Vohr B, Allan WC, Scott DT, Katz KH, Schneider KC, Makuch RW, et al. Early-onset intraventricular hemorrhage in preterm neonates: incidence of neurodevelopmental handicap. Seminars in Perinatology. 1999;23(3):212–7.

132. Domanico RS, Waldman JD, Lester LA, McPhillips HA, Catrambone JE, Covert RF. Prophylactic indomethacin reduces the incidence of pulmonary hemorrhage and patent ductus arteriosus in surfactant-treated infants. Pediatric Research. 1994;35:331A-331A.

133. Gutierrez NG, Lapasset M. Prophylactic indomethacin and the incidence of patent ductus arteriosus in preterm neonates. Proceedings of the 3rd Argentinian Congress of Perinatology, Buenos Aires. 1987;62.

134. Puckett CG, Cox MA, Haskins KS, Fisher DJ. Prophylactic indomethacin (I) for the prevention of patent ductus arteriosus (PDA). Pediatric Research. 1985;19:358–358.

135. Zarkesh MR, Nili F, Akbari Asbagh P, Nayeri FS, Naeem A. Prophylactic treatment with oral paracetamol for patent ductus arteriosus in preterm infants admitted in Nicu Vali-Asr Hospital In 2012. Iranian Journal Of Pediatrics. 2013;23(Suppl 1):54–5.

136. Meau-Petit V. Prophylactic ibuprofen vs placebo in very premature infants: a randomized, double blind, placebo-controlled trial. Archives de Pédiatrie. 2005;12:605–8.

137. Ment LR. Randomized low-dose indomethacin trial for the prevention of intraventricular hemorrhage in very low birth weight neonates. Annals of Neurology. 1987;22(3):406–7.

138. Morales-Suarez M, Lemus-Varela L, Udaeta-Mora E, Cardiel-Marmolejo L, Rodríguez-Balderrama I, Liz-Cedillo RE. Indomethacin in the prevention of subependymal-intraventricular hemorrhage in preterm newborns with conventional mechanical ventilation. Boletín Médico del Hospital Infantil de México. 1992;49(4):217–24.

139. Roze JC, Gournay V, Daoud P, Cambonie G, Chamboux C, Hascoet JM, et al. Multicenter double blind randomized placebo-controlled study comparing prophylactic versus curative ibuprofen treatment in premature infants less than 28 weeks of gestation. Pediatric Research. 2003;53:386A-386A.

140. Barrington KJ, Finer NN, Ment LR. Indomethacin for prevention of intraventricular hemorrhage. Journal of Pediatrics. 1986;109(2):396–8.

141. Hammerman C, Kaplan M. Prophylactic ibuprofen in premature infants: a multicenter, randomized, double-blind, placebo-controlled trial. Journal of Pediatrics. 2005;146(5):709–10.

142. McGuire W, Fowlie PW. Treating extremely low birthweight infants with prophylactic indomethacin. Evidence for short term benefits only. BMJ. 2002;324(7329):60–1.

143. Ment LR, Westerveld M, Makuch R, Vohr B, Allan WC. Cognitive outcome at 4 1/2 years of very low birth weight infants enrolled in the multicenter indomethacin intraventricular hemorrhage prevention trial. Pediatrics. 1998;102(1 Pt 1):159–60.

144. Schmidt B, Wright LL, Davis P, Solimano A, Roberts RS; Indomethacin Prophylaxis in Preterms I n. v. e. s. t. i. g. a. t. o. r. s. Ibuprofen prophylaxis in preterm neonates. Lancet. 2002;360(9331):492–492.

145. Tyson JE. . Does indomethacin prophylaxis benefit extremely low birth weight infants? Results of a placebo-controlled multicenter trial. Pediatric Research. 2002;51(1):1–1.

146. Hamrick SEG, Sallmon H, Rose AT, Porras D, Shelton EL, Reese J, et al. Patent Ductus Arteriosus of the Preterm Infant. Pediatrics. 2020 Nov;146(5):e20201209.

147. Ryan M, Lacaze-Masmonteil T, Mohammad K. Neuroprotection from acute brain injury in preterm infants. Paediatr Child Health. 2019 Jul;24(4):276–90.

148. Brignardello-Petersen R, Guyatt GH, Mustafa RA, Chu DK, Hultcrantz M, Schünemann HJ, et al. GRADE guidelines 33: Addressing imprecision in a network meta-analysis. Journal of Clinical Epidemiology. 2021;139:49–56.

149. Sangtawesin C, Sangtawesin V, Lertsutthiwong W, Kanjanapattanakul W, Khorana M, Ayudhaya JK. Prophylaxis of symptomatic patent ductus arteriosus with oral ibuprofen in very low birth weight infants. Journal of the Medical Association of Thailand. 2008;91(Suppl 3):S28–34.

150. Zeng L, Brignardello-Petersen R, Hultcrantz M, Siemieniuk RA, Santesso N, Traversy G, et al. GRADE guidelines 32: GRADE offers guidance on choosing targets of GRADE certainty of evidence ratings. Journal of Clinical Epidemiology. 2021;137:163–75.

Appendices

Appendix 1. Search strategies

Medline search strategy

Ovid MEDLINE(R) ALL <1946 to 8 December 2021>

Search history sorted by search number ascending		
#	**Searches**	**Results**
1	exp Infant, Premature/ or Premature Birth/ or Infant, Premature, Diseases/ or (preterm or pre term or prematur* or pre matur* or premie or premies or preemie*).ti,ab,kf.	243881
2	low birth weight.ti,ab,kf. or Infant, Low Birth Weight/	39717
3	very low birth weight.ti,ab,kf. or Infant, Very Low Birth Weight/	12850
4	Infant, Extremely Low Birth Weight/ or (elbw or vlbw or lbw).ti,ab,kf.	10790
5	((("37" or "36" or "35" or "34" or "33" or "32" or "31" or "30" or "29" or "28" or "27" or "26") adj1 (week? or wk?)) and (birth or neonat* or age or gestat* or pregnan*)).ti,ab,kf.	68360
6	1 or 2 or 3 or 4 or 5	300088
7	exp Cyclooxygenase Inhibitors/	133274
8	exp Anti-Inflammatory Agents, Non-Steroidal/	206693
9	Acetaminophen/	19358
10	(COXI or Indomethacin or indometacin or indocid or Ibuprofen or brufen or motrin or nuprin or rufen or advil or Ibumetin or Acetaminophen or paracetamol or Tylenol or anephen or acetaco or anacin* or datril or panadol or acamol or algotropyl or NSAID?).ti,ab,kf.	97044
11	((cyclo-oxygenase or Cyclooxygenase or Prostaglandin Synthase or Prostaglandin Synthesis or Prostaglandin Endoperoxide Synthase) adj2 (inhibitor* or antagonist*)).ti,ab,kf.	11988
12	((Anti-Inflammatory or antiinflammatory or aspirin-like or nonsteroidal or non-steroidal) adj2 (Analgesic? or agent? or drug? or medicine? or medication?)).ti,ab,kf.	68079
13	((Anti-Inflammatory or antiinflammatory or aspirin-like or nonsteroid* or non-steroid*) adj2 (Analgesic? or agent? or drug? or medicine? or medication?)).ti,ab,kf.	68298
14	"Mefenamic Acid".ti,ab,kf.	1391
15	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.	1299151
16	7 or 8 or 9 or 10 or 11 or 12 or 14	285794
17	6 and 15 and 16	922

Embase search strategy

No.	Query	Results
#15	#3 AND #13 AND #14	3927
#14	#4 OR #5 OR #6 OR #7	963514

#13	#8 OR #9 OR #10 OR #11 OR #12	1157104
#12	'mefenamic acid':ti,ab,kw	1856
#11	(('anti-inflammatory' OR antiinflammatory OR 'aspirin-like' OR nonsteroid* OR 'non- steroid*') NEAR/2 (analgesic* OR agent* OR drug* OR medicine* OR medication*)):ti,ab,kw	94572
#10	('cyclo-oxygenase' OR cyclooxygenase OR 'prostaglandin synthase' OR 'prostaglandin synthesis' OR 'prostaglandin endoperoxide synthase') NEAR/2 (inhibitor* OR antagonist*)	38175
#9	'nonsteroid antiinflammatory agent'/exp OR 'prostaglandin synthase inhibitor'/exp OR 'paracetamol'/de OR 'ibuprofen'/de OR 'indometacin'/de	1113616
#8	coxi:ti,ab,kw OR indomethacin:ti,ab,kw OR indometacin:ti,ab,kw OR indocid:ti,ab,kw OR ibuprofen:ti,ab,kw OR brufen:ti,ab,kw OR motrin:ti,ab,kw OR nuprin:ti,ab,kw OR rufen:ti,ab,kw OR advil:ti,ab,kw OR ibumetin:ti,ab,kw OR acetaminophen:ti,ab,kw OR paracetamol:ti,ab,kw OR tylenol:ti,ab,kw OR anephen:ti,ab,kw OR acetaco:ti,ab,kw OR anacin*:ti,ab,kw OR datril:ti,ab,kw OR panadol:ti,ab,kw OR acamol:ti,ab,kw OR algotropyl:ti,ab,kw OR nsaid*:ti,ab,kw	144274
#7	((('37' OR '36' OR '35' OR '34' OR '33' OR '32' OR '31' OR '30' OR '29' OR '28' OR '27' OR '26') NEAR/1 (week* OR wk*)):ti,ab,kw) AND (birth:ti,ab,kw OR neonat*:ti,ab,kw OR age:ti,ab,kw OR gestat*:ti,ab,kw OR pregnan*:ti,ab,kw)	104783
#6	'immature and premature labor'/exp	169587
#5	preterm:ti,ab,kw OR 'pre term':ti,ab,kw OR prematur*:ti,ab,kw OR 'pre matur*':ti,ab,kw OR premie:ti,ab,kw OR premies:ti,ab,kw OR preemie*:ti,ab,kw OR 'low birth weight':ti,ab,kw OR lbw:ti,ab,kw OR vlbw:ti,ab,kw OR elbw:ti,ab,kw	327721
#4	'prematurity'/exp OR 'very low birth weight'/exp OR 'low birth weight'/exp OR 'extremely low birth weight'/exp OR 'premature labor'/exp OR 'newborn'/exp	758481
#3	#1 OR #2	2986848
#2	'controlled clinical trial'/exp	864591
#1	'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti,kw OR factorial*:de,ab,ti,kw OR crossover*:de,ab,ti,kw OR ((cross NEXT/1 over*):de,ab,ti,kw) OR placebo*:de,ab,ti,kw OR ((doubl* NEAR/1 blind*):de,ab,ti,kw) OR ((singl* NEAR/1 blind*):de,ab,ti,kw) OR assign*:de,ab,ti,kw OR allocat*:de,ab,ti,kw OR volunteer*:de,ab,ti,kw	2856698

Cochrane CENTRAL search strategy

Cochrane CENTRAL via Cochrane Library (Wiley Issue 12, December 2021)

ID Search

#1 [mh "Infant, premature"] OR [mh "Premature Birth"] OR [mh "Infant,Premature,Diseases"] OR (preterm or pre term or premature* or pre matur* or premie or premies or preemie*):ti,ab,kw 43617

#2 ("low birth weight" OR Infant):ti,ab,kw OR [mh "Low Birth Weight"] 55060

#3 ("very low birth weight" OR Infant):ti,ab,kw OR [mh "Very low birth weight"] 54005

#4 [mh "infant, extremely low birth weight"] OR ("extremely low birth weight" OR elbw OR vlbw OR lbw):ti,ab,kw 2077

#5 ((("37" OR "36" OR "35" OR "34" OR "33" OR "32" OR "31" OR "30" OR "29" OR

"28" OR "27" OR "26") NEAR/1 (week? OR wk?)) AND (birth OR neonat* OR age OR gestat* OR pregnan*)):ti,ab,kw 18607

#6 #1 OR #2 OR #3 OR #4 OR #5 95858

#7 [mh "Cyclooxygenase Inhibitors"] 1581

#8 [mh "Anti-Inflammatory Agents, Non-Steroidal"] 7833

#9 [mh ^"Acetaminophen"] 3403

#10 (COXI or Indomethacin or indometacin or indocid or Ibuprofen or brufen or motrin or nuprin or rufen or advil or Ibumetin or Acetaminophen or paracetamol or Tylenol or anephen or acetaco or anacin* or datril or panadol or acamol or algotropyl or NSAID?):ti,ab,kw 23089

#11 (("cyclo-oxygenase" or Cyclooxygenase or "Prostaglandin Synthase" or "Prostaglandin Synthesis" or "Prostaglandin Endoperoxide Synthase") NEAR/2 (inhibitor* or antagonist*)):ti,ab,kw 2227

#12 ((Anti-Inflammatory or antiinflammatory or aspirin-like or nonsteroidal or non-steroidal) NEAR/2 (Analgesic? or agent? or drug? or medicine? or medication?)):ti,ab,kw 21861

#13 "Mefenamic Acid":ti,ab,kw 462

#14 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 39494

#15 #6 and #14 2414 =>2281 CENTRAL

Custom Date Range: 01102020 – 09122021 = 113

Trial registry and conference abstract search strategies
US National Library of Medicine (clinicaltrials.gov)

Search terms:

condition: premature AND other terms : Prong = 54 [Limit Child]

condition: neonate AND other terms : Prong = 51 [Limit Child]

Condition: premature AND Other terms: cpap = 278 [Limit Child]

Conditon: neonate AND Other terms: cpap = 263 [Limit Child]

Total: 646

Duplicates: 326

Net: 320

Conference websites: *35*

Appendix 2. Risk of bias tool

We used the standard methods of Cochrane and Cochrane Neonatal to assess the methodological quality of the trials. For each trial, we sought information regarding the method of randomization, blinding, and reporting of all outcomes of all the infants enrolled in the trial. We assessed each criterion as being at a low, high, or unclear risk of bias. Two review authors separately assessed each study. We resolved any disagreement by discussion. We added this information to the 'Characteristics of included studies' table.

We evaluated the following issues and entered the findings into the 'Risk of bias' table.

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we categorized the method used to generate the allocation sequence as being at:

1. low risk of bias (any truly random process, e.g. random number table; computer random number generator);
2. high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
3. unclear risk of bias.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we categorized the method used to conceal the allocation sequence as being at:

1. low risk of bias (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);

2. high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or

3. unclear risk of bias.

3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we categorized the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or class of outcomes. We categorized the methods as being at:

1. low, high, or unclear risk of bias for participants; and

2. low, high, or unclear risk of bias for personnel.

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we categorized the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or classes of outcomes. We categorized the methods as being at:

1. low risk of bias for outcome assessors;

2. high risk of bias for outcome assessors; or

3. unclear risk of bias for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared

with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where enough information was reported or supplied by the trial authors, we reincluded missing data in the analyses. We categorized the methods as being at:

1. low risk of bias (less than 20% missing data);
2. high risk of bias (20% missing data or greater); or
3. unclear risk of bias.

6. Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we compared prespecified outcomes versus the outcomes eventually reported in the published results. If the study protocol was not published in advance, we contacted study authors to gain access to the study protocol. We assessed the methods as being at:

1. low risk of bias (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
2. high risk of bias (where not all the study's prespecified outcomes have been reported; one or more of the reported primary outcomes were not prespecified outcomes of interest and were reported incompletely and so cannot be used; or where the study fails to include results of a key outcome that one would expect to have been reported); or
3. unclear risk of bias.

7. Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?

For each included study, we will describe any important concerns we had about other possible sources of bias (e.g. whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data- dependent process).

We assessed whether each study was at:

1. low risk of other sources of bias;
2. high risk of other sources of bias; or
3. unclear risk of other sources of bias.

If needed, we planned to undertake sensitivity analyses to explore the impact of the level of bias.

CHAPTER 3: VALUES AND PREFERENCES STUDY

Health-related values and preferences of former preterm infants and families of preterm infants on use of prophylactic cyclo-oxygenase inhibitor drugs: A cross-sectional mixed-methods study

Authors:

Souvik Mitra[1,2], Tara Hatfield[2], Marsha Campbell-Yeo[1,2], Jon Dorling[1,3], Bradley Johnston[1,4]

Affiliations:

[1]Dalhousie University, Halifax, Canada, [2]IWK Health Halifax, Canada; [3]Southampton Children's Hospital, Southampton UK, [4]Departments of Nutrition, Epidemiology and Biostatistics, Texas A&M University, College Station, US

Address of correspondence to:

Souvik Mitra, MD, MSc, FRCPC

Division of Neonatal-Perinatal Medicine; Department of Pediatrics; Department of Community Health and Epidemiology, Dalhousie University & IWK Health

Room G2214, 5850/5980 University Avenue P.O. Box 9700 Halifax, NS B3K 6R8

Tel: (902) 470-6490

Fax: (902) 470-6469

Email: Souvik.Mitra@iwk.nshealth.ca

STATUS: Manuscript ready for submission

Contributions of authors

SM conceived the project, under the mentorship of BCJ and JD. SM conducted all the interviews, analyzed the data, and drafted the manuscript. TH independently validated the qualitative analysis. SM, TH, MCY, BCJ and JD reviewed all drafts, and approved the final version of the manuscript.

Abstract

Background: There is wide variability in the use of prophylactic cyclo-oxygenase inhibitor (COX-I) drugs to prevent morbidity and mortality in preterm infants. Parents of preterm infants are rarely involved in this decision-making process.

Objective: To explore the health-related values and preferences of former preterm infants and families of preterm infants on the prophylactic use of indomethacin, ibuprofen and acetaminophen initiated within the first 24 hours after birth.

Study Design: A cross-sectional semi-structured mixed-methods study involving adults born very preterm (born <32 weeks of gestation) or families of very preterm infants currently in the NICU or having graduated from the NICU in the last 5 years was conducted in two phases: *(a) a pilot feasibility study (phase I)* and *(b) a formal values and preferences study (phase II)* with a pre-defined convenience sample. Participants were asked to rate the most important clinical outcomes. Subsequently, to elicit management preferences based on an up-to-date Cochrane systematic review of COX-I's for preterm infants, participants were presented with a direct choice experiment based on the best estimates of benefit and harm for the most important outcomes. Interviews were then conducted to document the determinants of their management choices.

Results: A total of 44 participants were enrolled during the study period, of whom 40 were included in the phase II study (31 parents; 9 adults born preterm). Death (median score 100, IQR [Interquartile range] 100-100) followed by severe intraventricular hemorrhage (IVH) (median score 90, IQR 80-100) were rated as the two most critically important outcomes in relation to prophylactic COX-I use. Based on the direct choice experiment, most participants were willing to consider the use of prophylactic indomethacin (90%) or ibuprofen (85%), but not acetaminophen (10%) when offered as the only option. Among participants who initially said yes to indomethacin (n=36), if prophylactic hydrocortisone was offered as a potential therapy to prevent death or chronic lung disease, with the caveat that both cannot be used simultaneously, only 33% (12/36) would still prefer to remain with indomethacin. There was some variability in the preference when all three COX-I

options were available, with indomethacin (47.5%) being the most preferred option followed by ibuprofen (40%).

Conclusion: There was minimal variability in how participants valued the main outcomes, with death and severe IVH being rated as the two most important undesirable outcomes. While indomethacin was the most preferred form of prophylaxis, variability was noted in the choice of COX-I interventions when participants were presented with the benefits and harms of each drug. This, the first available values and preferences study on COX-I pharmacoprophylaxis, based on the most recent systematic review, should be used to inform guideline recommendations in preterm infants.

Introduction

Preterm infants, especially those who are born extremely preterm (at or below 28 weeks of gestational age) are at a high risk of neonatal complications such as severe intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), chronic lung disease (CLD), neurodevelopmental impairment and death. A common contributor for all three of these pathophysiological mechanisms is postulated to be the patent ductus arteriosus (PDA)[1]. Currently available pharmacotherapeutic options to prevent a PDA and related complications include cyclo-oxygenase inhibitor (COX-I) drugs such as indomethacin, ibuprofen, and acetaminophen. COX-I drugs themselves are associated with serious adverse effects such as NEC and spontaneous gastrointestinal perforation (SIP)[2,3]. Recent availability of prophylactic hydrocortisone as a potential effective option to prevent death or CLD also presents a dilemma to clinicians as concomitant use of prophylactic indomethacin and hydrocortisone can significantly increase the risk of SIP[4]. Given the potential risks of COX-I use, it is not surprising that there is wide variation in clinical practice regarding COX-I prophylaxis in preterm infants. A retrospective cohort study of 4268 extremely preterm infants admitted to Canadian NICUs between 2010 and 2014 demonstrated marked variation (0-78%) in use of prophylactic COX-Is[3]. Similarly, a survey of 35 Neonatal Research Network hospitals across the United States showed that while one-third of NICUs never used COX-I prophylaxis, a third used pharmacoprophylaxis in 45%–98% of their extremely preterm neonates[5]. The decision on PDA pharmacoprophylaxis has primarily been driven by the perceived benefits versus potential risks as determined by the treating physician, with little or no input from families regarding their health outcome related values and preferences when faced with the benefits and harms of COX-I drugs.

Health-related values refer to the perspectives, beliefs, expectations, and goals for health and life of the parents/guardians for their infants, while preferences refer to the processes that families use in considering the potential benefits, harms, costs, and inconveniences of the management options in relation to one another[6]. Consequently, it is plausible that the preference for or against an intervention is determined by the relative importance of the health outcomes that the family attaches to available management strategies[6]. Recent work

from Weiss et al suggests that decisions that parents consider as involving big-picture goals and those that have the potential to harm the infant are associated with a greater preference for parent-centered decision-making[7], which in turn, may reduce later parental decision regret as shown by Soltys et al[8]. COX-I prophylaxis involves such a trade-off between long term benefits (reduction of death and IVH) and serious short term adverse effects (NEC and SIP). Therefore, it is imperative that family preferences are included in clinical guidelines for COX-I prophylaxis in preterm infants.

There is both a dearth of research on values and preferences of families and former preterm infants in this context, and no evidence from previous guidelines that the explicit values and preferences of families have been addressed and incorporated. To inform this study, a comprehensive electronic search of MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) for clinical practice guidelines on COX-I pharmacoprophylaxis in preterm infants was conducted in consultation with a research librarian. The review found only one study that explored maternal values and preferences for decision on PDA pharmacoprophylaxis[9]. This 2015 study was limited by the fact that it only considered indomethacin prophylaxis as a management option. Furthermore, while absolute estimates were presented for each health outcome, the outcomes were not accompanied by a judgment on the certainty of evidence using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach or a similar process. Based on our search of the literature, there are no clinical practice guidelines on PDA pharmacoprophylaxis that incorporate family values and preferences.

The objective of this study was to explore the health-related values and preferences of former preterm infants and families on the use of COX-I drugs for preventing PDA related morbidity and mortality using evidence from a recent Cochrane systematic review and network meta-analysis[10].

Methods

Study design and population

The study was conducted as a cross-sectional semi-structured mixed-methods study. The study involved families or former preterm infants from across Canada and the United

Kingdom. Adults born very preterm (born <32 weeks of gestation) or families of very preterm infants currently in the NICU or having graduated from the NICU in the last 5 years were included. The study was approved by the Izaak Walton Killam (IWK) Health Centre Research Ethics Board (IWK-REB project # 1026329).

The study was planned in two phases. The first phase, a pilot feasibility study (phase I) aimed to test our demographic questionnaire, rating of clinical outcomes and our direct choice experiment questions on values and preferences. The pilot study provided an opportunity to learn from and modify any logistic or methodological issues. The second phase, a formal values and preferences study (phase II) used our pre-tested interview questionnaire to describe the variability in health-related values and preferences of former preterm infants and families on use of prophylactic COX-I drugs.

Recruitment Strategy

A convenience sampling strategy was used with emphasis on recruitment of under-represented groups such as Black and Indigenous populations as well as participants with low educational status. Participants were contacted while their infants were admitted to the IWK NICU, through the IWK Perinatal Follow-up clinic, through representatives of local (IWK Health) and national (Canadian Premature Babies Foundation) parent partner organizations and through personal contacts of the primary author. Social media platforms such as Twitter, Facebook and Instagram were used to distribute study flyers in order to seek participation. Participants with limited understanding of English were excluded from this study. The entire study was conducted virtually using recorded video-conference interviews on the Zoom™ platform. All Zoom™ meeting links were password protected to ensure privacy. Virtual interviews were utilized due to the COVID-19 pandemic to minimize the risk of COVID exposure.

Study Procedures

A structured survey and semi-structured interview script developed by the research team was used (appendix A). The interview structure was modified based on the feedback obtained from participants in the pilot phase and updated with new evidence obtained from

the Cochrane systematic review and network meta-analysis[10]. The interview comprised of the following components:

1. *Baseline demographic questionnaire:* The questionnaire included type of participant (parent or adult born preterm), age range, highest level of education completed, ethnicity, country of origin and gestational age of the of the participant or their child at birth.
2. *Standardized description of health states (Appendix A):* In this section, the participants were provided with information on prematurity related complications including PDA, how a PDA can affect short and long-term outcomes and what are the preventive options available. The discussion specifically included a visual description and implications of the following health states in the pilot phase: severe intraventricular hemorrhage (severe IVH; grades 3 or 4), necrotizing enterocolitis (NEC; stage 2 or above), gastrointestinal perforation, chronic lung disease (CLD), severe neurodevelopmental impairment and cerebral palsy. Based on the on the feedback from participants in the pilot phase (detailed rationale presented in the results section) as well as recent work by Webbe et al[11], the description of health states and subsequent elicitation of values and preferences was reduced to the following 4 outcomes: death, severe IVH, NEC and CLD.
3. *Eliciting importance of outcomes:* A numeric rating scale was used to elicit the perceived importance of each of the following outcomes: death, severe IVH, NEC and CLD on a scale of 0-100, 0 being least important and 100 being most critically important undesirable (serious) outcome. PDA was also included in the numeric rating scale though it was not identified as a critical outcome as the standardized descriptions of health states included PDA in addition to severe IVH, NEC and CLD.

4. *Direct choice elicitation for treatment preferences*: A direct choice experimental design was used to assess the proportion of participants willing to accept prophylactic use of any of the three COX-I medications in preterm infants[12,13]. The systematic review evidence on benefits and harms for each of the three medications were presented for the outcomes of death, severe IVH, NEC and CLD, using a visual decision aid created from the MagicApp software (http://magicproject.org/research-projects/share-it/)

(Appendix B). The decision aid was accompanied by the baseline risk and absolute risk reduction for each outcome, followed by the overall GRADE (Grading of Recommendations Assessment, Development and Evaluation) certainty of evidence for each outcome. Participants were then asked to choose 'yes' or 'no' for each pharmacotherapeutic option. Given the increasing use of prophylactic hydrocortisone among neonatal practitioners, those participants who said 'yes' to indomethacin were presented with the benefits and harms of prophylactic hydrocortisone, with the caveat that both cannot be used together, to explore their choice when presented with the option of choosing between indomethacin and hydrocortisone.

5. *Semi-structured interview on determinants of treatment preferences:* To explore the determinants and any emerging themes that impacted how and why participants chose certain treatment preferences, participants were asked to list the most important factors behind their choice of prophylactic therapy.

6. *Relative importance of having family values and preferences included in decision-making:* Given the first 24 hours after birth of a preterm infant is physically and emotionally overwhelming for the family, involving them in critical decision making may further add to the information overload. Therefore, to obtain the family's perspective, participants were asked how important it was for them to have their values and preferences included in decision-making for use of prophylactic COX-Is. They were asked to choose one of the four options provided (not important; somewhat important; important; very important) with a brief description of the implications of each choice.

For the pilot study we used data on use of prophylactic indomethacin, ibuprofen and acetaminophen in preterm infants available from existing evidence published in the Cochrane Database of Systematic Reviews[14–16]. For the formal study, updated evidence from the recent Cochrane review and network meta-analysis by Mitra et al was used[10]. Evidence on prophylactic hydrocortisone was drawn from a 2019 individual patient data meta-analysis by Shaffer et al[17].

Outcomes

The outcome measures included: (a) the relative importance of PDA-related clinical outcomes on the numeric rating scale; (b) willingness to use each of the prophylactic COX-I drugs when presented as the only option; (c) preference for using prophylactic hydrocortisone versus indomethacin; (d) willingness to use any of the pharmacoprophylactic COX-I drugs when all three options are available; and (e) relative importance of having family values and preferences included in the decision making in this scenario. The qualitative component of the interview attempted to identify themes related to the choice of prophylaxis based on participants' perceptions of the therapeutic value of each COX-I drug.

Data synthesis and analysis

Quantitative analysis

Categorical data were expressed as frequencies and percentages. Continuous data were expressed as mean and standard deviation (SD) for parametric data, and median and interquartile range (IQR) for non-parametric data. Post-hoc exploratory analyses by participant group (parent of preterm infant vs adult born preterm) were conducted using the Mann Whitney U test, z-test, Chi-squared test, or Fisher's Exact test as applicable. Statistical inferences were based on 2-tailed tests with significance set at $P < 0.05$.

Qualitative analysis

The semi-structured interviews on Zoom™ were recorded and transcribed verbatim for qualitative analysis. A thematic analysis approach was used for qualitative analysis[18,19]. Transcripts were coded and then the codes were sorted into themes. One researcher (SM) conducted all the interviews, coded the transcripts and sorted relevant sections of the transcript into major themes using the NVivo 12 software. A second research coordinator (TH), not involved in any of the interviews, independently coded a randomly selected sample of 20 transcripts to validate the work. Validity of the original coding was established if no additional themes were identified. Coding frequency of the emerging major themes were presented as percentages.

Results

A total of 44 participants were enrolled during the study period between March 2021 to February 2022.

Pilot phase I study

Seven participants were enrolled during the phase I pilot study (5 parents; 2 adults born preterm; *Appendix C*) between March-May 2021. Based on the feedback of the participants, the following changes were made to the formal phase II study:

a) Gender was removed from the demographic questionnaire as both parents often participated together in the interviews.
b) In the pilot study, the participants were asked to rate five clinical outcomes (severe IVH, severe developmental delay, CLD, NEC and spontaneous intestinal perforation) on a numeric rating scale of 0-100, assuming 100 was the worst possible state of health, while 0 was the best possible state of health. Death was not included in these five outcomes as it was assumed to be the worst possible state of health. The participants felt that for some parents, death may not always be the worst possible state of health as compared to a very poor quality of life. Therefore, death was added as one of the clinical outcomes to also be rated on the numeric rating scale. The participants further felt that evidence on too many outcomes were presented in the direct choice experiments and four outcomes would be optimal. The unanimous consensus from all seven participants was to choose death, severe IVH, NEC and CLD as the four outcomes to be presented in the direct choice experiments in the phase II study.
c) Sample size: Based on the recruitment rate in the pilot phase (approximately 3-4 participants per month), a convenience sample target of 40 was determined, anticipating that 40 participants would allow for study completion in the winter of 2022.

Formal phase II study

40 participants were recruited in the formal phase II study between October 2021 and February 2022, that included 3 participants (2 parents, 1 adult) who had also participated

in the pilot phase. Out of the 40 participants recruited, 31 (77.5%) were parents of infants born very preterm, while 9 (22.5%) were adults who were born extremely preterm. The overall median gestational age of the participant or their child at birth was 26 weeks (IQR 25 to 28.8 weeks). The demographic profile of the participants in the formal phase II study is presented in Table 1.

Rating of importance of outcomes

On the numeric rating scale, death was rated as the most serious outcome (median score 100, IQR 100-100) followed by severe IVH (median score 90, IQR 80-100) (Table 2).

Direct choice elicitation of treatment preferences and rationale for choices

Results from the direct choice experiment showed that when offered as the only available option, most participants would choose indomethacin (90%) and ibuprofen (85%), while only a small proportion would choose acetaminophen (10%) (Table 3). Among participants who initially said yes to indomethacin (n=36), if prophylactic hydrocortisone was offered as a potential therapy to prevent death or CLD, with the caveat that both cannot be used simultaneously, only 33% (12/36) would still prefer to remain with indomethacin (Table 4).

Thematic analysis showed that for indomethacin, reduction in death and severe IVH with moderate certainty was the primary driver for the participants' choice in favor (Table 3). However, when prophylactic hydrocortisone was offered to those who said 'yes' to indomethacin, two-thirds of participants indicated that they would prefer hydrocortisone over indomethacin as hydrocortisone offered improved survival over indomethacin (table 4). Similar to indomethacin, the primary motivation behind choosing ibuprofen over no treatment was possible reduction in the critical outcomes of death and severe IVH. By contrast, the majority of participants opted against acetaminophen as they felt that the evidence was highly uncertain (Table 3).

When all three COX-I options were available, 47.5% (19/40) would choose indomethacin, 40% (16/40) would choose ibuprofen and the rest would opt for no COX-I prophylaxis (5/40; 12.5%). Thematic analysis revealed that those who said 'yes' to indomethacin

(47.5%) felt that the overall certainty for benefit was better with indomethacin; those who chose ibuprofen (40%) indicated that there seemed to be no overall harm and in addition they would like to keep the option of using prophylactic hydrocortisone open which is not possible if indomethacin is chosen. For the remaining 12.5% who opted for no prophylaxis, the primary motivation behind choosing no COX-I prophylaxis was preference for prophylactic hydrocortisone (Table 3).

Relative importance of having family values and preferences included in the decision making

Most participants felt that it was somewhat important (55%) or important (35%) to be informed of the benefits and harms of the pharmacoprophylactic options prior to making a clinical decision of giving the drug or refraining from it (Table 5). Those who indicated that it was 'somewhat important' felt that the first 24 hours after birth is quite overwhelming, therefore, though they would like to be informed about the benefits and harms of the therapies, they would trust the clinician's judgment. While those who indicated that it was 'important' felt the need to be actively involved in this decision-making process (Table 5).

Post-hoc exploratory analyses

Post-hoc exploratory analysis did not demonstrate any statistically significant differences in the responses between parents of preterm infants versus those adults who were born preterm (Appendix D).

Discussion

This cross-sectional semi-structured survey study included 44 participants, 40 of whom were included in the formal phase II study. Our results showed that death and severe IVH are the two most serious outcomes that participants would consider in relation to prophylactic COX-I use in preterm infants. Most participants were willing to consider the use of prophylactic indomethacin or ibuprofen, but not acetaminophen when offered as the only option. There was some variability in the preference when all three COX-I options are available, with indomethacin (47.5%) being the most preferred option followed by ibuprofen (40%).

To our knowledge this is the first study to explore the relative health-related values and preferences for use of all available pharmacoprophylactic COX-I drugs for preventing morbidity and mortality in preterm infants. The study was developed through an iterative process of pilot testing and feedback from all stakeholders including parents, adults born preterm, neonatal practitioners and experts in clinical epidemiology. The information was shared using decision aids that incorporate absolute risk differences and certainty of evidence, specifically designed for knowledge translation and dissemination by the GRADE working group[20,21]. It has been previously shown that families better understand absolute risk reduction and visual aids (such as icon arrays and bar graphs) for risk communication, and decision making is likely to be improved when decision makers have knowledge of the certainty of evidence[22,23].

There is generally limited evidence on family values and preferences for neonatal interventions and outcomes. The only previous study by AlFaleh et al, that explored maternal preference for indomethacin prophylaxis versus symptomatic PDA treatment in preterm infants shows findings similar to our study results despite distinct methodological differences[9]. The said study, conducted in Saudi Arabia, enrolled 290 participants, most of whom were healthy pregnant women at 23-28 weeks' gestational age (GA) (75%). Whereas in our study, all participants have had the experience of living through one or more of the clinical outcomes discussed in the interview. Despite the methodological differences, both studies' findings are very similar. In the Alfaleh study, severe IVH was viewed as the most serious outcome (out of severe IVH, CLD, PDA, PDA surgery, oliguria and neurodevelopmental impairment) and participants had a strong preference for prophylactic indomethacin (82%)[9]. Similarly, in our study, severe IVH was rated as the most serious outcome after death, and 90% of participants preferred prophylactic indomethacin if this was available as the only option. Of note, a recent study by Webbe et al who interviewed 414 former patients, parents, healthcare professionals and researchers to develop a core outcome set for neonatal research studies demonstrated that the four top-ranked outcomes by severity from a patient and parent perspective were death, NEC, sepsis and brain injury on imaging[11]. This suggests that despite limited evidence on how parents and patients value neonatal outcomes, regardless of the study type or setting, death and severe IVH are highly valued with respect to their seriousness.

One would expect that given potential benefits for outcomes that are highly valued by parents, prophylaxis with indomethacin and ibuprofen will be routinely used or offered to families of infants born extremely preterm. However, in the real-world, use of prophylactic COX-Is remain limited as decisions are likely driven by clinician's values with potential harms being perceived to outweigh the benefits. Out of 4720 infants born <750g or <26 weeks' GA in Canadian NICUs between 2010-2018, only 1045 (22.1%) received prophylactic indomethacin[24]. There could be several reasons for lower usage of prophylactic COX-Is. A Canadian retrospective cohort study of 4268 extremely low birth weight infants showed that prophylactic indomethacin was associated with increased odds of gastrointestinal perforation independently from early feeding (aOR [adjusted Odds Ratio] 2.43, 95% CI 1.41 to 4.19)[3]. In addition, another recent cohort study of infants born <750g or <26 weeks' GA showed that co-exposure of antenatal steroids and prophylactic indomethacin was associated with increased odds of spontaneous gastrointestinal perforation, especially if antenatal steroids were received within 7 days before birth (aOR 1.67, 95% CI 1.15-2.43)[24]. Moreover, the recent finding of increased risk of gastrointestinal perforation when concomitantly used with prophylactic hydrocortisone (OR 2.50; 95% CI, 1.33 to 4.69), from an individual patient data meta-analysis of 4 RCTs, has also concerned clinicians[17]. The latter was reflected in our study when we found that two-third of the participants who initially opted for indomethacin, subsequently opted out when presented with the benefits and harms of prophylactic hydrocortisone.

With regards to prophylactic ibuprofen, previous systematic reviews did not find a statistically significant benefit for severe IVH (RR 0.67; 95% CI 0.45 to 1.00) or death (RR 0.93, 95% CI 0.50 to 1.74)[15]. In addition, there are concerns regarding the increased risk of pulmonary hypertension with both the ibuprofen tromethamine (THAM) and lysine preparations[25–27]. As a result, ibuprofen as a prophylactic therapy has mostly been abandoned by clinicians. However, the results of our study bring to light the perspectives of parents and patients when presented with the updated evidence. Guideline developers should consider these perspectives while developing future guidelines on prophylactic COX-I use in preterm infants.

There are several limitations that should be considered while interpreting and applying the results of the study. First, our sample size for the formal phase II study was limited to only 40 and the study population was predominantly White (77.5%) with a much smaller representation of Black (2.5%) or Indigenous (5%) population. As a result, our sample size was insufficient to explore potential differences in responses based on ethnicity, education, geographic region, or healthcare system. The primary rationale for limiting the sample size to 40 was to ensure timely study completion so that evidence from this study and the corresponding systematic review[10] remained relevant and up-to-date for a guideline development exercise on this topic planned by members of the authoring team for March 2022. Additional large studies of participants from different socio-demographic backgrounds are required to explore if participant preferences and their rationale for prophylactic interventions vary based on ethnicity, education and socio-economic backgrounds. Second, all interviews were conducted by one individual, which increases the risk of implicit bias during the interview process despite having a structured interview format, which in turn may influence participant responses. However, independent thematic analysis of 20 participants by a second researcher failed to identify any additional themes from the interview transcripts. Third, participant preferences for or against an intervention may be directly related to the evidence presented. In this study, we chose to present evidence on clinically meaningful outcomes obtained from a systematic review of RCTs only as they are deemed to be the most unbiased source of evidence. Additional data on adverse events such as gastrointestinal perforation obtained from observational studies may have resulted in more conservative responses with more parents refraining from prophylactic COX-I therapy.

Conclusion

In summary, death and severe IVH were rated as the two most important undesirable outcomes in relation to prophylactic COX-I use in preterm infants. While indomethacin was the most preferred form of prophylaxis, variability was noted in the choice of COX-I interventions when participants were presented with the benefits and harms of each drug. Our study offers unique insights into how parents of preterms and former preterm infants value clinical outcomes and perceive the benefits and harms of interventions for preventing

morbidity and mortality. The knowledge of parent and patient preferences for COX-I pharmacoprophylaxis generated from our study should inform guideline developers as they formulate guideline recommendations on prophylactic COX-I use in preterm infants. This and similar studies on family preferences may therefore act as a novel bridge for translating the evidence generated through a systematic review of evidence into clinical practice guideline recommendations.

Acknowledgements

We would like to thank Ms. Fabiana Bacchini, Executive Director of the Canadian Premature Babies Foundation, for her help and support in recruitment of potential participants for the study.

Funding

The authors have no funding to disclose.

Conflict of Interest Statement

The authors do not have any conflicts of interest to disclose.

References

1. Benitz WE, Committee on Fetus and Newborn, American Academy of Pediatrics. Patent Ductus Arteriosus in Preterm Infants. Pediatrics. 2016 Jan;137(1). doi: 10.1542/peds.2015-3730. Epub 2015 Dec 15

2. Wolf WM, Snover DC, Leonard AS. Localized intestinal perforation following intravenous indomethacin in premature infants. J Pediatr Surg. 1989 Apr;24(4):409–10.

3. Stavel M, Wong J, Cieslak Z, Sherlock R, Claveau M, Shah PS. Effect of prophylactic indomethacin administration and early feeding on spontaneous intestinal perforation in extremely low-birth-weight infants. J Perinatol. 2017;37(2):188–93.

4. Mitra S, Reid M, McDougall B, Johnston BC. Are neonatal clinical practice guidelines truly evidence-based? A case for incorporating family values and preferences. Acta Paediatr. 2019 Sep;108(9):1564–6.

5. Reese J, Shelton EL, Slaughter JC, McNamara PJ. Prophylactic Indomethacin Revisited. J Pediatr. 2017 Jul;186:11-14.e1.

6. Zhang Y, Coello PA, Brożek J, Wiercioch W, Etxeandia-Ikobaltzeta I, Akl EA, et al. Using patient values and preferences to inform the importance of health outcomes in practice guideline development following the GRADE approach. Health Qual Life Outcomes. 2017 May 2;15(1):52.

7. Weiss EM, Xie D, Cook N, Coughlin K, Joffe S. Characteristics Associated With Preferences for Parent-Centered Decision Making in Neonatal Intensive Care. JAMA Pediatr. 2018 May 1;172(5):461–8.

8. Soltys F, Philpott-Streiff SE, Fuzzell L, Politi MC. The importance of shared decision-making in the neonatal intensive care unit. Journal of Perinatology. 2020 Mar;40(3):504–9.

9. AlFaleh K, Alluwaimi E, AlOsaimi A, Alrajebah S, AlOtaibi B, AlRasheed F, et al. A prospective study of maternal preference for indomethacin prophylaxis versus symptomatic treatment of a patent ductus arteriosus in preterm infants. BMC Pediatr. 2015 Apr 22;15:47.

10. Mitra S, Gardner CE, MacLellan A, Disher T, Styranko DM, Campbell-Yeo M, et al. Prophylactic cyclo-oxygenase inhibitor drugs for the prevention of morbidity and mortality in preterm infants: a network meta-analysis. Cochrane Database Syst Rev. 2022 Apr 1;4:CD013846.

11. Webbe JWH, Duffy JMN, Afonso E, Al-Muzaffar I, Brunton G, Greenough A, et al. Core outcomes in neonatology: development of a core outcome set for neonatal research. Arch Dis Child Fetal Neonatal Ed. 2020;105(4):425-431.

12. Alonso-Coello P, Ebrahim S, Guyatt GH, Tikkinen KAO, Eckman MH, Neumann I, et al. Evaluating patient values and preferences for thromboprophylaxis decision making during pregnancy: a study protocol. BMC Pregnancy Childbirth. 2012 May 30;12:40.

13. Eckman MH, Alonso-Coello P, Guyatt GH, Ebrahim S, Tikkinen KAO, Lopes LC, et al. Women's values and preferences for thromboprophylaxis during pregnancy: a comparison of direct-choice and decision analysis using patient specific utilities. Thromb Res. 2015 Aug;136(2):341–7.

14. Fowlie PW, Davis PG, McGuire W. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. Cochrane Database Syst Rev. 2010 Jul 7;(7):CD000174.

15. Ohlsson A, Shah SS. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev. 2019 21;6:CD004213.

16. Ohlsson A, Shah PS. Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants. Cochrane Database Syst Rev. 2020 27;1:CD010061.

17. Shaffer ML, Baud O, Lacaze-Masmonteil T, Peltoniemi OM, Bonsante F, Watterberg KL. Effect of Prophylaxis for Early Adrenal Insufficiency Using Low-Dose Hydrocortisone in Very Preterm Infants: An Individual Patient Data Meta-Analysis. J Pediatr. 2019 Apr;207:136-142.e5.

18. Boyatzis RE. Transforming qualitative information: thematic analysis and code development. 1998.

19. Applied Thematic Analysis [Internet]. SAGE Publications Inc. 2020 [cited 2020 Oct 28]. Available from: https://us.sagepub.com/en-us/nam/applied-thematic-analysis/book233379

20. Vandvik PO, Brandt L, Alonso-Coello P, Treweek S, Akl EA, Kristiansen A, et al. Creating clinical practice guidelines we can trust, use, and share: a new era is imminent. Chest. 2013 Aug;144(2):381–9.

21. Agoritsas T, Heen AF, Brandt L, Alonso-Coello P, Kristiansen A, Akl EA, et al. Decision aids that really promote shared decision making: the pace quickens. BMJ. 2015 Feb 10;350:g7624.

22. Zipkin DA, Umscheid CA, Keating NL, Allen E, Aung K, Beyth R, et al. Evidence-based risk communication: a systematic review. Ann Intern Med. 2014 Aug 19;161(4):270–80.

23. Hultcrantz M, Rind D, Akl EA, Treweek S, Mustafa RA, Iorio A, et al. The GRADE Working Group clarifies the construct of certainty of evidence. J Clin Epidemiol. 2017 Jul;87:4–13.

24. Kandraju H, Kanungo J, Lee KS, Daspal S, Adie MA, Dorling J, et al. Association of Co-Exposure of Antenatal Steroid and Prophylactic Indomethacin with Spontaneous Intestinal Perforation. J Pediatr. 2021 Aug;235:34-41.e1.

25. Bellini C, Campone F, Serra G. Pulmonary hypertension following L-lysine ibuprofen therapy in a preterm infant with patent ductus arteriosus. CMAJ. 2006 Jun 20;174(13):1843–4.

26. Gournay V. The ductus arteriosus: physiology, regulation, and functional and congenital anomalies. Arch Cardiovasc Dis. 2011 Nov;104(11):578–85.

27. Sehgal A, Kumarshingri PSN. Pulmonary hypertension in an infant treated with ibuprofen. Indian J Pediatr. 2013 Aug;80(8):697–9.

Table 1. Demographic profile of participants in the formal phase II study (n=40)

Characteristic	Measure
Type of participant [n (%)]	
Parent of a very preterm infant	31 (77.5%)
Adult former preterm infant	9 (22.5%)
Age [n (%)]	
18-24	7 (17.5%)
25-34	20 (50%)
35-44	12 (30%)
45-54	1 (2.5%)
Ethnicity [n (%)]	
Any visible minority	6 (15%)
Indigenous	2 (5%)
African descent	1 (2.5%)
Any other under-represented group	0 (0%)
None of the above	31 (77.5%)
Highest level of education completed [n (%)]	
Less than high school	0 (0%)
High school	5 (12.5%)
College or trade school certificate or diploma	8 (20%)
University undergraduate degree	16 (40%)
University post graduate degree	11 (27.5%)
Country of origin [n (%)]	
Canada	35 (87.5%)
United Kingdom	3 (7.5%)
Other	2 (5%)
Gestational age of the participant or their child at birth, weeks (interquartile range)	26 weeks (25 to 28.8 weeks)

Table 2. Value placed on outcomes

Outcome	Score [median (Interquartile Range)]
Death	100 (100-100)
Severe intraventricular hemorrhage	90 (80-100)
Chronic lung disease	70 (60-80)
Necrotizing enterocolitis	80 (70-90)
Patent ductus arteriosus	75 (52.5 – 90)

Table 3. Preference for prophylactic therapies

Drug	Frequency (percentage) of participants who said 'yes' [n=40]	Thematic analysis summary	
		Major themes	Coding frequency *[Number of participants who alluded to this theme out of the ones who said yes]*
When therapies are offered as the only option (vs no prophylaxis)			
Indomethacin	36 (90%)	Reduces death (critical outcome)	22 (61.1%)
		Reduces severe IVH (critical outcome)	21 (58.3%)
		Possible increase in CLD less worrisome	12 (33.3%)
		Higher certainty in evidence for benefit (reduction in death, sIVH, NEC), lower certainty in evidence for harm (increase in CLD)	9 (25%)
Ibuprofen	34 (85%)	Reduces death (critical outcome)	14 (41.2%)
		Reduces severe IVH (critical outcome)	15 (44.1%)
		No obvious evidence of harm	10 (29.4%)
Acetaminophen	4 (10%)	Not enough evidence, high uncertainty*	25 (69.4%)
		Possible harm with increased risk of IVH*	9 (25%)
When all 3 options are available (vs not choosing anything)			
Indomethacin	19 (47.5%)	Overall certainty of benefit better with indomethacin	13 (68.4%)
Ibuprofen	16 (40%)	No overall harm	8 (50%)
		Indomethacin cannot definitely be used with hydrocortisone, hence going with the 2nd best option	7 (43.6%)
No prophylaxis	5 (12.5%)	Would want to give hydrocortisone if offered	2 (40%)

* For acetaminophen, the major themes reflect the rationale of participants for not choosing acetaminophen
CLD, Chronic lung disease; IVH, Intraventricular hemorrhage; NEC, Necrotizing Enterocolitis

Table 4. Preference for indomethacin vs hydrocortisone prophylaxis among participants who initially opted for indomethacin

Drug	Frequency (percentage) of participants who said 'yes' [n=36]	Thematic analysis summary	
		Major themes	Coding frequency *[Number of participants who alluded to this theme out of the ones who said yes]*
Indomethacin	12 (33.3%)	Reduction of IVH is important; also reduces death	8 (66.7%)
Hydrocortisone	24 (66.7%)	Survival and survival without CLD better with hydrocortisone compared to indomethacin	18 (75%)

CLD, Chronic lung disease; IVH, Intraventricular hemorrhage

Table 5. Importance of having participant values and preferences included in decision-making

Choice	Frequency (percentage) [n=40]	Thematic analysis summary	
		Major themes	Coding frequency *[Number of participants who alluded to this theme out of the ones who said yes]*
Not important *(I do not want to know the details; I will defer this decision to the doctor)*	3 (7.5%)	–	–
Somewhat important *(I would like to know the benefits and harms of treatment and the rationale behind the doctor's decision; but I will follow what the doctor feels best)*	22 (55%)	First 24h after birth is overwhelming, lot of things to process; so would want to be aware of benefits and harms, but will trust clinician's judgment	17 (77.3%)
Important *(I want to have a discussion with the doctor regarding the benefits and harms related to the most important outcomes and then make a decision together)*	14 (35%)	Would like to be involved in the discussion regarding benefits and harms	6 (43%)
Highly Important *(I would like to make the decision myself based on the information provided)*	1 (2.5%)	–	–

Appendix A: Health conditions descriptions

Patent ductus arteriosus (PDA)

Ductus arteriosus is a small passage in the heart. Normally, this passage closes shortly after birth when the baby takes their first breaths. When the ductus arteriosus remains open after birth, it is called a patent ductus arteriosus or PDA. This is a heart defect that may resolve on its own, but it can increase the risk for more serious outcomes.

Potential complications of PDA

The following outcomes are the most common and most concerning outcomes associated with a PDA, affecting the brain, the gut and the lungs.

The impact of these outcomes can range from being transient with minimal long-term effects to very severe long-lasting effects and can even cause death. The following descriptions include the worst-case scenarios for each of these conditions. We will describe each outcome, then ask you how you perceive and rate the seriousness of these possible outcomes

Lung-related complications

A premature baby's lungs are not fully developed, and babies may require breathing support with the help of a ventilator device with or without a breathing tube for extended periods. Being born early and prolonged use of breathing support may cause injury or damage to the lungs, known as chronic lung disease. A PDA can lead to extra blood flow to the lungs, which increases the need for breathing support and as a result increases the risk of lung damage and chronic lung disease.

Chronic lung disease:

When the lungs are damaged, some of the damaged lung tissue may be replaced by scar tissue, and the lungs may be unable to work properly for several weeks and months. Babies with CLD will have trouble breathing and may require oxygen or hospitalization for long

periods of time, which may affect development. Babies with CLD often go home requiring oxygen therapy and have a higher chance of getting hospitalized multiple times with breathing problems, especially in the first year of life, and have a higher chance of dying compared to babies who do not have CLD.

Gut-related complications

Premature babies have underdeveloped digestive systems, and are at an increased risk of damage to their gut from many different causes. A PDA can reduce the blood flow to the gut, which increases the risk of damage.

Necrotizing enterocolitis (NEC) is a disease of the gut that primarily affects premature and medically fragile infants. In the most severe forms, large sections of the gut are damaged, becoming black and dead and may perforate. Many babies with NEC will require surgery to remove the dead and perforated bowel, followed by a prolonged course of hospital stay and intravenous nutrition. 20-30% of babies diagnosed with NEC will die in spite of medical/surgical treatment. Babies who survive following NEC may have lifelong developmental problems likely related to multiple surgeries, frequent hospitalizations and poor nutrition**.**

Brain-related complications

Blood vessels inside a premature baby's brain are thin and fragile. They are sensitive to changes in blood flow and they can tear easily. A PDA results in changes in normal blood flow, which increases the risk of torn blood vessels and bleeding in the brain.

Severe Intraventricular Hemorrhage (IVH):

Torn blood vessels may cause bleeding inside the ventricles of brain (ventricles are chambers inside the brain filled with fluid). This is called intraventricular hemorrhage (IVH). IVHs are graded from 1 to 4 based on their severity. When the bleeding fills up and stretches out the ventricles or involves the surrounding brain matter it is known as severe intraventricular hemorrhage (grades 3 and 4). Severe IVH increases the risk for long lasting brain damage and severe developmental delay later in life.

Appendix B. Structured interview slides

Medications to prevent PDA in preterm infants

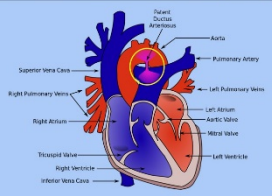
SURVEY OF HEALTH-RELATED VALUES AND PREFERENCES

Parts of the survey

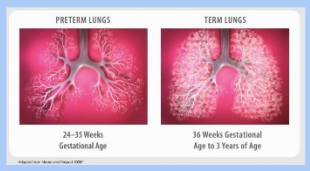
1. Information related to having a PDA, problems and important health outcomes
2. Reviewing and rating the risks and benefits or each medication
3. Further feedback related to your decisions and ratings, and the overall survey

Part 1: Information PDA and Associated Outcomes

Patent ductus arteriosus (PDA)

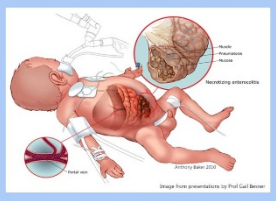


Potential impact on the lungs



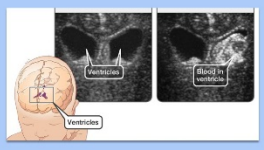
Chronic lung disease

Potential impact on the gut



Necrotizing enterocolitis (NEC)

Potential impact on the brain

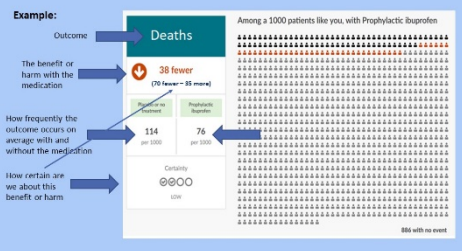


Severe Intraventricular Hemorrhage (IVH)

Part One Questions - Please rate the seriousness of each condition:

1. Death — 0 10 20 30 40 50 60 70 80 90 100
2. Severe intraventricular hemorrhage (IVH) — 0 10 20 30 40 50 60 70 80 90 100
3. Chronic lung disease (CLD) — 0 10 20 30 40 50 60 70 80 90 100
4. Necrotizing enterocolitis (NEC) — 0 10 20 30 40 50 60 70 80 90 100
5. Patent ductus arteriosus (PDA) — 0 10 20 30 40 50 60 70 80 90 100

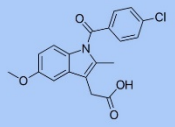
Part 2: Benefits and harms of preventative medications



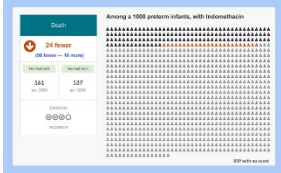
Medications used to prevent PDA

1. **Indomethacin**
2. **Ibuprofen**
3. **Acetaminophen**

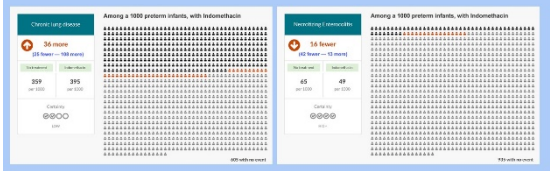
Medication 1: Indomethacin



Indomethacin



Indomethacin



Part Two Question 1. For indomethacin:

Would you give this medication to your baby? Yes/ No

Severe brain bleeding	Death	Chronic lung disease	Necrotizing Enterocolitis
43 fewer (65 fewer - 16 fewer)	24 fewer (58 fewer — 16 more)	36 more (25 fewer — 108 more)	16 fewer (42 fewer — 13 more)
127 per 1000 / 84 per 1000	161 per 1000 / 137 per 1000	359 per 1000 / 395 per 1000	65 per 1000 / 49 per 1000
Certainty ⊕⊕⊕○ MODERATE	Certainty ⊕⊕⊕○ MODERATE	Certainty ⊕⊕○○ LOW	Certainty ⊕⊕⊕⊕ HIGH

Answer if YES to indomethacin

Some doctors may offer to use a steroid medication at birth called **Hydrocortisone**

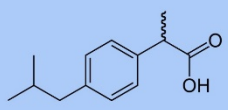
Potential benefits with hydrocortisone at birth

Indomethacin and hydrocortisone cannot be used together – The risk of gut perforation requiring surgery is 2.5-fold higher!

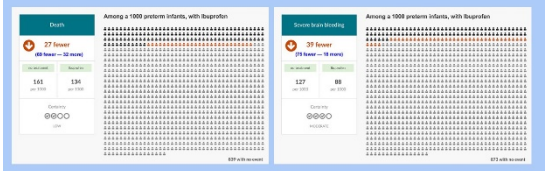
If you had to choose between indomethacin and hydrocortisone which one will you choose?

A. Indomethacin
B. Hydrocortisone

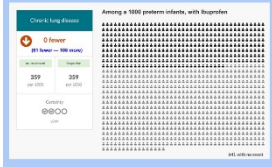
Medication 2: Ibuprofen



Ibuprofen



Ibuprofen

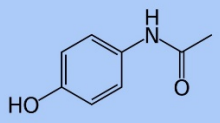


Part Two Question 2. For ibuprofen:

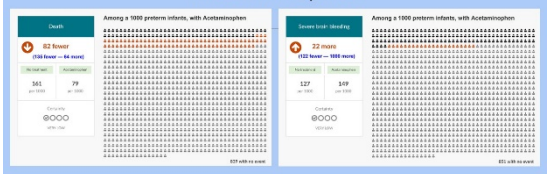
Would you give this medication to your baby? Yes/ No

Severe brain bleeding	Death	Chronic lung disease	Necrotizing Enterocolitis
39 fewer (75 fewer — 18 more)	27 fewer (69 fewer — 32 more)	0 fewer (61 fewer — 108 more)	18 fewer (45 fewer — 26 more)
127 per 1000 / 88 per 1000	161 per 1000 / 134 per 1000	359 per 1000 / 359 per 1000	65 per 1000 / 47 per 1000
Certainty ⊕⊕⊕○ MODERATE	Certainty ⊕⊕○○ LOW	Certainty ⊕⊕○○ LOW	Certainty ⊕⊕⊕⊕ HIGH

Medication 3: Acetaminophen



Acetaminophen



Part Two Question 3. For acetaminophen:

Would you give this medication to your baby? Yes/ No

Part Two Question 4.

If given the opportunity to give one of these medications to your own baby, which would you choose?:

1. Indomethacin
2. Ibuprofen
3. Acetaminophen
4. I prefer not to give my baby any of these medications at birth

Part Three Question 1.

How important it is to have your values and preferences included in decision-making for this particular scenario (use of indomethacin/ibuprofen/acetaminophen at birth)?

1. Not important (I do not want to know the details; I will defer this decision to the doctor)
2. Somewhat important (I would like to know the benefits and harms of treatment and the rationale behind the doctor's decision; but I will follow what the doctor feels best)
3. Important (I want to have a discussion with the doctor regarding the benefits and harms related to the most important outcomes and then make a decision together)
4. Highly Important (I would like to make the decision myself based on the information provided)

Part 3 Question 2.

What were the most important factors behind your decision?

Appendix C. Demographic profile of participants in the pilot phase I study (n=7)

Characteristic	Measure
Type of participant [n (%)]	
Parent of a very preterm infant	5 (71%)
Adult former preterm infant	2 (29%)
Age [n (%)]	
18-24	1 (14%)
25-34	1 (14%)
35-44	4 (57%)
45-54	1 (14%)
Ethnicity [n (%)]	
Any visible minority	0 (0%)
Indigenous	0 (0%)
African descent	0 (0%)
Any other under-represented group	0 (0%)
None of the above	7 (100%)
Highest level of education completed [n (%)]	
Less than high school	0 (0%)
High school	0 (0%)
College or trade school certificate or diploma	2 (29%)
University undergraduate degree	3 (43%)
University post graduate degree	2 (29%)
Country of origin [n (%)]	
Canada	6 (86%)
United Kingdom	1 (14%)

Appendix D. Post-hoc exploratory analysis: Responses by participant group

Value placed on outcomes

Outcome	Adult former preterm infant (n=9) [Median (IQR)]	Parent of preterm infant (n=31) [Median (IQR)]	2-sided P value (Mann-Whitney U test)
Death	100 (100-100)	100 (100-100)	Unable to compute
Severe IVH	80 (75-90)	90 (90-100)	0.08
CLD	60 (55-75)	80 (60-80)	0.15
NEC	80 (65-90)	80 (70-90)	0.47
PDA	60 (50-85)	80 (60-90)	0.25

Choice of pharmacoprophylaxis (when presented as the only option)

Choice of pharmacoprophylaxis	Adult former preterm infant (n=9)	Parent of preterm infant (n=31)	2-sided P value (z test)
Indomethacin	9	27	0.58
Ibuprofen	8	26	1.0
Acetaminophen	0	4	0.58

Choice between indomethacin and hydrocortisone

Choice between indomethacin and hydrocortisone	Adult former preterm infant (n=9)	Parent of preterm infant (n=27)	2-sided P value (Fisher's exact test)
Indomethacin	1 (11.1%)	11 (40.7)	0.22
Hydrocortisone	8 (88.9%)	16 (59.3%)	

Choice of pharmacoprophylaxis (when all 3 options are available)

Choice of pharmacoprophylaxis	Adult former preterm infant (n=9)	Parent of preterm infant (n=31)	2-sided P value (Fisher's exact test)
Indomethacin	5 (55.6%)	14 (45.2%)	0.43
Ibuprofen	4 (44.4%)	12 (38.7%)	
No prophylaxis	0	5 (16.1%)	

Importance of having participant values and preferences included in decision-making

Choice	Adult former preterm infant (n=9)	Parent of preterm infant (n=31)	2-sided P value (Fisher's exact test)
Not important	0	3 (9.7%)	0.69
Somewhat important	6 (66.7%)	16 (51.6%)	
Important	3 (33.3%)	11 (35.5%)	
Highly Important	0	1 (3.2%)	

CHAPTER 4: GUIDELINE DEVELOPMENT

A Clinical Practice Guideline on the use of Prophylactic Cyclo-oxygenase inhibitor drugs for the prevention of morbidity and mortality in extremely preterm infants

Authors:

Souvik Mitra[1,2], Leah Whitehead[2], Katie Smith[3], Breagh MacLean[4], Rebekah Nixon[5], Andrew Veysey[2], Marsha Campbell-Yeo[1,2], Stefan Kuhle[1], Chris Gale[6], Roger Soll[7], Jon Dorling[1,8], Bradley C. Johnston[1,9]

Affiliations:

[1]Dalhousie University, Halifax, Canada, [2]IWK Health Centre Halifax, Canada; [3]Nova Scotia Community College, Halifax, Canada; [4]Service Nova Scotia, Halifax, Canada; [5]Hampshire Hospitals NHS Foundation Trust, Winchester, UK; [6]Imperial College, London, UK; [7]University of Vermont, Burlington, US; [8]Southampton Children's Hospital, Southampton UK; [9]Departments of Nutrition, Epidemiology and Biostatistics, Texas A&M University, College Station, US

Address of correspondence to:

Souvik Mitra, MD, MSc, FRCPC
Division of Neonatal-Perinatal Medicine; Department of Pediatrics; Department of Community Health and Epidemiology, Dalhousie University & IWK Health
Room G2214, 5850/5980 University Avenue P.O. Box 9700 Halifax, NS B3K 6R8
Tel: (902) 470-6490; Fax: (902) 470-6469
Email: Souvik.Mitra@iwk.nshealth.ca

STATUS: Manuscript ready for submission

Contributions of authors

SM conceived the project, under the mentorship of BCJ and JD. SM and BCJ co-chaired the panel meetings. SM drafted the manuscript. SM, LW, KS, BM, RN, AV, MCY, SK, CG, RS, BCJ and JD reviewed all drafts, and approved the final version of the manuscript.

Abstract

Background: Prophylactic cyclooxygenase inhibitor (COX-I) drugs such as indomethacin, ibuprofen and acetaminophen may prevent morbidity and mortality in extremely preterm infants (born ≤28 weeks' gestational age). However, there is controversy around which COX-I drug is the most effective and safest in preterm infants, which has resulted in considerable variability in their use in clinical practice.

Objective: To develop rigorous and transparent clinical practice guideline recommendations for the prophylactic use of COX-I drugs for the prevention of mortality and morbidity in extremely preterm infants.

Methods: The GRADE (Grading of Recommendations Assessment, Development and Evaluation) Evidence-to-Decision (EtD) framework for multiple comparisons was used to develop the guideline recommendations. A 12-member expert panel, including five experienced neonatal care providers, two methods experts, one pharmacist, two parents of former extremely preterm infants and two adults born extremely preterm, was convened. A rating of the most important clinical outcomes was established a priori.

Results: Evidence from a Cochrane systematic review and network meta-analysis, and a cross-sectional mixed-methods study exploring family values and preferences, conducted in parallel and de novo to aid guideline development, were used as the primary sources of evidence. The guideline comprised three recommendations, one each for prophylactic indomethacin, ibuprofen and acetaminophen.

The panel recommended that prophylaxis with intravenous indomethacin may be considered in extremely preterm infants [conditional recommendation, moderate certainty in estimate of effects]. The panel recommended against routine use of ibuprofen prophylaxis in this gestational age group [conditional recommendation, low certainty in the estimate of effects]. The panel strongly recommended against use of prophylactic acetaminophen [strong recommendation, very low certainty in estimate of effects].

Interpretation: Based on our conditional recommendation for prophylactic indomethacin, shared decision making with parents of extremely preterm infants is encouraged to evaluate

their values and preferences. Although prophylactic ibuprofen therapy is conditionally not recommended, shared decision making with parents is encouraged in centers that lack access to indomethacin and have high rates of severe IVH and death in extremely preterm infants. Prophylactic acetaminophen is not recommended until further research evidence is available.

Rationale and purpose

Infants born extremely preterm (at or below 28 weeks of gestational age) are at a high risk for neonatal complications such as severe intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC) and chronic lung disease (CLD). A common contributor for all three of these pathophysiological mechanisms is postulated to be the patent ductus arteriosus (PDA)[1]. Currently available pharmacotherapeutic options to prevent a PDA and related complications include cyclo-oxygenase inhibitor (COX-I) drugs such as indomethacin, ibuprofen, and acetaminophen. COX-I drugs themselves are associated with catastrophic adverse effects such as NEC and spontaneous gastrointestinal perforation (SIP)[2,3]. Therefore, successful prevention of a symptomatic PDA may reduce the risk of severe IVH and CLD but at the same time increase the risk of SIP and NEC. As a result, for some care-providers the desirable consequences of COX-I prophylaxis may not clearly outweigh its undesirable consequences, and hence there is often a reluctance among neonatal practitioners to consider pharmacoprophylaxis for PDA in preterm infants. Unsurprisingly, there is wide variation in clinical practice regarding COX-I prophylaxis in preterm infants. A 2014 Canadian cohort study demonstrated marked variation (0-78%) in use of prophylactic COX-Is[3]. Similarly, a survey of 35 Neonatal Research Network hospitals across the United States showed that while one-third of neonatal intensive care units (NICUs) never used COX-I prophylaxis, a third used pharmacoprophylaxis in 45%–98% of their extremely preterm neonates[4]. The decision on PDA pharmacoprophylaxis has likely been driven by the perceived benefits versus potential risks as determined by the treating physician, with little or no input from families regarding their health outcome related values and preferences when faced with the benefits and risks of COX-I drugs. This variation in practice suggests that there is a need for a transparent clinical practice guideline on the prophylactic use of COX-Is for the prevention of morbidity and mortality in preterm infants.

Previous guidelines and statements

A comprehensive electronic search of MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) for clinical practice guidelines on COX-I pharmacoprophylaxis in preterm infants was conducted with the help of an expert librarian.

We identified two position statements from the Canadian Pediatric Society (CPS) that refer to the use of prophylactic indomethacin. The CPS position statement on "Neuroprotection from acute brain injury in preterm infants" recommends that "*prophylactic indomethacin should be targeted to high-risk, extremely preterm infants, and the decision to treat should be based on combined risk factors (Grade A recommendation)*"[5]. Similarly, the recent CPS position statement on "Management of the patent ductus arteriosus in preterm infants" recommend that "*selective prophylaxis with intravenous (IV) indomethacin may be considered for extremely low birth weight (ELBW) infants at high risk for severe intraventricular hemorrhage (IVH) (conditional recommendation)"*[6]. The latter statement does acknowledge the dearth of evidence on health-related patient and family values and preferences in relation to COX-I prophylaxis. In addition, a recent state-of-the-art review article from the American Academy of Pediatrics recommend: *"Consider early targeted prophylaxis of PDA with indomethacin (<24 hours) in selected infants by predefined criteria (e.g., male sex, ELBW, GA<26 weeks, low unit spontaneous closure rate)"*[7].

To our knowledge, there are no clinical practice guidelines that provide explicit recommendations on the use of all three available COX-I drugs (indomethacin, ibuprofen and acetaminophen). We have not been able to identify any clinical practice guideline for preterms where explicit values and preferences of families have been addressed and incorporated.

The purpose of this guideline was to provide rigorous and transparent practice recommendations for the prophylactic use of COX-Is for prevention of PDA-related complications including death, severe IVH, CLD, and NEC in extremely preterm infants, incorporating family values and preferences. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) Evidence to decision (EtD) framework was used to transparently formulate the guideline recommendations[8,9]. The GRADE approach is a system for rating the certainty of a body of evidence on an outcome-by-outcome basis based on a systematic literature review and meta-analysis[10]. GRADE also offers a transparent and rigorously structured process for developing clinical practice guideline recommendations, either strong or weak (conditional), and either for or against an intervention[11].

Target population and key stakeholders

The specific target population that is intended to benefit from this guideline are extremely preterm (born ≤28 weeks' gestational age) infants, admitted to a tertiary care NICU. The key stakeholders and users for this guideline document include neonatal intensive care providers (physicians, nurse practitioners, nurses, respiratory therapists) and families of preterm infants being cared for in the NICU.

Perspective

While developing the recommendations, the perspective of the individual patients and their families were considered. This perspective allowed us to focus solely on the potential clinical benefits and harms of the patient with respect to family important outcomes.

Stakeholder involvement

a) Guideline Committee

i) Panel members: A guideline committee with relevant expertise and stakeholders was convened including (i) five neonatal practitioners (four neonatologists and one neonatal nurse practitioner, each with more than five years of experience working in a tertiary care NICU); (ii) two methodologists with expertise in advanced evidence synthesis methods; (iii) a pharmacist; (iv) two parents of infants born extremely preterm; (v) two adults born extremely preterm (12 panel members in total).

ii) Declaration and management of conflict of interest: Intellectual and financial conflicts of interest are common and can affect judgments and recommendations. Therefore, all panel members were required to declare any financial or intellectual conflicts in accordance with the American College of Physicians (ACP) Clinical Guidelines Committee (CGC) methods for the disclosure and management of conflict of interest (COI)[12].

b) *Incorporation of values and preferences of the target population:* Given the dearth of available evidence on family values and preferences, a cross-sectional mixed methods study including 40 participants (9 adults born extremely preterm; 31 parents of preterm infants) was conducted by members of the authoring team. The complete

results of the study were considered by the panel while formulating the recommendations.

Guideline Question

Should prophylactic cyclo-oxygenase inhibitors (COX-Is; indomethacin, ibuprofen or acetaminophen) be used to prevent morbidity and mortality in extremely preterm infants (born ≤28 weeks of gestational age)? Prophylaxis was defined as intravenous administration of the medication within 24 hours of birth without knowledge of presence of a PDA.

Health Outcomes

The guideline panel (n=12) that included relevant stakeholders initially generated the following list of health outcomes to consider for development of the guideline recommendations: all-cause mortality, severe IVH, NEC, gastrointestinal perforation, CLD, PDA ligation and neurodevelopmental impairment. Given the lack of evidence on neurodevelopmental impairment for all the three drugs on the SRNMA, neurodevelopmental impairment was replaced by cerebral palsy when considering the evidence for benefits and harms. The total number of outcomes considered was limited to seven to avoid overwhelming the panel and to facilitate effective decision-making[13].

Guideline panel meeting process

The Evidence-to-Decision framework for multiple comparisons, developed by the GRADE working group, was used to guide the panel meetings[9]. The panel was co-chaired by SM and BCJ. One week prior to the first meeting the panelists were provided with a draft EtD framework with provisional judgements and recommendations, the relevant scientific evidence, and a brief orientation video. The panel met virtually using Zoom™ three times for a total of four hours. In the first meeting the panelists were given an overview of the project, including a summary of the GRADE approach and the EtD framework to ensure that panelists understood their purpose, and how they would be asked to use this structured EtD information to inform their perspective, judgements and recommendations. The following process was followed to structure the panel meetings[8].

(a) *Judgements in relation to the EtD criteria:* One member of the panel (SM) presented the research evidence and the tentative judgement along with his rationale for the panel to discuss.

(b) *Voting process and criteria for reaching consensus:* Following discussion on each criterion, the panel was asked to vote using the Zoom Polling option. The members were encouraged to provide comments to explain their vote. Recommendations that reached 80% agreement from the panel were accepted as 'consensus'. The 80% threshold was based on the work by Lynn et al suggesting that at least 80% of experts must agree on an item in order to achieve content validity when there are at least 10 experts participating in consensus development[14]. Criteria that failed to reach 80% agreement were further discussed followed by a repeat voting until a reasonable consensus (75-79%) or consensus (80%) was reached.

(c) *Conclusions:* For the final recommendations, consensus was strictly defined as at least 80% agreement. Once 80% agreement was reached on all the recommendations (three in total; one for each medication) following one or multiple rounds of discussion and voting as required, the final conclusions were drafted by SM, edited by BCJ and circulated to the panel for approval.

Results

The panel recommended that prophylaxis with intravenous indomethacin may be considered in extremely preterm infants [conditional recommendation, moderate certainty in estimate of effects]. The panel recommended against routine use of ibuprofen prophylaxis in this gestational age group [conditional recommendation, low certainty in estimate of effects]. The panel strongly recommended against use of prophylactic acetaminophen [strong recommendation, very low certainty in estimate of effects]. The guideline panel's final recommendations are summarized in Table 1.

Review of the evidence

Evidence searches

Medline, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effectiveness (DARE), National Institute of Health Clinical Practice Guidelines databases were searched for existing reviews on prophylactic use of COX-I

drugs in preterm infants. Three previous Cochrane reviews were identified that had separately compared placebo/no treatment against prophylactic indomethacin, ibuprofen, or acetaminophen[15–17]. None of the reviews provided head-to-head comparisons between the three available pharmacoprophylactic agents. Therefore, for the purpose of the guideline development, a Cochrane network meta-analysis (NMA) was conducted to compare available pharmacoprophylactic options based on both direct and indirect evidence, and to subsequently provide the panel with up to date comparative effectiveness evidence with increased precision[18]. The search strategy for the NMA was last updated on December 9, 2021.

Summary of the evidence for benefits and harms of COX-Is

The evidence on benefits and harms were obtained from our team's 2022 Cochrane systematic review and NMA[18]. Certainty of evidence was assessed using the GRADE guidance for NMA[19], which was adopted by the panel for the purpose of assessing the certainty of desirable and undesirable outcomes. For the purpose of the EtD framework, desirable outcomes were defined as reduction of mortality, severe IVH, surgical PDA closure and cerebral palsy. Undesirable outcomes were defined as increase in NEC, gastrointestinal perforation and CLD. Thresholds for benefit or harm were defined a priori in the review using a partially contextualized approach as follows[18]: (a) For the outcome of mortality: small benefit/harm was defined as <20 fewer or more events per 1000, respectively. Moderate benefit/harm was defined as 20 to 50 fewer or more per 1000, respectively. Large benefit/harm was defined as >50 fewer or more per 1000 respectively; (b) For all other outcomes: Any effect <20 fewer or more per 1000 was defined as a trivial benefit or harm. No direction of effect was specified for trivial effects. Small benefit/harm was defined as 20-50 fewer or more per 1000 respectively. Moderate benefit/harm was defined as 50-100 fewer or more per 1000 respectively. Large benefit/harm was defined as >100 fewer or more per 1000, respectively. Language for interpretation for size of effect (benefit or harm) was based on the GRADE informative statements to communicate the findings of systematic reviews of interventions by Santesso et al[20]. The detailed summary of findings is presented in Appendix A and has been adapted from the study team's 2022 Cochrane systematic review and NMA[18].

Twenty-eight randomized controlled trials (RCTs) enrolling 3999 infants were included. Nineteen RCTs (2877 infants) compared indomethacin vs placebo, 7 RCTs (914 infants) compared ibuprofen vs placebo and 2 RCTs (208 infants) compared acetaminophen vs placebo.

The NMA demonstrated that indomethacin prophylaxis probably led to a small reduction in severe IVH (network Relative Risk [RR] 0.66, 95% Credible Intervals [CrI] 0.49 to 0.87; absolute risk difference [ARD] 43 fewer [95% CrI, 65 fewer to 16 fewer] per 1000; moderate-certainty), and a moderate reduction in mortality (network RR 0.85, 95% CrI 0.64 to 1.1; ARD 24 fewer [95% CrI, 58 fewer to 16 more] per 1000; moderate-certainty) compared to placebo.

Ibuprofen prophylaxis probably led to a small reduction in severe IVH (network RR 0.69, 95% CrI 0.41 to 1.14; ARD 39 fewer [95% CrI, 75 fewer to 18 more] per 1000; moderate-certainty) and a moderate reduction in surgical PDA closure (network RR 0.24, 95% CrI 0.06 to 0.64; ARD 66 fewer [95% CrI, from 82 fewer to 31 fewer] per 1000; moderate-certainty) compared to placebo.

The evidence was very uncertain on the effect of acetaminophen prophylaxis on severe IVH (network RR 1.17, 95% CrI 0.04 to 55.2; very low-certainty) or mortality (network RR 0.49, 95% CrI 0.16 to 1.4; very low-certainty).

Summary of the evidence for values and preferences of COX-Is

The evidence on patient values and preferences was obtained from a recently concluded cross-sectional semi-structured mixed-methods study involving adults born very preterm (born <32 weeks of gestation) or families of very preterm infants currently in the NICU, or having graduated from the NICU in the last 5 years. The study showed that for parents and patients, mortality (median score 100, Interquartile range [IQR] 100-100) and severe IVH (median score 90, IQR 80-100) were the two most serious outcomes in relation to prophylactic COX-I use. The majority of the participants were willing to consider prophylactic indomethacin (90%) or ibuprofen (85%), but not acetaminophen (10%) when offered as the only option. There was some variability in the preference when all three COX-I options were available, with indomethacin (47.5%) being the most preferred option followed by ibuprofen (40%), while the remaining 12.5% opted for no prophylaxis.

Evidence to decision framework

The detailed evidence-to-decision framework is presented in Appendix B. A summary of the panel's considerations is presented below:

Desirable outcomes

For the *desirable health consequences*, the panel felt that out of all three interventions, indomethacin had the best evidence of benefit (with no risk of harm) with regards to the critical outcome of severe IVH. For ibuprofen, although there appeared to be a benefit with respect to severe IVH, a trivial harm could not be ruled out. Therefore, indomethacin was voted as most effective (12/12 panel members) followed by ibuprofen (12/12 of panel members). Acetaminophen was voted as least effective (11/12 of panel members) as the panel was not confident in its potential desirable effects given the very low certainty of the current evidence.

Undesirable outcomes

For the *undesirable health consequences*, there was no definite evidence of harm for indomethacin and ibuprofen, although the upper bound of 95% CrIs for both drugs suggested possibility of trivial harm with respect to NEC and large harm with respect to gastrointestinal perforation and CLD. After voting, neither indomethacin nor ibuprofen were ranked as least harmful. The panel noted that there was no available RCT data on any of the potential undesirable effects for acetaminophen.

Values

Regarding patient values, 75% of the panel members felt that there was no substantial variability in how the participants of the values and preferences study valued the main outcomes, i.e., death and severe IVH. Twenty-five percent of the panel members felt that there was some uncertainty as all the main outcomes were scored fairly highly by the study participants and there was no clear distinction between them. After two rounds of voting and discussion, the final consensus was that there was "probably no important uncertainty" in how much people value the main outcomes.

Balance of effects

Overall, the panel felt that indomethacin had the best balance out of all the three medications, followed by ibuprofen, while acetaminophen had the worst balance.

Acceptability

For prophylactic indomethacin, the panel critically appraised the evidence from observational studies that have suggested an increased risk of gastrointestinal perforation and felt that the association was questionable given the methodological quality of the studies[3,21]. However, the panel did acknowledge the evidence from RCTs that demonstrated a significantly increased risk of gastrointestinal perforation (Odds Ratio [OR] 2.50; 95% Confidence Intervals [CI], 1.33 to 4.69) with co-administration of indomethacin and hydrocortisone[22]. The panel therefore unanimously agreed that these two medications should not be co-administered and acknowledged that acceptability of prophylactic indomethacin may be lower in centers that have adopted the use of prophylactic hydrocortisone.

For ibuprofen, the panel agreed that the evidence suggesting increased risk of pulmonary hypertension was of low quality[23,24]. Therefore, similar to indomethacin, ibuprofen was deemed to have "intermediate acceptability".

For acetaminophen, the panel was divided on their opinion. Half of the panel felt that since prophylactic acetaminophen had no proven benefit, and possible harm, albeit from low quality observational studies, this had the "worst acceptability" of the 3 drugs, while the remainder of the panel felt it should be placed in the "intermediate acceptability" category with indomethacin and ibuprofen.

Feasibility

There was consensus among panel members that intravenous ibuprofen was the most feasible given it is most widely available. For indomethacin, 75% of the panel members felt that it was of intermediate feasibility, given it is unavailable in the United Kingdom. For acetaminophen, 75% of the panel members felt that it was least feasible given the intravenous formulation is still not widely available. Given that infants born extremely preterm are on minimal to no enteral feeds in the first 24 hours after birth, administering the medications through the enteral route was not considered as a feasible alternative by the panel. Therefore, the oral formulations of the COX-I drugs were not considered for the purpose of this guideline.

Rationale for recommendations

Prophylactic indomethacin

The panel determined that overall, there was moderate certainty of evidence from RCTs suggesting prophylactic indomethacin may reduce severe IVH and death without increasing the risk of NEC or gastrointestinal perforation. The panel especially highlighted the fact that indomethacin was the only intervention which was associated with a statistically significant reduction in severe IVH. Compared to the other COX-I options, the certainty for benefit for the most important clinical outcomes (death and severe IVH) was the best for indomethacin. However, the panel noted that there was some variability in preference for use of prophylactic indomethacin among parents of preterm infants as well as adults born preterm, though prophylactic indomethacin was still the most preferred option (47.5% of participants from the values and preferences study opting for indomethacin). There were also some concerns noted with possible increased risk of gastrointestinal perforation, especially in conjunction with prophylactic hydrocortisone use. Therefore, the panel conditionally recommended in favor of using prophylactic indomethacin, especially in centers with high rates of severe IVH and death in extremely preterm infants. The panel encouraged shared decision making with the parents/guardians to evaluate their values and preferences with respect to desirable versus undesirable outcomes. The panel also recommended against using prophylactic indomethacin and prophylactic hydrocortisone concomitantly in extremely preterm infants.

Prophylactic ibuprofen

The panel determined that overall, there was low certainty of evidence from RCTs to suggest that prophylactic ibuprofen may reduce death and severe IVH. However, the panel did note that majority of parents of preterm infants as well as adults born preterm would still opt for prophylactic ibuprofen when presented as the only choice; when asked to choose between all three COX-I drugs, ibuprofen was the second choice following indomethacin.

The majority of the panel members felt that it was inappropriate to recommend a prophylactic therapy given the overall low certainty of evidence for the most important clinical outcomes (death and severe IVH). Therefore, the panel conditionally recommended against using prophylactic ibuprofen. However, the panel acknowledged that if indomethacin is unavailable, prophylactic ibuprofen could be an acceptable alternative to

prophylactic indomethacin in centers with high rates of severe IVH and death in extremely preterm infants.

Prophylactic acetaminophen

Given that there was insufficient evidence to demonstrate benefit for clinically important outcomes, unknown long-term consequences, and almost all parents of preterm infants (87%) and all adults born preterm in the values and preferences study opting against its use, the panel recommended against use of acetaminophen prophylaxis in extremely preterm infants.

Discussion

Using the GRADE Evidence-to-Decision (EtD) framework for multiple comparisons, the 12-member guideline panel provided a conditional recommendation in favor of indomethacin prophylaxis, a conditional recommendation against ibuprofen prophylaxis and a strong recommendation against acetaminophen prophylaxis in extremely preterm infants. Prior to prescribing prophylactic indomethacin, shared decision making with parents was strongly encouraged to evaluate their values and preferences. Although prophylactic ibuprofen therapy was conditionally not recommended, shared decision making with parents was encouraged in centers that lack access to indomethacin and have high rates of severe IVH and death in extremely preterm infants.

Our recommendations for prophylactic indomethacin do align with the recent position statements from the CPS and the AAP, both of which have suggested using indomethacin prophylaxis in higher risk extremely preterm infants. However, our panel further emphasized that since the benefits of routine indomethacin use in this population do not clearly outweigh the possible harms, a discussion with the parents prior to using indomethacin should be offered. Our guideline is also the first to provide evidence-based recommendations on the use of prophylactic ibuprofen and acetaminophen in extremely preterm infants, recommending against their routine use in this population.

To our knowledge, this is the first neonatal clinical practice guideline linked to a de novo systematic review and network meta-analysis developed using GRADE methodology. The recently developed GRADE guidance on assessing the certainty of evidence from a NMA was used in our systematic review of evidence[19]. Further, thresholds for benefit or harm for each outcome was explicitly defined using a partially contextualized approach prior to

assessing certainty of evidence using the GRADE methodology[25]. In addition, this guideline document was developed in accordance with the Guideline International Network (GIN)-McMaster Guideline Development Checklist and the AGREE II instrument, reporting guides that promote GRADE methods[26,27]. We believe that incorporation of family values and active promotion of shared decision making in the guideline recommendations will encourage engagement of families in clinical decision-making for their critically-ill children.

Certain limitations of the guideline development process need to be considered when applying these recommendations in practice. First, it is important to remember that the recommendations were developed following the GRADE evidence-to-decision framework, which has largely been used in the context of decision making in adult medicine[28]. There is little evidence on how neonatal care providers and parents interpret the GRADE certainties of evidence (high, moderate, low or very low) and how that affects their decision making. Second, the decision thresholds for benefit or harm for each outcome, which directly impacts the certainty in estimate of treatment effects and eventually the strength of recommendations, were defined based on the consensus of the study team. These decision thresholds, and therefore the assigned certainties of evidence, may not hold true at an individual level. Therefore, it may be important that clinicians not only present the certainty of evidence, but the actual effect estimates and their precision to families when engaging in shared decision making.

Implementation Considerations

A conditional recommendation in favor in indomethacin allows for some degree of center-specific individualization of care. Centers may use their local or provincial datasets to identify which infants (below a certain gestational age and/or birth weight threshold) are at the highest risk for severe IVH, death and gastrointestinal perforation, and only those families may be engaged in shared decision making after birth. For example, a recent large retrospective cohort study from the Canadian Neonatal Network demonstrated that prophylactic indomethacin was associated with reduced odds of early death or severe neurologic injury and early death or gastrointestinal perforation in infants born at 23-24 weeks' gestational age, but resulted in increased odds of early mortality or gastrointestinal

perforation for infants born at 26-28 weeks' gestational age[29]. Similarly, a predictive model for severe IVH risk in preterm infants was developed from the Vermont Oxford Network database that incorporates several perinatal factors such as gestational age, birth weight, sex, 5-min Apgar score, antenatal steroid use, location and mode of delivery[30]. A severe IVH risk calculator based on this predictive model is currently being used in several NICUs across the United States. This and similar models may be locally used to identify families for shared decision making through targeted quality improvement projects.

Centers who have adopted the use of prophylactic hydrocortisone should put our recommendations in the context of the totality of evidence on postnatal systemic corticosteroids. While later initiation of indomethacin, following diagnosis of a symptomatic PDA, has not been shown to improve clinically meaningful outcomes such as severe IVH or death[31], systemic corticosteroids initiated at or after 7 days of age have been shown to reduce mortality (RR 0.81, 95% Confidence Intervals [CIs] 0.66 to 0.99; 21 RCTs, 1428 infants; high-certainty evidence) and CLD (RR 0.89, 95% CIs 0.80 to 0.99; 14 RCTs, 988 infants; moderate-certainty evidence)[32]. Therefore, care providers engaged in shared decision-making with families should ensure that all treatment approaches are discussed in detail so that families do not feel giving indomethacin prophylaxis to their infant will automatically deprive them of the option of providing corticosteroid therapy, which can reduce CLD and death. There still remains an option of later use of systemic corticosteroids with moderate-high certainty of benefit.

With respect to ibuprofen prophylaxis, though the panel put forward a conditional recommendation against its use, the decision was made with the assumption that all three therapies (indomethacin, ibuprofen and acetaminophen) are available to choose from. However, the panel acknowledged that indomethacin is not available in several NICUs, especially across the United Kingdom. In such situations, especially in centers with high rates of morbidity and mortality in extremely preterm infants, it may be worthwhile for caregivers to engage in shared decision making with the parents with regards to use of ibuprofen prophylaxis.

For the purpose of shared decision making, decision aids have been created using the MagicApp software (https://app.magicapp.org/#/guidelines) (Appendix C).

Updating Policy

For prophylactic indomethacin, given the concern regarding gastrointestinal perforation, the panel will continually monitor for emerging research evidence both in relation to concomitant exposure to antenatal as well as postnatal corticosteroids. For ibuprofen, the panel will monitor for emerging research evidence on its association with adverse outcomes such as GI perforation, NEC and acute pulmonary hypertension. The panel will also monitor for updated systematic reviews that synthesize evidence from new RCTs on the benefits and harms of prophylactic acetaminophen use. Upon identification of potentially relevant new evidence, recommendations will be reconsidered and, if necessary, revised.

Endorsement

The process of incorporating family values and preferences in neonatal clinical practice guidelines, that was emphasized in the development of these practice recommendations, was endorsed by the Canadian Premature Babies' Foundation.

Funding sources

None

Conflict of interest

No panel member had any conflicts to disclose

Table 1. Recommendations

Prophylactic Indomethacin
Clinicians may consider prophylaxis with intravenous indomethacin in extremely preterm infants ***[conditional recommendation, moderate certainty in estimate of effects].***
The panel encourages shared decision making with the parents/guardians to evaluate their values and preferences with respect to desirable vs undesirable outcomes. The panel also recommends against using prophylactic indomethacin and prophylactic hydrocortisone concomitantly in extremely preterm infants.

Prophylactic Ibuprofen
Prophylaxis with intravenous ibuprofen in extremely preterm infants is not recommended ***[conditional recommendation, low certainty in estimate of effects].***
The panel encourages shared decision making with the parents/guardians to evaluate their values and preferences with respect to desirable vs undesirable outcomes in centers that lack access to intravenous indomethacin and have high rates of severe IVH and death in extremely preterm infants.

Prophylactic Acetaminophen
Clinicians should not use prophylactic acetaminophen in extremely preterm infants ***[strong recommendation, very low certainty in estimate of effects].***

What do the recommendations mean?

For clinicians:

- It is suggested that intravenous indomethacin be used as pharmacoprophylaxis in extremely preterm infants. However, clinicians should encourage shared decision making with parents as the strength of the recommendation is conditional, and the certainty of the evidence is moderate.
- It is suggested that intravenous ibuprofen be not routinely offered as pharmacoprophylaxis in extremely preterm infants. However, clinicians should encourage shared decision making with parents in centers that lack access to indomethacin and have high rates of severe IVH and death in extremely preterm infants.
- Acetaminophen should not be used as prophylactic therapy in extremely preterm infants.

For members of the public:

- Most neonatal care providers would choose intravenous indomethacin for prophylaxis in extremely preterm infants, but a substantial number would not as the probable small reduction in severe brain bleeding and moderate reduction in death may not justify its routine use in all extremely preterm infants.
- Most neonatal care providers would not choose intravenous ibuprofen for prophylaxis in extremely preterm infants, but a substantial number would, especially in absence of intravenous indomethacin given the probable small reduction in severe brain bleeding and possible moderate reduction in death with intravenous ibuprofen.
- Neonatal care providers would not use acetaminophen as a prophylactic therapy in extremely preterm infants given the current lack of evidence on benefits and harms.

References

1. Benitz WE, Committee on Fetus and Newborn, American Academy of Pediatrics. Patent Ductus Arteriosus in Preterm Infants. Pediatrics. 2016 Jan;137(1). doi: 10.1542/peds.2015-3730. Epub 2015 Dec 15

2. Wolf WM, Snover DC, Leonard AS. Localized intestinal perforation following intravenous indomethacin in premature infants. J Pediatr Surg. 1989 Apr;24(4):409–10.

3. Stavel M, Wong J, Cieslak Z, Sherlock R, Claveau M, Shah PS. Effect of prophylactic indomethacin administration and early feeding on spontaneous intestinal perforation in extremely low-birth-weight infants. J Perinatol. 2017;37(2):188–93.

4. Reese J, Shelton EL, Slaughter JC, McNamara PJ. Prophylactic Indomethacin Revisited. J Pediatr. 2017 Jul;186:11-14.e1.

5. Ryan M, Lacaze-Masmonteil T, Mohammad K. Neuroprotection from acute brain injury in preterm infants. Paediatr Child Health. 2019 Jul;24(4):276–90.

6. Mitra S, Weisz D, Jain A, Jong G 't. Management of the patent ductus arteriosus in preterm infants. Paediatrics & Child Health. 2022 Mar 1;27(1):63–63.

7. Hamrick SEG, Sallmon H, Rose AT, Porras D, Shelton EL, Reese J, et al. Patent Ductus Arteriosus of the Preterm Infant. Pediatrics. 2020 Nov;146(5):e20201209.

8. Moberg J, Alonso-Coello P, Oxman AD. GRADE Evidence to Decision (EtD) Frameworks Guidance. Version 1.1 [updated May 2015] [Internet]. The GRADE Working Group; 2015. Available from: https://ietd.epistemonikos.org/#/help/guidance

9. Piggott T, Brozek J, Nowak A, Dietl H, Dietl B, Saz-Parkinson Z, et al. Using GRADE evidence to decision frameworks to choose from multiple interventions. J Clin Epidemiol. 2021 Feb;130:117–24.

10. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008 Apr 26;336(7650):924–6.

11. Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. BMJ [Internet]. 2016 Jun 28 [cited 2019 Dec 4];353. Available from: https://www.bmj.com/content/353/bmj.i2016

12. Qaseem A, Wilt TJ, Clinical Guidelines Committee of the American College of Physicians. Disclosure of Interests and Management of Conflicts of Interest in Clinical Guidelines and Guidance Statements: Methods From the Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med. 2019 03;171(5):354–61.

13. Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiol. 2011 Apr;64(4):395–400.

14. Lynn MR. Determination and quantification of content validity. Nurs Res. 1986 Dec;35(6):382–5.

15. Fowlie PW, Davis PG, McGuire W. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. Cochrane Database Syst Rev. 2010 Jul 7;(7):CD000174.

16. Ohlsson A, Shah SS. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev. 2019 21;6:CD004213.

17. Ohlsson A, Shah PS. Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants. Cochrane Database Syst Rev. 2020 27;1:CD010061.

18. Mitra S, Gardner CE, MacLellan A, Disher T, Styranko DM, Campbell-Yeo M, et al. Prophylactic cyclo-oxygenase inhibitor drugs for the prevention of morbidity and mortality in preterm infants: a network meta-analysis. Cochrane Database Syst Rev. 2022 Apr 1;4:CD013846.

19. Yepes-Nuñez JJ, Li SA, Guyatt G, Jack SM, Brozek JL, Beyene J, et al. Development of the summary of findings table for network meta-analysis. J Clin Epidemiol. 2019 Nov;115:1–13.

20. Santesso N, Glenton C, Dahm P, Garner P, Akl EA, Alper B, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. J Clin Epidemiol. 2020 Mar;119:126–35.

21. Kelleher J, Salas AA, Bhat R, Ambalavanan N, Saha S, Stoll BJ, et al. Prophylactic Indomethacin and Intestinal Perforation in Extremely Low Birth Weight Infants. Pediatrics. 2014 Nov;134(5):e1369–77.

22. Shaffer ML, Baud O, Lacaze-Masmonteil T, Peltoniemi OM, Bonsante F, Watterberg KL. Effect of Prophylaxis for Early Adrenal Insufficiency Using Low-Dose Hydrocortisone in Very Preterm Infants: An Individual Patient Data Meta-Analysis. J Pediatr. 2019 Apr;207:136-142.e5.

23. Bellini C, Campone F, Serra G. Pulmonary hypertension following L-lysine ibuprofen therapy in a preterm infant with patent ductus arteriosus. CMAJ. 2006 Jun 20;174(13):1843–4.

24. Sehgal A, Kumarshingri PSN. Pulmonary hypertension in an infant treated with ibuprofen. Indian J Pediatr. 2013 Aug;80(8):697–9.

25. Brignardello-Petersen R, Izcovich A, Rochwerg B, Florez ID, Hazlewood G, Alhazanni W, et al. GRADE approach to drawing conclusions from a network meta-analysis using a partially contextualised framework. BMJ. 2020 Nov 10;371:m3907.

26. McMaster University > CE&B Grade > Guideline Development Checklist [Internet]. [cited 2019 Dec 4]. Available from: https://cebgrade.mcmaster.ca/guidecheck.html

27. Brouwers MC, Kerkvliet K, Spithoff K, AGREE Next Steps Consortium. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. BMJ. 2016 Mar 8;i1152.

28. Neumann I, Brignardello-Petersen R, Wiercioch W, Carrasco-Labra A, Cuello C, Akl E, et al. The GRADE evidence-to-decision framework: a report of its testing and application in 15 international guideline panels. Implement Sci. 2016 Jul 15;11:93.

29. Qureshi M, Shah PS, Abdelgadir D, Ye XY, Afifi J, Yuen R, et al. Gestational Age-Dependent Variations in Effects of Prophylactic Indomethacin on Brain Injury and Intestinal Injury. J Pediatr. 2021 Aug;235:26-33.e2.

30. Singh R, Gorstein SV, Bednarek F, Chou JH, McGowan EC, Visintainer PF. A predictive model for SIVH risk in preterm infants and targeted indomethacin therapy for prevention. Sci Rep. 2013;3:2539.

31. Evans P, O'Reilly D, Flyer JN, Soll R, Mitra S. Indomethacin for symptomatic patent ductus arteriosus in preterm infants. Cochrane Database Syst Rev. 2021 Jan 15;1:CD013133.

32. Doyle LW, Cheong JL, Hay S, Manley BJ, Halliday HL. Late (≥ 7 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. Cochrane Database Syst Rev. 2021 Nov 11;11:CD001145.

33. Mitra S, Campbell-Yeo M, Kuhle S, Dorling J, Johnston BC. Exploring health-related values and preferences of former preterm infants and families of preterm infants on use of prophylactic cyclo-oxygenase inhibitor drugs for patent ductus arteriosus: a cross-sectional mixed-methods study. *[Manuscript in preparation]*

34. Baud O, Maury L, Lebail F, Ramful D, El Moussawi F, Nicaise C, et al. Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMILOC): a double-blind, placebo-controlled, multicentre, randomised trial. Lancet. 2016 Apr 30;387(10030):1827–36.

35. Turck CJ, Marsh W, Stevenson JG, York JM, Miller H, Patel S. Pharmacoeconomics of Surgical Interventions vs. Cyclooxygenase Inhibitors for the Treatment of Patent Ductus Arteriosus. J Pediatr Pharmacol Ther. 2007;12(3):183–93.

36. Moya MP, Goldberg RN. Cost-effectiveness of prophylactic indomethacin in very-low-birth-weight infants. Ann Pharmacother. 2002 Feb;36(2):218–24.

37. Zupancic JAF, Richardson DK, O'Brien BJ, Cronin CG, Schmidt B, Roberts R, et al. Retrospective economic evaluation of a controlled trial of indomethacin prophylaxis for patent ductus arteriosus in premature infants. Early Hum Dev. 2006 Feb;82(2):97–103.

38. Kandraju H, Kanungo J, Lee KS, Daspal S, Adie MA, Dorling J, et al. Association of Co-Exposure of Antenatal Steroid and Prophylactic Indomethacin with Spontaneous Intestinal Perforation. J Pediatr. 2021 Aug;235:34-41.e1.

39. Gournay V, Roze JC, Kuster A, Daoud P, Cambonie G, Hascoet JM, et al. Prophylactic ibuprofen versus placebo in very premature infants: a randomised, double-blind, placebo-controlled trial. Lancet. 2004 Dec 27;364(9449):1939–44.

40. Sehgal A, Kumarshingri PSN. Pulmonary hypertension in an infant treated with ibuprofen. Indian J Pediatr. 2013 Aug;80(8):697–9.

41. Bauer AZ, Kriebel D. Prenatal and perinatal analgesic exposure and autism: an ecological link. Environ Health. 2013 May 9;12:41.

42. Avella-Garcia CB, Julvez J, Fortuny J, Rebordosa C, García-Esteban R, Galán IR, et al. Acetaminophen use in pregnancy and neurodevelopment: attention function and autism spectrum symptoms. Int J Epidemiol. 2016 01;45(6):1987–96.

Appendix A. Summary of Findings

Desirable Effects

Outcome	Effects and confidence in the effect estimates						Comments [GRADE interpretation]
	Indomethacin		**Ibuprofen**		**Acetaminophen**		
Severe Intraventricular Hemorrhage							
Placebo comparator **127 per 1000 (12.7%)**	***Network RR*** **0.66 (0.49, 0.87)**	***Network absolute risk difference**** **43 fewer per 1000 (from 65 fewer to 16 fewer)**	***Network RR*** **0.69 (0.41, 1.14)**	***Network absolute risk difference*** **39 fewer per 1000 (from 75 fewer to 18 more)**	***Network RR*** **1.17 (0.04, 55.2)**	***Network absolute risk difference*** **22 more per 1000 (from 122 fewer to 1000 more)**	Prophylactic indomethacin probably results in a small reduction in severe IVH Prophylactic ibuprofen probably results in a small reduction in severe IVH The evidence is very uncertain about the effect of prophylactic acetaminophen on severe IVH
	Moderate ⊕⊕⊕◯ Confidence in estimate due to imprecision		**Moderate ⊕⊕⊕◯** Confidence in estimate due to imprecision		**Very Low ⊕◯◯◯** Confidence in estimate due to imprecision		
	Based on 2629 infants (16 RCTs)		**Based on 863 infants (6 RCTs)**		**Based on 48 infants (1 RCT)**		
Mortality							
Placebo comparator **161 per 1000 (16.1%)**	***Network RR*** **0.85 (0.64 to 1.1)**	***Network absolute risk difference*** **24 fewer per 1000 (from 58 fewer to 16 more)**	***Network RR*** **0.83 (0.57 to 1.2)**	***Network absolute risk difference*** **27 fewer per 1000 (from 69 fewer to 32 more)**	***Network RR*** **0.49 (0.16 to 1.4)**	***Network absolute risk difference*** **82 fewer per 1000 (from 135 fewer to 64 more)**	Prophylactic indomethacin probably results in a moderate reduction in mortality Prophylactic ibuprofen may result in a moderate reduction in mortality The evidence is very uncertain about the effect of prophylactic acetaminophen on mortality
	Moderate ⊕⊕⊕◯ Confidence in estimate due to imprecision		**Low ⊕⊕◯◯** Confidence in estimate due to imprecision		**Very Low ⊕◯◯◯** Confidence in estimate due to risk of bias and imprecision		
	Based on 2877 infants (19 RCTs)		**Based on 914 infants (7 RCTs)**		**Based on 208 infants (2 RCTs)**		

Outcome	Effects and confidence in the effect estimates						Comments [GRADE interpretation]
	Indomethacin		Ibuprofen		Acetaminophen		
Surgical PDA closure							
Placebo comparator **87 per 1000 (8.7%)**	***Network RR*** **0.40 (0.14 to 0.66)**	***Network absolute risk difference*** **52 fewer per 1000 (from 75 fewer to 30 fewer)**	***Network RR*** **0.24 (0.06 to 0.64)**	***Network absolute risk difference*** **66 fewer per 1000 (from 82 fewer to 31 fewer)**	_____	_____	Prophylactic indomethacin probably results in a moderate reduction in need for surgical PDA closure Prophylactic ibuprofen probably results in a moderate reduction in need for surgical PDA closure There is no evidence on the effect of prophylactic acetaminophen on need for surgical PDA closure
	Moderate ⊕⊕⊕◯ **Confidence in estimate due to imprecision**		**Moderate ⊕⊕⊕◯** **Confidence in estimate due to imprecision**		_____		
	Based on 1800 infants (11 RCTs)		**Based on 873 infants (6 RCTs)**		_____		
Cerebral Palsy							
Placebo comparator **110 per 1000 (11%)**	***Network RR*** **0.97 (0.44 to 2.1)**	***Network absolute risk difference*** **3 fewer per 1000 (from 62 fewer to 121 more)**	_____	_____	***Network RR*** **0.36 (0.01 to 6.3)**	***Network absolute risk difference*** **70 fewer per 1000 (from 109 fewer to 583 more)**	Prophylactic indomethacin may result in trivial difference in cerebral palsy There is no evidence on the effect of prophylactic ibuprofen on cerebral palsy The evidence is very uncertain about the effect of prophylactic acetaminophen on cerebral palsy
	Low ⊕⊕◯◯ **Confidence in estimate due to imprecision**		_____		**Very Low ⊕◯◯◯** **Confidence in estimate due to imprecision**		
	Based on 1367 infants (4 RCTs)		_____		**Based on 35 infants (1 RCT)**		

Undesirable Effects

Outcome	Effects and confidence in the effect estimates						Comments [GRADE interpretation]
	Indomethacin		Ibuprofen		Acetaminophen		
Necrotizing Enterocolitis							
Placebo comparator **65 per 1000 (6.5%)**	***Network RR*** **0.76 (0.35 to 1.2)**	***Network absolute risk difference*** **16 fewer per 1000 (from 42 fewer to 13 more)**	***Network RR*** **0.73 (0.31 to 1.4)**	***Network absolute risk difference*** **18 fewer per 1000 (from 45 fewer to 26 more)**	_____	_____	Prophylactic indomethacin results in trivial difference in NEC Prophylactic ibuprofen results in trivial difference in NEC There is no evidence on the effect of prophylactic acetaminophen on NEC
	High ⊕⊕⊕⊕ **Confidence in estimate**		**High ⊕⊕⊕⊕** **Confidence in estimate**		_____		
	Based on 2543 infants (14 RCTs)		**Based on 905 infants (7 RCTs)**		_____		
Gastrointestinal perforation							
Placebo comparator **47 per 1000 (4.7%)**	***Network RR*** **0.92 (0.11 to 3.9)**	***Network absolute risk difference*** **4 fewer per 1000 (from 42 fewer to 137 more)**	***Network RR*** **2.6 (0.42 to 20.0)**	***Network absolute risk difference*** **76 more per 1000 (from 27 fewer to 897 more)**	_____	_____	Prophylactic indomethacin probably results in trivial difference in gastrointestinal perforation The evidence is very uncertain about the effect of prophylactic ibuprofen on gastrointestinal perforation There is no evidence on the effect of prophylactic acetaminophen on gastrointestinal perforation
	Moderate ⊕⊕⊕◯ **Confidence in estimate due to imprecision**		**Very Low ⊕◯◯◯** **Confidence in estimate due to imprecision**		_____		
	Based on 1221 infants (2 RCTs)		**Based on 177 infants (2 RCTs)**		_____		

Outcome	Effects and confidence in the effect estimates						Comments [GRADE interpretation]
	Indomethacin		Ibuprofen		Acetaminophen		
Chronic Lung Disease							
Placebo comparator **359 per 1000 (35.9%)**	***Network RR*** **1.10 (0.93 to 1.3)**	***Network absolute risk difference*** **36 more per 1000 (from 25 fewer to 108 more)**	***Network RR*** **1.00 (0.83 to 1.3)**	***Network absolute risk difference*** **0 fewer per 1000 (from 61 fewer to 108 more)**	_____	_____	Prophylactic indomethacin may result in a small increase in chronic lung disease Prophylactic ibuprofen may result in trivial difference in chronic lung disease There is no evidence on the effect of prophylactic acetaminophen on chronic lung disease
	Low ⊕⊕◯◯ **Confidence in estimate due to imprecision**[11]		**Low ⊕⊕◯◯** **Confidence in estimate due to imprecision**[12]		_____		
	Based on 2106 infants (10 RCTs)		**Based on 904 infants (7 RCTs)**		_____		

[Adapted from: Mitra S, Gardner CE, MacLellan A, Disher T, Styranko DM, Campbell-Yeo M, et al. Prophylactic cyclo-oxygenase inhibitor drugs for the prevention of morbidity and mortality in preterm infants: a network meta-analysis. Cochrane Database Syst Rev. 2022 Apr 1;4:CD013846]

Appendix B. Evidence-to-Decision Framework

Question: Should prophylactic cyclo-oxygenase inhibitors (COX-Is; indomethacin, ibuprofen or acetaminophen) be used to prevent morbidity and mortality in extremely preterm infants (born ≤28 weeks of gestational age)?

Intervention(s):

- Prophylactic indomethacin
- Prophylactic ibuprofen
- Prophylactic acetaminophen

Comparison: No pharmacoprophylaxis

Population: Infants born extremely preterm (≤28 weeks of gestational age)

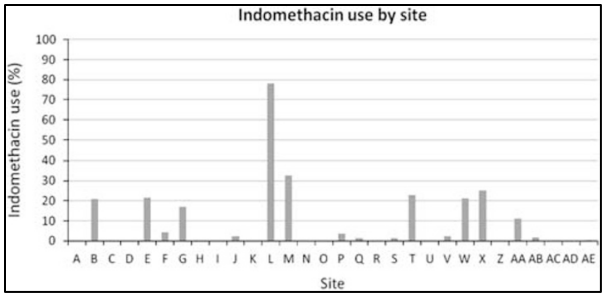
Setting: Neonatal intensive care unit

Panel co-chairs: Souvik Mitra, Bradley Johnston

Panel members: Leah Whitehead, Katie Smith, Breagh MacLean, Rebekah Nixon, Marsha Campbell-Yeo, Stefan Kuhle, Andrew Veysey, Chris Gale, Roger Soll, Jon Dorling

Assessment

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS & COMMENTS FROM GUIDELINE PANEL**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cyclo-oxygenase inhibitor (COX-I) drugs may be used in preterm infants to prevent prematurity-related complications such as intraventricular hemorrhage (IVH) and chronic lung disease (CLD). However, COX-Is themselves may be associated with adverse effects such as necrotizing enterocolitis (NEC) and gastrointestinal perforation. Therefore, controversy exists on whether exposing preterm infants to COX-Is prophylactically will actually help to improve patient-important clinical outcomes. The choice of COX-I prophylaxis is largely driven by clinician preferences with little or no input from families regarding their values and preferences. Given the potential risks of COX-I use, it is not surprising that there is wide variation in clinical practice regarding the prophylactic use of COX-Is in preterm infants. A retrospective cohort study of 4268 extremely preterm infants admitted to Canadian neonatal units between 2010 and 2014 demonstrated marked variation (0-78%) in use of prophylactic COX-Is across Canadian NICUs[3].	



Desirable Effects

How substantial are the desirable anticipated effects for each intervention?

JUDGEMENT

Most effective: Prophylactic indomethacin

Intermediate effectiveness: Prophylactic ibuprofen

Least effective: Prophylactic acetaminophen

RESEARCH EVIDENCE[18]

Outcome	Effects and confidence in the effect estimates						Comments **
	Indomethacin		Ibuprofen		Acetaminophen		
Severe Intraventricular Hemorrhage							
Placebo comparator 127 per 1000 (12.7%)	*Network RR* 0.66 (0.49, 0.87)	*Network absolute risk difference** 43 fewer per 1000 (from 65 fewer to 16 fewer)	*Network RR* 0.69 (0.41, 1.14)	*Network absolute risk difference* 39 fewer per 1000 (from 75 fewer to 18 more)	*Network RR* 1.17 (0.04, 55.2)	*Network absolute risk difference* 22 more per 1000 (from 122 fewer to 1000 more)	Prophylactic indomethacin probably results in a small reduction in severe IVH Prophylactic ibuprofen probably results in a small reduction in severe IVH The evidence is very uncertain about the effect of prophylactic acetaminophen on severe IVH
	Moderate ⊕⊕⊕◯ Confidence in estimate due to imprecision[1]		**Moderate** ⊕⊕⊕◯ Confidence in estimate due to imprecision[2]		**Very Low** ⊕◯◯◯ Confidence in estimate due to imprecision[3]		
Rank [Median (95% CrIs)] 3 (2-4)	**Rank** 2 (1-3)		**Rank** 2 (1-4)		**Rank** 4 (1-4)		
	Based on 2629 infants (16 RCTs)		Based on 863 infants (6 RCTs)		Based on 48 infants (1 RCT)		
Mortality							
Placebo comparator 161 per 1000 (16.1%)	*Network RR* 0.85 (0.64 to 1.1)	*Network absolute risk difference* 24 fewer per 1000 (from 58 fewer to 16 more)	*Network RR* 0.83 (0.57 to 1.2)	*Network absolute risk difference* 27 fewer per 1000 (from 69 fewer to 32 more)	*Network RR* 0.49 (0.16 to 1.4)	*Network absolute risk difference* 82 fewer per 1000 (from 135 fewer to 64 more)	Prophylactic indomethacin probably results in a moderate reduction in mortality Prophylactic ibuprofen may result in a moderate reduction in mortality

ADDITIONAL CONSIDERATIONS & COMMENTS FROM GUIDELINE PANEL

Voting results from panel discussion:

	Responses	Percentage
Most effective		
Indomethacin	12/12	100%
Ibuprofen		
Acetaminophen		
None		

	Responses	Percentage
Intermediate effectiveness		
Indomethacin		
Ibuprofen	12/12	100%
Acetaminophen		
None		

	Responses	Percentage
Least effective		
Indomethacin		
Ibuprofen		
Acetaminophen	11/12	91.7%
None	1/12	8%

Comments:

The panel felt that out of all the interventions, indomethacin had definite benefit (and no harm) with regards to the critical outcome of severe IVH. For ibuprofen, though there appeared to be a benefit with respect to severe IVH, a trivial harm could not be ruled out (18 more per 1000).

Similarly for death, the panel was less confident in the beneficial effect of ibuprofen given the upper bound of the 95% CrIs was 32 more per 1000, which was felt to be high for a critical outcome such as death. It

	Moderate ⊕⊕⊕◯ Confidence in estimate due to imprecision[4]		**Low ⊕⊕◯◯** Confidence in estimate due to imprecision[5]		**Very Low ⊕◯◯◯** Confidence in estimate due to risk of bias and imprecision[6]		The evidence is very uncertain about the effect of prophylactic acetaminophen on mortality
Rank [Median (95% CrIs)] 4 (3-4)	**Rank** 2 (1-4) Based on 2877 infants (19 RCTs)		**Rank** 2 (1-4) Based on 914 infants (7 RCTs)		**Rank** 1 (1-4) Based on 208 infants (2 RCTs)		
Surgical PDA closure							
Placebo comparator 87 per 1000 (8.7%)	*Network RR* 0.40 (0.14 to 0.66)	*Network absolute risk difference* 52 fewer per 1000 (from 75 fewer to 30 fewer)	*Network RR* 0.24 (0.06 to 0.64)	*Network absolute risk difference* 66 fewer per 1000 (from 82 fewer to 31 fewer)	_____	_____	Prophylactic indomethacin probably results in a moderate reduction in need for surgical PDA closure Prophylactic ibuprofen probably results in a moderate reduction in need for surgical PDA closure There is no evidence on the effect of prophylactic acetaminophen on need for surgical PDA closure
	Moderate ⊕⊕⊕◯ Confidence in estimate due to imprecision[7]		**Moderate ⊕⊕⊕◯** Confidence in estimate due to imprecision[8]		_____		
Rank [Median (95% CrIs)] 3 (3-3)	**Rank** 2 (1-2) Based on 1800 infants (11 RCTs)		**Rank** 1 (1-2) Based on 873 infants (6 RCTs)		_____		
Cerebral Palsy							
Placebo comparator 110 per 1000 (11%)	*Network RR* 0.97 (0.44 to 2.1)	*Network absolute risk difference* 3 fewer per 1000 (from 62 fewer to 121 more)	_____	_____	*Network RR* 0.36 (0.01 to 6.3)	*Network absolute risk difference* 70 fewer per 1000 (from 109 fewer to 583 more)	Prophylactic indomethacin may result in trivial difference in cerebral palsy There is no evidence on the effect of prophylactic ibuprofen on cerebral palsy The evidence is very uncertain about the effect of prophylactic acetaminophen on
	Low ⊕⊕◯◯ Confidence in estimate due to imprecision[13]		_____		**Very Low ⊕◯◯◯** Confidence in estimate due to imprecision[14]		
Rank [Median	**Rank** 2 (1-3)		_____		**Rank** 1 (1-3)		

was pointed out that though ibuprofen appeared best for preventing surgical PDA closure, this outcome was less important for driving a recommendation as compared to severe IVH or death. Therefore, indomethacin was voted as most effective followed by ibuprofen.

Acetaminophen was voted as least effective as the panel was not confident in its potential desirable effects given the dearth of current evidence.

(95% CrIs)] 2 (1-3)	Based on 1367 infants (4 RCTs)	_____	Based on 35 infants (1 RCT)	cerebral palsy

Undesirable Effects

How substantial are the undesirable anticipated effects for each intervention?

JUDGEMENT

Least harmful:

Intermediate: Prophylactic indomethacin Prophylactic ibuprofen

More harmful:

RESEARCH EVIDENCE[18]

Outcome	Effects and confidence in the effect estimates						Comments**
	Indomethacin		Ibuprofen		Acetaminophen		
Necrotizing Enterocolitis							
Placebo comparator 65 per 1000 (6.5%)	*Network RR* 0.76 (0.35 to 1.2)	*Network absolute risk difference* 16 fewer per 1000 (from 42 fewer to 13 more)	*Network RR* 0.73 (0.31 to 1.4)	*Network absolute risk difference* 18 fewer per 1000 (from 45 fewer to 26 more)	_____	_____	Prophylactic indomethacin results in trivial difference in NEC Prophylactic ibuprofen results in trivial difference in NEC There is no evidence on the effect of prophylactic acetaminophen on NEC
	High ⊕⊕⊕⊕ Confidence in estimate		**High ⊕⊕⊕⊕** Confidence in estimate		_____		
Rank [Median (95% CrIs)] 3 (3-3)	**Rank** 2 (1-3)		**Rank** 1 (1-3)		_____		
	Based on 2543 infants (14 RCTs)		Based on 905 infants (7 RCTs)		_____		
Gastrointestinal perforation							
Placebo comparator 47 per 1000 (4.7%)	*Network RR* 0.92 (0.11 to 3.9)	*Network absolute risk difference* 4 fewer per 1000 (from 42 fewer to 137 more)	*Network RR* 2.6 (0.42 to 20.0)	*Network absolute risk difference* 76 more per 1000 (from 27 fewer to 897 more)	_____	_____	Prophylactic indomethacin probably results in trivial difference in gastrointestinal perforation The evidence is very uncertain about the effect of prophylactic ibuprofen on gastrointestinal perforation There is no evidence on the effect of prophylactic
	Moderate ⊕⊕⊕◯ Confidence in estimate due to imprecision[9]		**Very Low** ⊕◯◯◯ Confidence in estimate due to imprecision[10]		_____		
Rank [Median	**Rank** 1 (1-3)		**Rank** 3 (1-3)		_____		

ADDITIONAL CONSIDERATIONS & COMMENTS FROM GUIDELINE PANEL

Voting results from panel discussion:

	Responses	Percentage
Least harmful		
Indomethacin		
Ibuprofen		
Acetaminophen		
None	12/12	100%

	Responses	Percentage
Intermediate		
Indomethacin	10/12	83%
Ibuprofen	12/12	100%
Acetaminophen	1/12	8%
None		

	Responses	Percentage
More harmful		
Indomethacin	1/12	8%
Ibuprofen		
Acetaminophen		
None	11/12	92%

Comments:

Regarding indomethacin and ibuprofen, there was no definite evidence of harm, though the upper bound of 95% CrIs for both drugs suggested possibility of trivial harm with respect to NEC and large harm with respect to GI perforation and CLD. Therefore, none of these medications were ranked as least harmful.

Of note, one panel member did point out the substantial uncertainty with respect to GI perforation with ibuprofen, with the upper bound of the 95% CrI being 897 more per 1000 suggesting that there is a possibility ibuprofen could turn out to be very harmful with more evidence.

The panel did note that we do not have RCT data on any of the

	(95% CrIs)] 2 (1-3)	Based on 1221 infants (2 RCTs)		Based on 177 infants (2 RCTs)		_____	acetaminophen on gastrointestinal perforation
	Chronic Lung Disease						
	Placebo comparator 359 per 1000 (35.9%)	*Network RR* 1.10 (0.93 to 1.3)	*Network absolute risk difference* 36 more per 1000 (from 25 fewer to 108 more)	*Network RR* 1.00 (0.83 to 1.3)	*Network absolute risk difference* 0 fewer per 1000 (from 61 fewer to 108 more)	_____ __	_____ __	Prophylactic indomethacin may result in a small increase in chronic lung disease Prophylactic ibuprofen may result in trivial difference in chronic lung disease There is no evidence on the effect of prophylactic acetaminophen on chronic lung disease
		Low ⊕⊕◯◯ Confidence in estimate due to imprecision[11]		**Low ⊕⊕◯◯** Confidence in estimate due to imprecision[12]		_____	
	Rank [Median (95% CrIs)] 1 (1-3)	**Rank** 3 (1-3)		**Rank** 2 (1-3)		_____	
		Based on 2106 infants (10 RCTs)		Based on 904 infants (7 RCTs)		_____	

potential undesirable effects for acetaminophen. Therefore, majority of the panel refrained from voting on its potential undesirable effects.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS & COMMENTS FROM GUIDELINE PANEL
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	*From a patient and family perspective the two most important outcomes were death and severe IVH* For **indomethacin**, the certainty of evidence for both death and sIVH was **moderate – Overall: MODERATE** For **ibuprofen**, the certainty of evidence was **low** for death, **moderate** for sIVH – **Overall: LOW** For acetaminophen, the certainty of evidence for both death and sIVH was **very low – Overall: VERY LOW**	Voting results from panel discussion: **Indomethacin – MODERATE (12/12 - 100%)** **Ibuprofen – LOW (12/12 – 100%)** **Acetaminophen – VERY LOW (12/12 – 100%)** The panel unanimously agreed that the 2 most important outcomes in this context are death and severe IVH.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT

○ Important uncertainty or variability
○ Possibly important uncertainty or variability
● Probably no important uncertainty or variability
○ No important uncertainty or variability

RESEARCH EVIDENCE[33]

Value placed on outcomes
(Utility assessment using numeric rating scale)

Outcome	Score [median (IQR)]
Death	100 (100-100)
Severe IVH	90 (80-100)
CLD	70 (60-80)
NEC	80 (70-90)
PDA	75 (52.5 – 90)

Preference for prophylactic therapies

Drug	Frequency (percentage) of participants who said 'yes' [n=40]	Thematic analysis summary: Major themes	Thematic analysis summary: Coding frequency *[Number of participants who alluded to this theme out of the ones who said yes]*
When therapies are offered as the only option (vs no prophylaxis)			
Indomethacin	36 (90%)	Reduces death (critical outcome)	22 (61.1%)
		Reduces severe IVH (critical outcome)	21 (58.3%)
		Possible increase in CLD less worrisome	12 (33.3%)
		Higher certainty in evidence for benefit (reduction in death, sIVH, NEC), lower certainty in evidence for harm (increase in CLD)	9 (25%)
Ibuprofen	34 (85%)	Reduces death (critical outcome)	14 (41.2%)
		Reduces severe IVH (critical outcome)	15 (44.1%)
		No obvious evidence of harm	10 (29.4%)
Acetaminophen	4 (10%)	Not enough evidence, high uncertainty*	25 (69.4%)
		Possible harm with increased risk of IVH*	9 (25%)
When all 3 options are available (vs not choosing anything)			
Indomethacin	19 (47.5%)	Overall certainty of benefit better with indomethacin	13 (68.4%)
Ibuprofen	16 (40%)	No overall harm	8 (50%)
		Indomethacin cannot definitely be used with hydrocortisone, hence going with the 2nd best option	7 (43.6%)
No prophylaxis	5 (12.5%)	Would want to give hydrocortisone if offered	2 (40%)

* For acetaminophen, the major themes reflect the rationale of participants for not choosing acetaminophen

ADDITIONAL CONSIDERATIONS & COMMENTS FROM GUIDELINE PANEL

Voting results from panel discussion:

	Responses	Percentage
Important uncertainty or variability	1/12	8%
Possibly important uncertainty or variability	2/12	17%
Probably no important uncertainty or variability	9/12	75%
No important uncertainty or variability		

Comments:

The panel's votes reflect their response to the question: ***Is there "important" uncertainty about or variability in how much people value the "main outcomes".***

Majority of the panel (75%) felt that there was no substantial variability in how the participants of the values and preferences study valued the main outcomes, i.e., death and severe IVH. Some of the panel members felt that there was some uncertainty as each of the five main outcomes were scored fairly highly by the study participants and there was no clear distinction between the highly scored important outcomes and poorly scored outcomes of lesser importance. Therefore, the final consensus was that there was "probably no important uncertainty" in how much people value the main outcomes. The panel was unable to conclusively rule out important uncertainty in patient values based on the available evidence.

Of note, the panel's votes did not take into account the variability in

Preference for indomethacin vs hydrocortisone prophylaxis among participants who initially opted for indomethacin

Drug	Frequency (percentage) of participants who said 'yes' [n=36]	Thematic analysis summary	
		Major themes	Coding frequency *[Number of participants who alluded to this theme out of the ones who said yes]*
Indomethacin	12 (33.3%)	Reduction of IVH is important; also reduces death	8 (66.7%)
Hydrocortisone	24 (66.7%)	Survival and survival without CLD better with hydrocortisone compared to indomethacin	18 (75%)

Importance of having participant values and preferences included in decision-making

Choice	Frequency (percentage) [n=40]	Thematic analysis summary	
		Major themes	Coding frequency *[Number of participants who alluded to this theme out of the ones who said yes]*
Not important *(I do not want to know the details; I will defer this decision to the doctor)*	3 (7.5%)	–	–
Somewhat important *(I would like to know the benefits and harms of treatment and the rationale behind the doctor's decision; but I will follow what the doctor feels best)*	22 (55%)	First 24h after birth is overwhelming, lot of things to process; so would want to be aware of benefits and harms, but will trust clinician's judgment	17 (77.3%)
Important *(I want to have a discussion with the doctor regarding the benefits and harms related to the most important outcomes and then make a decision together)*	14 (35%)	Would like to be involved in the discussion regarding benefits and harms	6 (43%)
Highly Important *(I would like to make the decision myself based on the information provided)*	1 (2.5%)	–	–

patient preferences. Though the majority of the study participants (87.5%) opted for an NSAID prophylaxis (indomethacin or ibuprofen), there was some variability in the choice (indomethacin – 47.5%; ibuprofen – 40%). Some of the panel members felt that the decision of the study participants was heavily influenced by the evidence on prophylactic hydrocortisone, and that this variability may not be reflective of how people valued the main outcomes. Therefore, the panel decided that the variability in choice of prophylactic therapy will be duly considered when making the final recommendation; however, when voting on this criterion on "Values" they would only consider how the study participants rated the most important outcomes.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison for each intervention?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS & COMMENTS FROM GUIDELINE PANEL
Best balance: Prophylactic indomethacin **Intermediate:** Prophylactic ibuprofen **Worst balance:** Prophylactic acetaminophen	**Prophylactic indomethacin** Out of the desirable effects, there is moderate certainty of evidence that prophylactic indomethacin probably results in a small reduction in severe IVH an moderate reduction in death. There is low certainty of evidence that prophylactic indomethacin may not alter the risk of cerebral palsy. Out of the undesirable effects, prophylactic indomethacin does not increase the risk of NEC (high certainty) and probably does not increase the risk of gastrointestinal perforation (moderate certainty). There is low certainty evidence that prophylactic indomethacin may increase risk of CLD. *Additional consideration – Potential interaction with Prophylactic Hydrocortisone initiated in the same time frame:* A recent individual patient data (IPD) meta-analysis of 4 RCTs (982 infants) showed that early low dose hydrocortisone prophylaxis in extremely preterm or extremely low birth weight infants was associated with a significant increase in survival without CLD [OR (Odds Ratio) 1.45, 95% CI 1.11 to 1.90) and a significant reduction in death before discharge (OR 0.70, 95% CI 0.51 to 0.97). The IPD meta-analysis also noted that concomitant use of prophylactic hydrocortisone and indomethacin increased the risk of spontaneous intestinal perforation (OR 2.50; 95% CI, 1.33 to 4.69)[22]. So, the 2 drugs cannot be used together. ***Balance of effects:*** Probably favors the intervention **Prophylactic ibuprofen** Out of the desirable effects, there is moderate certainty of evidence that severe IVH is probably reduced and low certainty of evidence that death may be reduced with prophylactic ibuprofen. There is low certainty of evidence that prophylactic ibuprofen may not alter the risk of cerebral palsy. Out of the undesirable effects, prophylactic ibuprofen does not appear to increase the risk of NEC (high certainty). There is low certainty evidence that prophylactic ibuprofen may not affect the outcome of CLD. There is insufficient evidence on the effect of prophylactic ibuprofen on GI perforation. With regards to concomitant use with prophylactic hydrocortisone, no similar effect has been demonstrated with use of prophylactic ibuprofen and prophylactic hydrocortisone. In the PREMILOC trial (accounting for 53% of the weight of the IPD meta-analysis by Shaffer et al) 47% of the enrolled infants in the hydrocortisone group (54% in 24-25 weeks' GA group) received ibuprofen. There were no differences in NEC rates between the 2 groups (7% vs 5%)[34]. ***Balance of effects:*** Probably favors the comparison **Prophylactic acetaminophen** There is insufficient evidence to comment on the effect of prophylactic acetaminophen on severe IVH, mortality and cerebral palsy. ***Balance of effects:*** Favors the comparison	Voting results from panel discussion: **Best balance** Indomethacin: 12/12 (100%) Ibuprofen: 1/12 (8%) Acetaminophen: None: **Intermediate balance** Indomethacin: Ibuprofen: 12/12 (100%) Acetaminophen: None: **Worst balance** Indomethacin: Ibuprofen: Acetaminophen: 10/12 (83%) None: 2/12 (17%) **Comments:** The panel was unanimous in their judgment for balance of effects. One of the panel members pointed out that though we rated acetaminophen as having the worst balance, there was insufficient evidence to judge balance of effects for acetaminophen due to dearth of evidence on undesirable effects of acetaminophen.

Resources required

How large are the resource requirements (costs) for each intervention?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS & COMMENTS FROM GUIDELINE PANEL
Less costs: **Intermediate costs:** **Most costs:**	**<u>Prophylactic indomethacin</u>** Assuming that the cost of 1 vial of IV indomethacin is $98.97 (Canadian dollars), that the contents of the vial in excess of the dose must be discarded (in accordance with United States Pharmacopeia Chapter <797> requirements and the Joint Commission's Medication Management standard 4.4015), and that 1 vial must be used per dose with 3 doses total, then the cost of indomethacin therapy for a singleton preterm infant normally would be $296.91[35] **<u>Prophylactic ibuprofen</u>** The intravenous formulation comes in a 2 mL single-use vial (10 mg/mL as a clear sterile preservative-free solution of the L-lysine salt of ibuprofen). The cost of 1 vial of intravenous ibuprofen is $360.81 (CAD). 1 vial of ibuprofen is usually required for each dose in the standard dose ibuprofen regimen (10 mg/kg followed by 2 doses of 5mg/kg at 24 h intervals). Therefore, the total cost of a course of standard dose intravenous ibuprofen is $1082.43. **<u>Prophylactic acetaminophen</u>** Acetaminophen: Injectable acetaminophen = $15.00/100mL bag - Estimated cost of 3-day treatment course (3 bags) per patient= $60.00	'Resources required' are less important for this guideline for the following reasons: 1. The guideline is being developed considering the perspective of the individual patients and their families. This perspective allows us to focus solely on the clinical benefit of the patient with respect to family important outcomes. 2. In publicly funded healthcare systems (Canada and the UK), the cost is borne by the hospital Therefore, the panel refrained from voting on costs and this criterion was not considered while voting on the final recommendations.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS & COMMENTS FROM GUIDELINE PANEL
○ Very low ○ Low ○ Moderate ○ High	Evidence related to cost of indomethacin therapy is obtained from a review article exploring pharmacoeconomics of surgical interventions vs. COX-Is for the treatment of the PDA in the United States as well as from personal communication with hospital pharmacists in Canada.	The panel refrained from voting on this criterion for reasons mentioned in the "Resources Required" section
○ No included studies	Data on treatment costs with ibuprofen and acetaminophen (mentioned above) was obtained from personal communication with the hospital Pharmacist of the Neonatal Intensive Care Unit, IWK Health Center, Halifax, NS	

Cost effectiveness

Which intervention does the cost effectiveness favor?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS & COMMENTS FROM GUIDELINE PANEL
Best cost-effectiveness: **Intermediate cost-effectiveness:** **Worst cost-effectiveness:**	**<u>Prophylactic indomethacin</u>** There exists some evidence on cost-effectiveness of using prophylactic indomethacin in preterm infants. Two studies were identified: Moya et al conducted a systematic review of RCTs, cohort studies and retrospective case—control studies. The study demonstrated that there was a significant difference between prophylactic indomethacin and control when effectiveness was measured as quality-adjusted life years (QALYs), resulting in 11 and 10 years for the indomethacin and control groups, respectively. The cost-effectiveness analysis per QALY was $8443 for the indomethacin treatment and $9168 for the control group. Therefore, prophylactic use of indomethacin was concluded to be "less costly and more effective within an important range of certainty"[36]. Zupancic et al conducted a retrospective economic evaluation to determine the incremental cost-effectiveness of indomethacin prophylaxis in extremely low birth weight infants enrolled in the Trial of Indomethacin Prophylaxis in Preterms (TIPP). The study showed that indomethacin prophylaxis "cost an additional $67,500 per death or impairment averted. The precision of their estimate was low, such that the probability that the estimate was lower than $300,000 per death or impairment averted was 61%". Therefore, this study did not provide an economic rationale for the use of indomethacin prophylaxis in extremely low birth weight infants[37]. No direct research evidence on cost-effectiveness of **prophylactic ibuprofen** use in preterm infants was identified. No direct research evidence on cost-effectiveness of **prophylactic acetaminophen** use in preterm infants was identified.	Given that no research evidence on the cost-effectiveness of ibuprofen or acetaminophen was identified, the panel refrained from voting on this criterion and this criterion was not considered while voting on the final recommendations.

Equity

If recommended, which intervention would reduce health inequities the most?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS & COMMENTS FROM GUIDELINE PANEL
They are all acceptable	This is an intervention instituted in neonatal intensive care in a very specific population of preterm neonates. Therefore, no difference in effectiveness is anticipated in any disadvantaged subgroup in this particular situation and hence no equity impacts are anticipated	No voting was held for this criterion

Acceptability

Which intervention is more acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS & COMMENTS FROM GUIDELINE PANEL
Best acceptability: None **Intermediate acceptability:** Prophylactic indomethacin, Prophylactic ibuprofen **Worst acceptability:** Prophylactic acetaminophen	**Prophylactic indomethacin** • A recent retrospective cohort study of 4268 extremely low birth weight infants born at <30 weeks' gestation admitted to Canadian neonatal units between 2010 and 2014 showed that prophylactic indomethacin was associated with increased odds of spontaneous intestinal perforation independently from early feeding in this cohort (aOR 2.43, 95% CI 1.41 to 4.19)[3]. • However, a previous 2014 cohort study of 15751 extremely low birth weight infants in the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network showed that among infants exposed to prophylactic indomethacin, the risk of spontaneous intestinal perforation did not differ between the indomethacin/early-feeding group compared with the indomethacin/no-early-feeding group (adjusted relative risk [RR] 0.74, 95% confidence interval [CI] 0.49-1.11)[21]. • Another recent retrospective cohort study of 4720 extremely low gestational age (<26 weeks) or extremely low birth weight (<750g) infants admitted to Canadian neonatal units between 2010 and 2018 showed co-exposure of antenatal steroids and prophylactic indomethacin was associated with increased odds of spontaneous gastrointestinal perforation, especially if antenatal steroids was received within 7 days before birth (aOR 1.67, 95% CI 1.15-2.43)[38]. • A recent individual patient data meta-analysis has shown that concomitant use of prophylactic hydrocortisone to improve survival without CLD and use of prophylactic indomethacin to prevent IVH significantly increases the risk of spontaneous intestinal perforation (OR 2.50; 95% CI, 1.33 to 4.69)[22]. Therefore, controversy exists on whether prophylactic indomethacin potentially increases the risk of GI perforation. This might be a reason why some care providers may choose not to use prophylactic indomethacin in centers with low IVH rates in extremely preterm infants, or in centers which routinely use prophylactic hydrocortisone in preterm infants. **Prophylactic ibuprofen** • Use of prophylactic ibuprofen may be less acceptable in extremely preterm infants (<28 weeks) following reports of severe pulmonary hypertension in the ibuprofen treated infants which led to premature termination of an RCT on prophylactic ibuprofen in extremely preterm infants[39]. • Further reports of pulmonary hypertension following early ibuprofen administration has been reported as case-reports[23,40]. This might be a reason why care providers may choose not to use prophylactic ibuprofen in centers with low IVH or death rates in extremely preterm infants. **Prophylactic acetaminophen** Recent studies have raised concerns regarding the effect of acetaminophen on long-term neurodevelopment. In an ecological study using country level data, prenatal use of acetaminophen was associated with autism or autism spectrum disorder	Voting results from panel discussion: **Best acceptability** Indomethacin: 3/12 (25%) Ibuprofen: Acetaminophen: None: 10/12 (83%) **Intermediate acceptability** Indomethacin: 9/12 (75%) Ibuprofen: 11/12 (92%) Acetaminophen: 4/12 (33%) None: 1/12 (8%) **Worst acceptability** Indomethacin: Ibuprofen: Acetaminophen: 6/12 (50%) None: 6/12 (50%) **Comments:** One panel member pointed out that adverse effects of interventions are often brought to light through observational studies after the interventions are employed in the real world. Another panel member acknowledged the importance of carefully considering signals for potential adverse effects outside the realm of RCT evidence as a recommendation in favor of a prophylactic intervention would mean all infants below a certain GA threshold will be exposed to the drug(s) and their potential adverse effects. For prophylactic indomethacin, the panel therefore carefully considered the evidence from observational studies as some studies have suggested an increased risk of GI perforation. One panel member pointed out that there were methodological issues (risk of collider bias) with one study that demonstrated an increased risk of GI perforation[3]; while a similar observational study failed to

<table>
<tr>
<td></td>
<td>(ASD)[41]. In another Spanish birth cohort study, prenatal acetaminophen exposure was associated with an increased incidence autism-spectrum symptoms in males and showed adverse effects on attention-related outcomes for both genders[42].
However, no studies have definitively established a link between acetaminophen and autism.</td>
<td>demonstrate such association[21], thereby lowering the confidence of the panel on such an association. The panel acknowledged that there was not enough evidence to put indomethacin in the ‘worst acceptable’ category, neither there was overwhelming evidence confirming safety. Hence, indomethacin was put in the “intermediate acceptability” category.

For ibuprofen, the panel agreed that the evidence suggesting increased risk of pulmonary hypertension was of low quality; therefore, the acceptability of ibuprofen was deemed similar to indomethacin.

For acetaminophen, the panel was divided on their opinion. Half of the panel felt that since prophylactic acetaminophen had no proven benefit, and possible harm, albeit from low quality observational studies, this had the “worst acceptability” of the 3 drugs.</td>
</tr>
<tr>
<td colspan="3">Feasibility
Which intervention is more feasible to implement?</td>
</tr>
<tr>
<td>JUDGEMENT</td>
<td>RESEARCH EVIDENCE</td>
<td>ADDITIONAL CONSIDERATIONS</td>
</tr>
<tr>
<td>Most feasible: Prophylactic ibuprofen

Intermediate feasibility: Prophylactic indomethacin

Least feasible: Prophylactic acetaminophen</td>
<td><u>Prophylactic indomethacin</u>

Intravenous indomethacin has been used for a long time in North American NICUs and most preterm infants, especially those born extremely preterm (<28 weeks) have an intravenous access. So, the intervention is feasible to implement. However, IV indomethacin is not available in most NICUs in the United Kingdom.

<u>Prophylactic ibuprofen</u>

Intravenous Ibuprofen is readily available in most North American & European NICUs

<u>Prophylactic acetaminophen</u>

Acetaminophen is widely used in enteral formulation for pain management in the NICU. However, the intravenous formulation may not be universally available in all NICUs across North America and Europe. If prophylactic treatment is considered, then the intravenous formulation will mostly be used as most infants will likely be on minimal or no feeds. Therefore, use of prophylactic acetaminophen will be contingent on the availability of the intravenous formulation</td>
<td>Voting results from panel discussion:
<table>
<tr><td></td><td>Responses</td><td>Percentage</td></tr>
<tr><td>Most feasible</td><td></td><td></td></tr>
<tr><td>Indomethacin</td><td>2/12</td><td>16.7%</td></tr>
<tr><td>Ibuprofen</td><td>10/12</td><td>83%</td></tr>
<tr><td>Acetaminophen</td><td>1/12</td><td>8.3%</td></tr>
<tr><td>None</td><td></td><td></td></tr>
</table>

<table>
<tr><td></td><td>Responses</td><td>Percentage</td></tr>
<tr><td>Intermediate feasibility</td><td></td><td></td></tr>
<tr><td>Indomethacin</td><td>9/12</td><td>75%</td></tr>
<tr><td>Ibuprofen</td><td>1/12</td><td>8%</td></tr>
<tr><td>Acetaminophen</td><td>3/12</td><td>25%</td></tr>
<tr><td>None</td><td>1/12</td><td>8%</td></tr>
</table>

<table>
<tr><td></td><td>Responses</td><td>Percentage</td></tr>
<tr><td>Least feasible</td><td></td><td></td></tr>
<tr><td>Indomethacin</td><td>1/12</td><td>8%</td></tr>
<tr><td>Ibuprofen</td><td></td><td></td></tr>
<tr><td>Acetaminophen</td><td>9/12</td><td>75%</td></tr>
<tr><td>None</td><td>2/12</td><td>16.7%</td></tr>
</table>
</td>
</tr>
</table>

		Comments: There was a consensus among panel members that intravenous ibuprofen was the most feasible given it is most widely available. For indomethacin, 75% of the panel members felt that it was of intermediate feasibility, given it is unavailable in the UK. For acetaminophen, 75% of the panel members felt that it was least feasible given the IV formulation is still not widely available ***Oral formulations*** Given this guideline is being developed for prophylactic therapy in extremely preterm infants, the infants will be on minimal to no enteral feeds in the first 24 hours after birth. Therefore, the oral formulations of these medications were not considered for the purpose of this guideline.

Summary of judgements

CRITERIA	PROPHYLACTIC INDOMETHACIN	PROPHYLACTIC IBUPROFEN	PROPHYLACTIC ACETAMINOPHEN	Importance for decision making
DESIRABLE EFFECTS	★★★	★★	★	HIGH
UNDESIRABLE EFFECTS	★★	★★		HIGH
CERTAINTY OF EVIDENCE	INDOMETHACIN – MODERATE IBUPROFEN – LOW ACETAMINOPHEN – VERY LOW			HIGH
VALUES	PROBABLY NO IMPORTANT UNCERTAINTY OR VARIABILITY *(IN HOW MUCH PEOPLE VALUE THE MAIN OUTCOMES)*			HIGH
BALANCE OF EFFECTS	★★★	★★	★	HIGH
RESOURCES REQUIRED	*NO JUDGEMENT*			LOW
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	*NO JUDGEMENT*			LOW
COST EFFECTIVENESS	*NO JUDGEMENT*			LOW
EQUITY	ALL ACCEPTABLE			LOW
ACCEPTABILITY	★★	★★	★	MODERATE
FEASIBILITY	★★	★★★	★	MODERATE

★★★Ranked as best option in the factor considered for making the recommendation
★★Ranked as intermediate option in the factor considered for making the recommendation
★Ranked as worst option in the factor considered for making the recommendation

Conclusions

Recommendation(s)

Prophylactic indomethacin [Conditional (weak) recommendation for the intervention]

Clinicians may consider prophylaxis with intravenous indomethacin in extremely preterm infants *[conditional recommendation, moderate certainty in estimate of effects].*

The panel encourages shared decision making with the parents/guardians to evaluate their values and preferences with respect to desirable (severe IVH reduction) vs undesirable (CLD increase) outcomes.

The panel also recommends against using prophylactic indomethacin and prophylactic hydrocortisone concomitantly in extremely preterm infants.

Prophylactic ibuprofen [Conditional (weak) recommendation against the intervention]

Prophylaxis with intravenous ibuprofen in extremely preterm infants is not recommended *[conditional recommendation, low certainty in estimate of effects].*

The panel encourages shared decision making with the parents/guardians to evaluate their values and preferences with respect to desirable vs undesirable outcomes in centers that lack intravenous indomethacin and have high rates of severe IVH and death in extremely preterm infants.

Prophylactic acetaminophen [Strong recommendation against the intervention]

Clinicians should not use prophylactic acetaminophen in extremely preterm infants *[strong recommendation, very low certainty in estimate of effects]*

Justification

Prophylactic indomethacin

Voting results: 11 out of the 12 members of the panel voted for **conditional (weak) recommendation for the intervention.**

The panel determined that overall, there was moderate certainty of evidence from RCTs suggesting prophylactic indomethacin may reduce severe IVH and death without worsening NEC or gastrointestinal perforation. The panel especially highlighted the fact that indomethacin was the only intervention which was associated with a statistically significant reduction in severe IVH. Compared to the other COX-I options, the certainty for benefit for the most important clinical outcomes (death and severe IVH) was the best for indomethacin.

However, the panel noted that there was some variability in preference for use of prophylactic indomethacin among parents of preterm infants as well as adults born preterm, though prophylactic indomethacin was still the most preferred option (47.5% of participants from the values and preferences study opting for indomethacin). There were also some concerns noted with possible increased risk of gastrointestinal perforation, especially in conjunction with prophylactic hydrocortisone.

Therefore, the panel conditionally recommended in favor of using prophylactic intravenous indomethacin, especially in centers with high rates of severe IVH and death in extremely preterm infants. The panel encouraged shared decision making with the parents/guardians to evaluate their values and

preferences with respect to desirable vs undesirable outcomes. The panel also recommended against using prophylactic indomethacin and prophylactic hydrocortisone concomitantly in extremely preterm infants.

Prophylactic ibuprofen

Voting results: 11 out of the 12 members of the panel voted for **conditional (weak) recommendation against the intervention.**

The panel determined that overall, there was low certainty of evidence from RCTs suggesting prophylactic ibuprofen may reduce death and severe IVH. However, the panel did note that majority of parents of preterm infants as well as adults born preterm would opt for prophylactic ibuprofen when presented as the only choice; when asked to choose between all 3 COX-I drugs, ibuprofen was the 2nd choice following indomethacin.

Given the low certainty of evidence for benefit for the most important clinical outcomes (death and severe IVH), majority of the panel members felt that it was inappropriate to recommend a prophylactic therapy given the overall low certainty of evidence for benefit. However, the panel acknowledged that prophylactic ibuprofen could be an acceptable alternative to prophylactic indomethacin in centers with high rates of severe IVH and death in extremely preterm infants that do not stock indomethacin.

Therefore, the panel conditionally recommended against using prophylactic ibuprofen. The panel did encourage shared decision making with the parents/guardians to evaluate their values and preferences with respect to desirable vs undesirable outcomes in centers that lack intravenous indomethacin and have high rates of severe IVH and death in extremely preterm infants.

Prophylactic acetaminophen

Voting results: All 12 members of the panel voted for **strong recommendation against the intervention.**

Given that there was insufficient evidence to demonstrate benefit for clinically important outcomes, unknown long-term consequences, and based on our survey almost all parents of preterm infants (87%) and all adults born preterm opting against its use, the panel recommended against use of acetaminophen prophylaxis in extremely preterm infants.

Implementation considerations

Lack of availability of indomethacin

Prophylactic ibuprofen could be an acceptable alternative to prophylactic indomethacin in centers with high rates of severe IVH and death in extremely preterm infants that do not stock indomethacin.

Monitoring and evaluation

Prophylactic indomethacin

Given the concern regarding NEC and spontaneous intestinal perforation (in relation to use of antenatal corticosteroid within 7 days prior to birth as well as exposure to postnatal corticosteroids) with use of indomethacin in extremely preterm infants among neonatal care providers, the panel will continually monitor emerging research evidence on the association between use of prophylactic indomethacin and

adverse outcomes. Upon identification of potentially relevant new evidence, recommendations will be reconsidered and, if necessary, revised.

Prophylactic ibuprofen

If prophylactic ibuprofen is used as an alternative to indomethacin, the panel will continually monitor emerging research evidence on the association between use of prophylactic ibuprofen and adverse outcomes such as GI perforation, NEC and acute pulmonary hypertension. Upon identification of potentially relevant new evidence, recommendations will be reconsidered and, if necessary, revised.

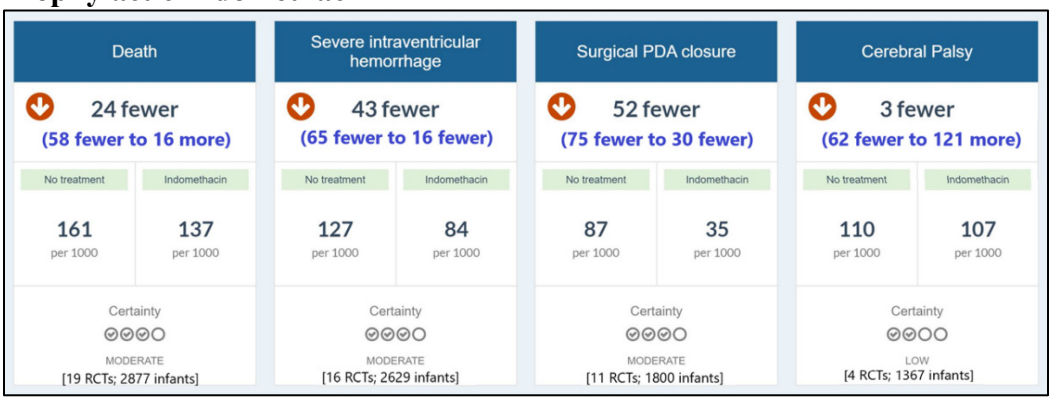
Research priorities

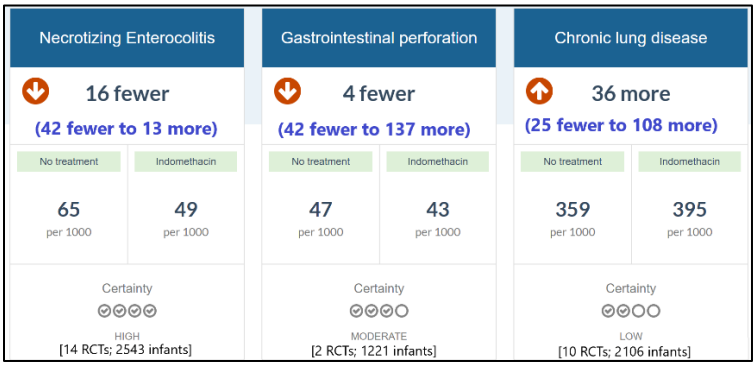
Further research is required in the following specific areas:

1. Effect of prophylactic acetaminophen on critical outcomes such as death, severe IVH, CLD and NEC
2. Effect of prophylactic indomethacin on adverse GI outcomes such as GI perforation and NEC.
3. Research on long term neurodevelopmental outcomes with ibuprofen and acetaminophen
4. Further research on values and preferences of parents of preterm infants and adults born preterm in lower income countries, and countries with varying health care systems
5. Research on cost-effectiveness of prophylactic ibuprofen and acetaminophen (if effectiveness is demonstrated with these drugs in future studies)

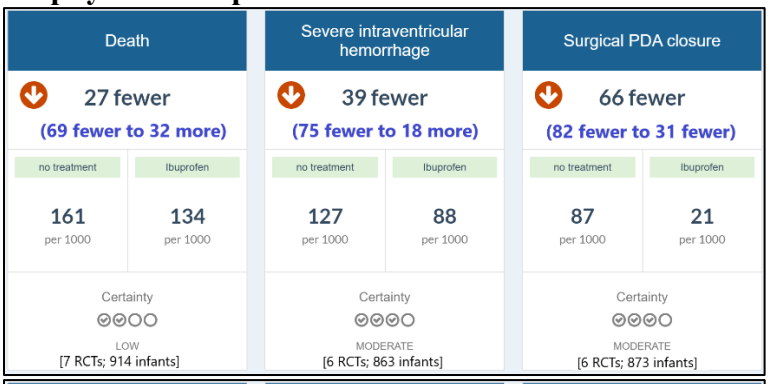
Appendix C. Decision Aids

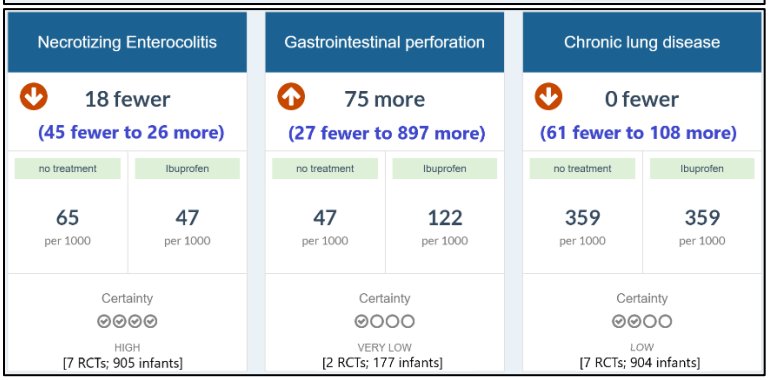
Prophylactic Indomethacin



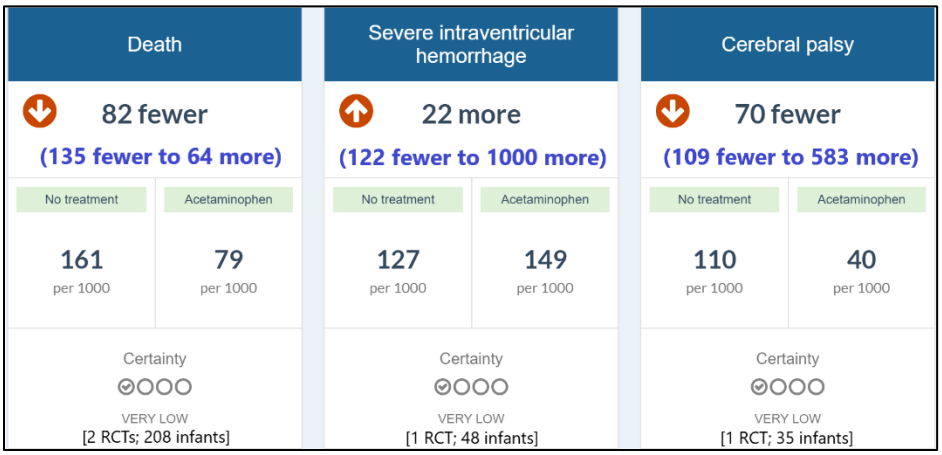


Prophylactic Ibuprofen





Prophylactic Acetaminophen



CHAPTER 5: CONCLUSION

This chapter summarizes the results, discusses the relative merits and limitations of this project, and explores the possible future directions that may help enhance family-centered evidence-based decision making in the neonatal intensive care unit. This project, designed to develop rigorous and transparent clinical practice guideline recommendations for the prophylactic use of cyclo-oxygenase inhibitor (COX-I) drugs for prevention of mortality and morbidity in extremely preterm infants through a de novo synthesis of evidence from randomized controlled trials (RCTs) using a network meta-analysis (NMA), and a cross-sectional mixed-methods study exploring family values and preferences conducted in parallel, demonstrated the following findings:

The Bayesian random-effects NMA of 28 RCTs (including 3999 infants) demonstrated that prophylactic indomethacin probably resulted in a small reduction in severe intraventricular hemorrhage (IVH) and a moderate reduction in death. Prophylactic ibuprofen probably resulted in a small reduction in severe IVH and may result in a moderate reduction in death. The evidence was very uncertain about the effect of acetaminophen on any of the clinically relevant outcomes. Evidence from this NMA was then used to explore the values and preferences of parents of very preterm infants and adults born very preterm on the use of COX-I prophylaxis. This two-phase cross-sectional mixed methods study that included 44 participants (34 parents of very preterm infants; 10 adults born very preterm) from across Canada and the United Kingdom showed that there was minimal variability in how participants valued the main outcomes, with death and severe IVH being rated as the two most important undesirable outcomes. While indomethacin was the most preferred form of prophylaxis, variability was noted in the choice of COX-I interventions when participants were presented with the benefits and harms of each drug. Finally, the 12-member guideline panel, that included five experienced neonatal care providers, two methods experts, one pharmacist, two parents of former extremely preterm infants and two adults born extremely preterm, was presented with the results from the above-mentioned NMA and the cross-sectional mixed methods study. Using the GRADE Evidence-to-Decision (EtD) framework for multiple comparisons, the panel provided a conditional recommendation in favor of indomethacin prophylaxis, a conditional recommendation against ibuprofen prophylaxis

and a strong recommendation against acetaminophen prophylaxis in extremely preterm infants. The panel strongly encouraged shared decision making with parents to evaluate their values and preferences prior to prescribing prophylactic indomethacin. Though prophylactic ibuprofen therapy was conditionally not recommended, the panel encouraged shared decision making with parents in centers that lack access to indomethacin and have high rates of severe IVH and death in extremely preterm infants.

Strengths and Limitations

Neonatology is a branch of medicine rich in evidence generated from clinical research. Yet, substantial deficiencies exist when it comes to practice of evidence-based medicine in neonatology. Practice of 'evidence-based medicine', as first defined by faculty at McMaster University, involves two fundamental principles: first, the use of the best available evidence to guide clinical decision-making, ideally based on the hierarchy of evidence[1]. Second, the application of clinical experience to conscientiously work with the health-related values and preferences of families and patients to help them make decisions that typically involve trading off benefits with the potential harms, inconvenience and costs associated with available management strategies[1]. As discussed in the introductory chapter, neonatal care is largely driven by guidelines and position statements developed almost exclusively by healthcare professionals, with little or no input from the parents of the infants being cared for, or from adults who have lived through the short- and long-term consequences of neonatal complications[2]. Therefore, current neonatal clinical guidelines, while they claim to be evidence-based through rigorous synthesis of available evidence, usually do not meet the necessary criteria for practice of evidence-based medicine, as the majority fail to systematically incorporate patient and parent values and preferences. Through our project we, therefore, attempted to develop rigorous and trustworthy practice guidelines for the use of prophylactic COX-I drugs in extremely preterm infants, using the GRADE methodology, that conforms to the principles of 'evidence-based medicine' with due emphasis on incorporation of family values and preferences. The following are some of the strengths of this project that deserve a mention.

Strengths of the project

First, this project addresses an important management dilemma with regards to use of COX-Is in extremely preterm infants to prevent mortality as well as morbidity that is clinically relevant to the families of these infants. Data from the Canadian Neonatal Network show that despite continuous quality improvement measures, the rate of the composite outcome of death or severe IVH among extremely preterm infants born in Canada has increased from 18.2% (391/2151) in 2017 to 20.2% (410/2025) in 2020, while the said rate in the smallest and sickest preterm population, born less than 26 weeks' gestational age, has increased from 31.4% (300/955) in 2017 to 34.2% (286/837) in 2020. Therefore, this project aligns with one of Canadian Institutes of Health Research's (CIHR) Institute of Human Development, Child and Youth Health (IHDCYH) priority research themes (https://cihr-irsc.gc.ca/e/49819.html), that is preventing preterm birth and its potential adverse health outcomes.

Second, to our knowledge, this is the first neonatal clinical practice guideline linked to a de novo systematic review and network meta-analysis developed using GRADE methodology. The recently developed GRADE guidance on assessing the certainty of evidence from a NMA was used in our systematic review of evidence[3]. Further, thresholds for benefit or harm for each outcome were explicitly defined using a partially contextualized approach prior to assessing certainty of evidence using the GRADE methodology[4]. These novel approaches for assessing certainty of a complex body of evidence such as a NMA were used for the first time in any review with the Cochrane Neonatal Group[5]. We believe that pre-defining the thresholds of benefit or harm to ascertain precision of the estimate of treatment effects will help systematic review authors provide an unbiased assessment of the certainty of synthesized evidence. Furthermore, the assigned certainties can be more readily applied by guideline developers given the certainties in estimate of effects are based on clinically relevant decision thresholds agreed upon by relevant stakeholders.

Third, this project placed a special emphasis on evaluating and incorporating the values and perspectives of parents of preterm infants and of adults who have lived experience of prematurity-related complications into the guideline recommendations. Therefore, the

project attempted to address this important gap in current neonatal clinical practice guidelines. Our study on health-related values and preferences (chapter 3) not only helped us understand how parents and former preterm infants value different clinical outcomes, but also provided us with helpful insights on how parents might weigh the benefits and harms when presented with the research evidence while making a shared clinical decision with a healthcare provider. Further, having all key stakeholders, including parents of extremely preterm infants and adults born extremely preterm, in the guideline panel ensured that patient perspectives were duly considered, and the importance of shared decision making was emphasized while formulating the guideline recommendations. This process of systematic incorporation of family values and active promotion of shared decision making in guideline recommendations will help to reduce unwarranted practice variation that is based on the care providers' values and biases, while allowing for some degree of warranted practice variation, that is based on the parents' values and preferences. Further, incorporation of family values and preferences will encourage engagement of families in clinical decision-making for their children.

Potential limitations and mitigation strategies

There are several limitations to consider while interpreting and applying results of this project. First, it is important to remember that the guideline recommendations in our project were developed following the GRADE evidence-to-decision framework, which has largely been used in the context of decision making in adult medicine[6]. There is little evidence on how neonatal care providers and parents interpret the GRADE certainties of evidence (high, moderate, low or very low) and how that affects their decision making. Moreover, the decision thresholds for benefit or harm for each outcome, that directly impacted the certainty in our estimate of treatment effects and eventually the strength of our recommendations, were defined based on the consensus of the study team. These decision thresholds, and therefore the assigned certainties of evidence, may not hold true at an individual level. Therefore, it may be important that clinicians not only present the certainty of evidence, but the actual effect estimates and their precision to families when engaging in shared decision making.

Second, there are certain unique challenges to shared decision making in the NICU that remain beyond the scope of the GRADE EtD framework, in its current form. The foremost, is the ethical complexity around who determines an infant's best interest, and what should be the course of action if a clinician strongly felt that the parental preferences were at odds with their own view of the infant's best interest. One possible way to prevent such a conflict is to try and identify outcomes that are critical to most parents, which in turn means including all relevant stakeholders in the guideline development process and involving them in outcome prioritization at the outset before delving into evidence synthesis. This was our rationale behind ensuring that one-third of our 12-member guideline panel were non-clinicians and included parents of infants born extremely preterm as well as adults who were born extremely preterm and have lived through one or more of the short- and long-term outcomes relevant to this guideline.

Third, is the issue of information overload in an already stressed NICU environment and whether the parents can fully comprehend the short- and long-term impacts of their child's current clinical condition. For example, our values and preferences study (chapter 3) showed that a majority of the parents (55%) felt the first 24 hours after birth was overwhelming, therefore, though they would like to be informed about the benefits and harms of the therapies, they will most likely trust the clinician's judgment. Consequently, a conditional recommendation promoting shared decision making should not automatically imply that the stressed and exhausted parents are burdened with more complex information and are forced to engage in a decision-making process. Rather, a conditional recommendation should encourage clinicians to routinely offer a discussion on the benefits and harms of therapies, and only engage in a detailed discussion if the parents are open to it.

Finally, it is important to acknowledge that the NICU is a high intensity environment where complex medical decisions need to be taken promptly for critically ill infants. Though there could be significant benefits and harms related to such interventions (for example delivery room interventions such as milking of the umbilical cord, sustained lung inflation etc.), they are not always amenable to shared decision-making at the bedside. However, as these interventions are most likely to differentially impact patient-important clinical outcomes,

it is important that voices of the parents are incorporated in the decision-making process. Therefore, it is imperative that parents are involved, and parental preferences are incorporated while developing neonatal clinical practice guidelines. Clinical guidelines developed through such a rigorous process of incorporating family values will ensure that the clinical team has followed the core principles of practice of evidence-based medicine, i.e., application of best available evidence while considering local clinical expertise as well as family values and preferences, even for urgent interventions where a discussion with parents at the bedside is not feasible.

Implications for Future Research

Decision-making in the NICU is a complex and evolving field. With respect to neonatal clinical practice guideline development and use, further research on some of the following issues will be helpful.

Effective presentation of evidence

The concept of incorporating parent values and preferences in clinical guidelines is still novel in neonatal medicine. Parental preferences may be affected by what evidence is presented to them and how the evidence is presented. There is scope for further refinement of both these aspects:

What evidence is presented

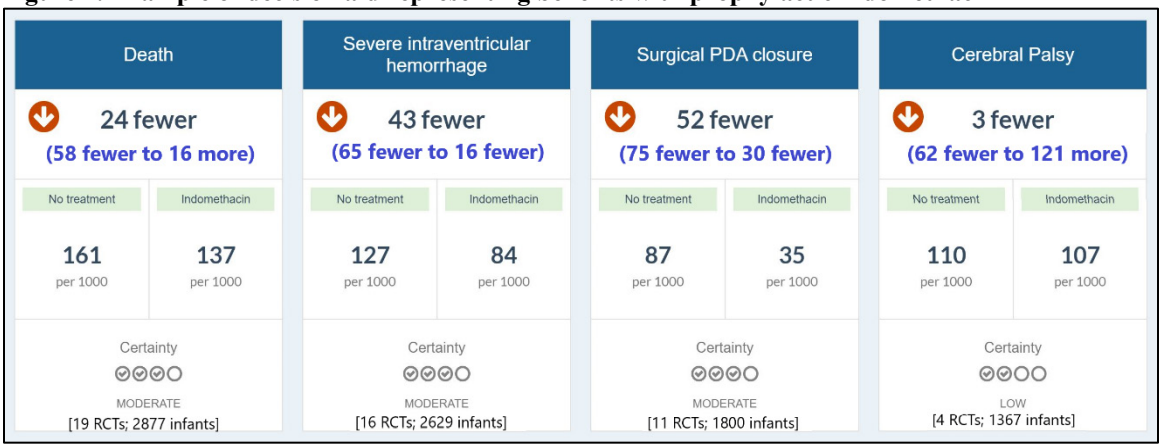
In neonatal medicine we may often find ourselves in scenarios where we have imprecise effect estimates or no evidence at all on patient-important outcomes (such as neurodevelopmental impairment) from higher quality studies such as RCTs, but we do have lower certainty evidence on such outcomes from observational studies of lower quality. Our values and preferences study (chapter 3) demonstrated that families can easily get overwhelmed when presented with evidence on more than four outcomes. Therefore, it is important to carefully select which patient-important outcomes should be included in the decision aids. Consequently, future research should explore whether presenting evidence of lower certainty on critical outcomes at all helps the shared decision-making process and how they impact guideline recommendations.

Another issue that needs to be explored is the presentation of evidence on competing outcomes. For example, if a systematic review of RCTs shows that an intervention results in a moderate reduction in death but a moderate increase in cerebral palsy, this information may come across as directly competing for the families who may perceive the increased risk of cerebral palsy as harm caused by the intervention. It is highly likely that since more sick and vulnerable infants survived due to this hypothetical intervention, there were more cases of cerebral palsy in the surviving cohort of infants in the intervention group. So, the perceived harm may or may not be related to the effect of the intervention. Future research should explore how such nuances can be easily communicated when exploring parent preferences for or against an intervention as they may directly impact the strength and direction of guideline recommendations.

How evidence is presented

In our project we used the MAGICApp software developed by members of the GRADE working group to generate our decision aids[7]. Though these decision aids have helped to clearly communicate complex information to the families as well as to the guideline committee panel, some potential scope for improvement was identified by members of the guideline panel. These decision aids appear to overemphasize the direction of benefit or harm without proportionally highlighting the magnitude, thereby leaving potential for misinterpretation by parents. For example, in this figure below (Figure 1, generated using the MAGICApp software and used in our project) that shows the potential benefits of prophylactic indomethacin, a moderate and precise reduction in surgical PDA closure (52 fewer per 1000; 95% CrIs 75 fewer to 30 fewer) is represented with a downward arrow of similar size and color, just as it is for a trivial and imprecise reduction in cerebral palsy (3 fewer per 1000; 95% CrIs 62 fewer to 121 more). There remains a possibility that a parent may interpret both effects as very similar in magnitude and direction when weighing benefits and harms, which in turn might influence the strength and direction of recommendations.

Figure 1. Example of decision aid representing benefits with prophylactic indomethacin



There are other available methods for communication of evidence such as the interactive summary of findings (iSOF) platform, also developed by the GRADE working group[8]. However, there is little evidence on which evidence presentation methods are well-suited for shared decision making with parents in a busy ICU environment. Therefore, future work should explore how to improve the content and presentation of decision aids so that they succinctly highlight the magnitude, direction and certainty of benefit or harm without overwhelming the parents.

Evaluation of parent values and preferences

There has been dearth of good quality research on family values and preferences in neonatal medicine until recent years[9–11]. The neoEPOCH group in the United Kingdom has led the way through their COIN (core outcome sets in neonatology) project, where, through an e-Delphi survey of former patients, parents, healthcare professionals and researchers, the group has developed a core outcome set for clinical trials and other research studies involving infants receiving neonatal care in a high-income setting[12]. However, there still remains limited evidence on parent preferences when presented with evidence on benefits and harms with specific interventions in different clinical scenarios. Our values and preferences study (chapter 3) is a small step towards encouraging further similar research projects on other neonatal decision-making dilemmas that entail patient-important benefit-harm tradeoffs.

Impact of shared decision-making on parents

As previously mentioned, the NICU is a high intensity environment where any interaction with healthcare providers in relation to their critically ill child can be stressful for parents. Therefore, regardless of whether the parents engage in the shared decision-making process, being offered a discussion on the benefits and harms of interventions, that may have a lasting impact on their child's future, may be a source of significant stress and can adversely affect their mental health. On the contrary, shared decision making, by improving parental engagement in their child's clinical care, may also positively impact their mental health, similar to the Family Integrated Care model that has been shown to significantly reduce both maternal and paternal stress and anxiety in the NICU[13,14]. Therefore, future research should explore the effects of shared decision-making exercises on parental mental and physical health, especially in the ICU setting. This will help researchers and clinicians refine the approach to shared decision-making thereby making it a less stressful experience for parents in the ICU.

Implementation research

This project was specifically designed to develop a clinical practice guideline on the use of prophylactic COX-I drugs in extremely preterm infants. It indeed needs to be acknowledged that this project is only the first step towards improving patient-important clinical outcomes for extremely preterm infants in an evidence-based, family-centered way. In order to achieve this goal, the practice guidelines need to be effectively implemented in the NICU setting. The issues around implementation and uptake of the guideline recommendations by clinicians in a busy NICU setting were out of the scope of the current project. However, it is imperative that guideline developers collaborate with implementation scientists to explore ways in which this and similar neonatal guidelines that involve shared decision making with families can be effectively implemented in order to improve outcomes in these critically ill neonates.

Implications for Practice

The methodology used in this thesis project has potential practice implications within and beyond the field of neonatal medicine. There are several clinical management conundrums

within the field of neonatal intensive care where the balance of benefits and harms of interventions do not clearly outweigh one another, which leads to substantial variation in clinical practice. These include, but are not limited to, use of systemic corticosteroids in chronically ventilated preterm infants, medical treatment of symptomatic PDA and use of inhaled nitric oxide in hypoxemic respiratory failure in preterm infants[15–17]. These and similar management dilemmas may benefit from rigorous clinical practice guidelines that have carefully considered the magnitude and certainty of benefits and harms of the respective interventions with regards to clinical outcomes that are deemed critical by patients and their families.

Though this project specifically focuses on decision-making in the neonatal ICU, clinicians and researchers should explore if the unique methodological aspects of this project can be translated to decision-making in other branches of critical care medicine. For example, decision making by family surrogates for hospitalized older adults remain complex and challenging, with limited evidence to guide family-centered care in the adult ICU [18,19]. Our approach of developing guideline recommendations with due emphasis on family values and preferences may have potential implications in clinical decision-making involving family surrogates in the adult ICU. Overall, this thesis project provides clinicians and researchers an approach to objectively combine the three pillars of evidence-based medicine, i.e., relevant scientific evidence, clinical judgement, and patients' values and preferences, which can help enhance evidence-based family centered decision-making in a critical care setting.

References

1. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ. 1996 Jan 13;312(7023):71–2.

2. Mitra S, Reid M, McDougall B, Johnston BC. Are neonatal clinical practice guidelines truly evidence-based? A case for incorporating family values and preferences. Acta Paediatr. 2019 Sep;108(9):1564–6.

3. Yepes-Nuñez JJ, Li SA, Guyatt G, Jack SM, Brozek JL, Beyene J, et al. Development of the summary of findings table for network meta-analysis. J Clin Epidemiol. 2019 Nov;115:1–13.

4. Brignardello-Petersen R, Izcovich A, Rochwerg B, Florez ID, Hazlewood G, Alhazanni W, et al. GRADE approach to drawing conclusions from a network meta-analysis using a partially contextualised framework. BMJ. 2020 Nov 10;371:m3907.

5. Mitra S, Gardner CE, MacLellan A, Disher T, Styranko DM, Campbell-Yeo M, et al. Prophylactic cyclo-oxygenase inhibitor drugs for the prevention of morbidity and mortality in preterm infants: a network meta-analysis. Cochrane Database Syst Rev. 2022 Apr 1;4:CD013846.

6. Neumann I, Brignardello-Petersen R, Wiercioch W, Carrasco-Labra A, Cuello C, Akl E, et al. The GRADE evidence-to-decision framework: a report of its testing and application in 15 international guideline panels. Implement Sci. 2016 Jul 15;11:93.

7. Agoritsas T, Heen AF, Brandt L, Alonso-Coello P, Kristiansen A, Akl EA, et al. Decision aids that really promote shared decision making: the pace quickens. BMJ. 2015 Feb 10;350:g7624.

8. Schünemann HJ, Santesso N, Brozek JL. Interactive Summary of Findings tables: the way to present and understand results of systematic reviews. JBI Database of Systematic Reviews and Implementation Reports. 2019 Mar;17(3):259.

9. Webbe JWH, Ali S, Sakonidou S, Webbe T, Duffy JMN, Brunton G, et al. Inconsistent outcome reporting in large neonatal trials: a systematic review. Arch Dis Child Fetal Neonatal Ed. 2020;105(1):69-75

10. Weiss EM, Barg FK, Cook N, Black E, Joffe S. Parental Decision-Making Preferences in Neonatal Intensive Care. J Pediatr. 2016;179:36-41.e3.

11. Weiss EM, Xie D, Cook N, Coughlin K, Joffe S. Characteristics Associated With Preferences for Parent-Centered Decision Making in Neonatal Intensive Care. JAMA Pediatr. 2018 May 1;172(5):461–8.

12. Webbe JWH, Duffy JMN, Afonso E, Al-Muzaffar I, Brunton G, Greenough A, et al. Core outcomes in neonatology: development of a core outcome set for neonatal research. Arch Dis Child Fetal Neonatal Ed. 2020;105(4):425-431.

13. van Veenendaal NR, van der Schoor SRD, Broekman BFP, de Groof F, van Laerhoven H, van den Heuvel MEN, et al. Association of a Family Integrated Care Model With Paternal Mental Health Outcomes During Neonatal Hospitalization. JAMA Netw Open. 2022 Jan 24;5(1):e2144720.

14. Cheng C, Franck LS, Ye XY, Hutchinson SA, Lee SK, O'Brien K. Evaluating the effect of Family Integrated Care on maternal stress and anxiety in neonatal intensive care units. J Reprod Infant Psychol. 2021 Apr;39(2):166–79.

15. Lakshminrusimha S, Kinsella JP, Krishnan US, Van Meurs K, Edwards EM, Bhatt DR, et al. Just Say No to iNO in Preterms-Really? J Pediatr. 2020 Mar;218:243–52.

16. Benitz WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? J Perinatol. 2010 Apr;30(4):241–52.

17. Steinhorn RH. Adding to the controversy of postnatal steroids for preterm infants. J Pediatr. 2019 Aug;211:1–3.

18. Bynum JP, Barre L, Reed C, Passow H. Participation of Very Old Adults in Healthcare Decisions. Med Decis Making. 2014 Feb;34(2):216–30.

19. Davidson JE, Aslakson RA, Long AC, Puntillo KA, Kross EK, Hart J, et al. Guidelines for Family-Centered Care in the Neonatal, Pediatric, and Adult ICU. Crit Care Med. 2017 Jan;45(1):103–28.

COMBINED REFERENCE LIST

1. Government of Canada, Canadian Institutes of Health Research, and Institute of Human Development, Child and Youth Health. “New Pan-Canadian Network Aims to Boost Health Outcomes for Preterm Infants." [Internet]. CIHR; Available from: http://www.cihr-irsc.gc.ca/e/50654.html.

2. Lim G, Tracey J, Boom N, Karmakar S, Wang J, Berthelot JM, et al. CIHI survey: Hospital costs for preterm and small-for-gestational age babies in Canada. Healthc Q. 2009;12(4):20–4.

3. Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm birth. N Engl J Med. 2008 Jul 17;359(3):262–73.

4. Lewandowski AJ. The preterm heart: a unique cardiomyopathy? Pediatr Res. 2019;85(6):738–9.

5. Crump C, Sundquist J, Winkleby MA, Sundquist K. Preterm birth and risk of chronic kidney disease from childhood into mid-adulthood: national cohort study. BMJ. 2019 01;365:l1346.

6. Gournay V. The ductus arteriosus: physiology, regulation, and functional and congenital anomalies. Arch Cardiovasc Dis. 2011 Nov;104(11):578–85.

7. Benitz WE, Committee on Fetus and Newborn, American Academy of Pediatrics. Patent Ductus Arteriosus in Preterm Infants. Pediatrics. 2016 Jan;137(1). doi: 10.1542/peds.2015-3730. Epub 2015 Dec 15

8. Clyman RI. The role of patent ductus arteriosus and its treatments in the development of bronchopulmonary dysplasia. Semin Perinatol. 2013 Apr;37(2):102–7.

9. Ballabh P. Intraventricular hemorrhage in premature infants: mechanism of disease. Pediatr Res. 2010 Jan;67(1):1–8.

10. Drougia A, Giapros V, Krallis N, Theocharis P, Nikaki A, Tzoufi M, et al. Incidence and risk factors for cerebral palsy in infants with perinatal problems: a 15-year review. Early Hum Dev. 2007 Aug;83(8):541–7.

11. Chung MY, Fang PC, Chung CH, Huang CB, Ou Yang MH, Chen CC. Risk factors for hemodynamically-unrelated cystic periventricular leukomalacia in very low birth weight premature infants. J Formos Med Assoc. 2005 Aug;104(8):571–7.

12. Dollberg S, Lusky A, Reichman B. Patent ductus arteriosus, indomethacin and necrotizing enterocolitis in very low birth weight infants: a population-based study. J Pediatr Gastroenterol Nutr. 2005 Feb;40(2):184–8.

13. Brown ER. Increased risk of bronchopulmonary dysplasia in infants with patent ductus arteriosus. J Pediatr. 1979 Nov;95(5 Pt 2):865–6.

14. Dice JE, Bhatia J. Patent Ductus Arteriosus: An Overview. J Pediatr Pharmacol Ther. 2007;12(3):138–46.

15. The Canadian Neonatal Network™ [Internet]. [cited 2019 Dec 4]. Available from: http://www.canadianneonatalnetwork.org/portal/CNNHome.aspx

16. Howes A, Hilditch C, Keir A. What clinical practice strategies have been shown to decrease incidence rates of intraventricular haemorrhage in preterm infants? Journal of Paediatrics and Child Health. 2019;55(10):1269–78.

17. Jain A, Shah PS. Diagnosis, Evaluation, and Management of Patent Ductus Arteriosus in Preterm Neonates. JAMA Pediatr. 2015 Sep;169(9):863–72.

18. Ohlsson A, Shah SS. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev. 2019 21;6:CD004213.

19. Allegaert K, Anderson B, Simons S, van Overmeire B. Paracetamol to induce ductus arteriosus closure: is it valid? Arch Dis Child. 2013 Jun;98(6):462–6.

20. Gillam-Krakauer M, Reese J. Diagnosis and Management of Patent Ductus Arteriosus. NeoReviews. 2018 Jul 1;19(7):e394–402.

21. Ferguson JM. Pharmacotherapy for patent ductus arteriosus closure. Congenit Heart Dis. 2019 Jan;14(1):52–6.

22. Ment LR, Stewart WB, Ardito TA, Huang E, Madri JA. Indomethacin promotes germinal matrix microvessel maturation in the newborn beagle pup. Stroke. 1992 Aug;23(8):1132–7.

23. Härmä A, Aikio O, Härkin P, Leskinen M, Valkama M, Saarela T, et al. Subgroup analysis of the early paracetamol trial to preterm infants found haemodynamic changes and improved oxygenation. Early Hum Dev. 2020 Jun;145:105042.

24. Enzmann D, Murphy-Irwin K, Stevenson D, Ariagno R, Barton J, Sunshine P. The natural history of subependymal germinal matrix hemorrhage. Am J Perinatol. 1985 Apr;2(2):123–33.

25. Fowlie PW, Davis PG, McGuire W. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. Cochrane Database Syst Rev. 2010 Jul 7;(7):CD000174.

26. Liebowitz M, Clyman RI. Prophylactic Indomethacin Compared with Delayed Conservative Management of the Patent Ductus Arteriosus in Extremely Preterm Infants: Effects on Neonatal Outcomes. J Pediatr. 2017;187:119-126.e1.

27. Seyberth HW, Rascher W, Hackenthal R, Wille L. Effect of prolonged indomethacin therapy on renal function and selected vasoactive hormones in very-low-birth-weight infants with symptomatic patent ductus arteriosus. J Pediatr. 1983 Dec;103(6):979–84.

28. Coombs RC, Morgan ME, Durbin GM, Booth IW, McNeish AS. Gut blood flow velocities in the newborn: effects of patent ductus arteriosus and parenteral indomethacin. Arch Dis Child. 1991 Oct;66(10):1261.

29. Wolf WM, Snover DC, Leonard AS. Localized intestinal perforation following intravenous indomethacin in premature infants. J Pediatr Surg. 1989 Apr;24(4):409–10.

30. Friedman WF, Hirschklau MJ, Printz MP, Pitlick PT, Kirkpatrick SE. Pharmacologic closure of patent ductus arteriosus in the premature infant. N Engl J Med. 1976 Sep 2;295(10):526–9.

31. Ohlsson A, Bottu J, Govan J, Ryan ML, Fong K, Myhr T. Effect of indomethacin on cerebral blood flow velocities in very low birth weight neonates with a patent ductus arteriosus. Dev Pharmacol Ther. 1993;20(1–2):100–6.

32. Mitra S, Rønnestad A, Holmstrøm H. Management of patent ductus arteriosus in preterm infants--where do we stand? Congenit Heart Dis. 2013 Dec;8(6):500–12.

33. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. Cochrane Database Syst Rev. 2018 28;9:CD003481.

34. Ohlsson A, Shah PS. Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants. Cochrane Database Syst Rev. 2018 06;4:CD010061.

35. Ji Y, Azuine RE, Zhang Y, Hou W, Hong X, Wang G, et al. Association of Cord Plasma Biomarkers of In Utero Acetaminophen Exposure With Risk of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in Childhood. JAMA Psychiatry. 2019 Oct 30;1–11.

36. Ystrom E, Gustavson K, Brandlistuen RE, Knudsen GP, Magnus P, Susser E, et al. Prenatal Exposure to Acetaminophen and Risk of ADHD. Pediatrics. 2017 Nov;140(5):e20163840.

37. Stavel M, Wong J, Cieslak Z, Sherlock R, Claveau M, Shah PS. Effect of prophylactic indomethacin administration and early feeding on spontaneous intestinal perforation in extremely low-birth-weight infants. J Perinatol. 2017;37(2):188–93.

38. Reese J, Shelton EL, Slaughter JC, McNamara PJ. Prophylactic Indomethacin Revisited. J Pediatr. 2017 Jul;186:11-14.e1.

39. Shaffer ML, Baud O, Lacaze-Masmonteil T, Peltoniemi OM, Bonsante F, Watterberg KL. Effect of Prophylaxis for Early Adrenal Insufficiency Using Low-Dose Hydrocortisone in Very Preterm Infants: An Individual Patient Data Meta-Analysis. J Pediatr. 2019 Apr;207:136-142.e5.

40. Montori VM, Elwyn G, Devereaux P, Straus SE, Haynes RB, Guyatt G. Decision Making and the Patient. In: Guyatt G, Rennie D, Meade MO, Cook DJ, editors. Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice, 3rd ed [Internet]. New York, NY: McGraw-Hill Education; 2015 [cited 2022 Apr 17]. Available from: jamaevidence.mhmedical.com/content.aspx?aid=1183878213

41. Zhang Y, Coello PA, Brożek J, Wiercioch W, Etxeandia-Ikobaltzeta I, Akl EA, et al. Using patient values and preferences to inform the importance of health outcomes in practice guideline development following the GRADE approach. Health Qual Life Outcomes. 2017 May 2;15(1):52.

42. Mitra S, Reid M, McDougall B, Johnston BC. Are neonatal clinical practice guidelines truly evidence-based? A case for incorporating family values and preferences. Acta Paediatr. 2019 Sep;108(9):1564–6.

43. Weiss EM, Barg FK, Cook N, Black E, Joffe S. Parental Decision-Making Preferences in Neonatal Intensive Care. J Pediatr. 2016;179:36-41.e3.

44. AlFaleh K, Alluwaimi E, AlOsaimi A, Alrajebah S, AlOtaibi B, AlRasheed F, et al. A prospective study of maternal preference for indomethacin prophylaxis versus symptomatic treatment of a patent ductus arteriosus in preterm infants. BMC Pediatr. 2015 Apr 22;15:47.

45. Zipkin DA, Umscheid CA, Keating NL, Allen E, Aung K, Beyth R, et al. Evidence-based risk communication: a systematic review. Ann Intern Med. 2014 Aug 19;161(4):270–80.

46. Hultcrantz M, Rind D, Akl EA, Treweek S, Mustafa RA, Iorio A, et al. The GRADE Working Group clarifies the construct of certainty of evidence. J Clin Epidemiol. 2017 Jul;87:4–13.

47. Schünemann HJ, Wiercioch W, Brozek J, Etxeandia-Ikobaltzeta I, Mustafa RA, Manja V, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. Journal of Clinical Epidemiology. 2017 Jan 1;81:101–10.

48. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008 Apr 26;336(7650):924–6.

49. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol. 2013 Jul;66(7):719–25.

50. McMaster University > CE&B Grade > Guideline Development Checklist [Internet]. [cited 2019 Dec 4]. Available from: https://cebgrade.mcmaster.ca/guidecheck.html

51. Brouwers MC, Kerkvliet K, Spithoff K, AGREE Next Steps Consortium. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. BMJ. 2016 Mar 8;i1152.

52. Mitra S, Gardner CE, MacLellan A, Disher T, Styranko DM, Campbell-Yeo M, et al. Prophylactic cyclo-oxygenase inhibitor drugs for the prevention of morbidity and mortality in preterm infants: a network meta-analysis. Cochrane Database Syst Rev. 2022 Apr 1;4:CD013846.

53. Clyman RI, Couto J, Murphy GM. Patent ductus arteriosus: are current neonatal treatment options better or worse than no treatment at all? Semin Perinatol. 2012 Apr;36(2):123–9.

54. Mitra S, Florez ID, Tamayo ME, Mbuagbaw L, Vanniyasingam T, Veroniki AA, et al. Association of Placebo, Indomethacin, Ibuprofen, and Acetaminophen With Closure of Hemodynamically Significant Patent Ductus Arteriosus in Preterm Infants. JAMA. 2018 Mar 27;319(12):1221–38.

55. Le J, Gales MA, Gales BJ. Acetaminophen for patent ductus arteriosus. Annals of Pharmacotherapy. 2015;49(2):241–6.

56. Grèen K, Drvota V, Vesterqvist O. Pronounced reduction of in vivo prostacyclin synthesis in humans by acetaminophen (paracetamol). Prostaglandins. 1989;37(3):311–5.

57. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. Cochrane Database Syst Rev. 2020 11;2:CD003481.

58. Bauer AZ, Kriebel D. Prenatal and perinatal analgesic exposure and autism: an ecological link. Environ Health. 2013 May 9;12:41.

59. Ji Y, Azuine RE, Zhang Y, Hou W, Hong X, Wang G, et al. Association of cord plasma biomarkers of In utero acetaminophen exposure with risk of attention-deficit/hyperactivity disorder and autism spectrum disorder in childhood. JAMA Psychiatry. 2020;77(2):180–9.

60. Ystrom E, Gustavson K, Brandlistuen RE, Knudsen GP, Magnus P, Susser E, et al. Prenatal exposure to acetaminophen and risk of ADHD. Pediatrics. 2017;140(5):e20163840–e20163840.

61. Ohlsson A, Shah PS. Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants. Cochrane Database Syst Rev. 2020 27;1:CD010061.

62. Ment LR, Stewart WB, Ardito TA, Huang E, Madri JA. Indomethacin promotes germinal matrix microvessel maturation in the newborn beagle pup. Stroke. 1992;23(8):1132–7.

63. Ohlsson A, Shah SS. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database of Systematic Reviews. 2020;(1).

64. Härmä A, Aikio O, Härkin P, Leskinen M, Valkama M, Saarela T, et al. Subgroup analysis of the early paracetamol trial to preterm infants found haemodynamic changes and improved oxygenation. Early Human Development. 2020;145:105042–105042.

65. Harkin P, Harma A, Aikio O, Valkama M, Leskinen M, Saarela T, et al. Paracetamol accelerates closure of the ductus arteriosus after premature birth: a randomized trial. Journal of Pediatrics. 2016;177:72-7.e2.

66. Bisaglia M, Venezia V, Piccioli P, Stanzione S, Porcile C, Russo C, et al. Acetaminophen protects hippocampal neurons and PC12 cultures from amyloid beta-peptides induced oxidative stress and reduces NF-kappaB activation. Neurochemistry International. 2002;41(1):43–54.

67. Vergeade A, Bertram CC, Bikineyeva AT, Zackert WE, Zinkel SS, May JM, et al. Cardiolipin fatty acid remodeling regulates mitochondrial function by modifying the electron entry point in the respiratory chain. Mitochondrion. 2016;28:88–95.

68. Baik N, Urlesberger B, Schwaberger B, Schmölzer GM, Avian A, Pichler G. Cerebral haemorrhage in preterm neonates: does cerebral regional oxygen saturation during the immediate transition matter? Archives of Disease in Childhood: Fetal and Neonatal Edition. 2015;100(5):F422–7.

69. Cimatti AG, Martini S, Galletti S, Vitali F, Aceti A, Frabboni G, et al. Cerebral Oxygenation and Autoregulation in Very Preterm Infants Developing IVH During the Transitional Period: A Pilot Study. Front Pediatr [Internet]. 2020 Jul 15 [cited 2020 Oct 21];8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7373744/

70. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr. 1978 Apr;92(4):529–34.

71. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg. 1978 Jan;187(1):1–7.

72. Meyer CL, Payne NR, Roback SA. Spontaneous, isolated intestinal perforations in neonates with birth weight less than 1,000 g not associated with necrotizing enterocolitis. J Pediatr Surg. 1991 Jun;26(6):714–7.

73. Pumberger W, Mayr M, Kohlhauser C, Weninger M. Spontaneous localized intestinal perforation in very-low-birth-weight infants: a distinct clinical entity different from necrotizing enterocolitis. J Am Coll Surg. 2002 Dec;195(6):796–803.

74. Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA, et al. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics. 2005;116(6):1353–60.

75. de Vries LS, Eken P, Dubowitz LM. The spectrum of leukomalacia using cranial ultrasound. Behavioural Brain Research. 1992;49(1):1–6.

76. Steiner S. Bayley Scales of Infant Development. San Antonio, TX: The Psychological Corporation; 1993.

77. Bayley N. Bayley Scales of Infant and Toddler Development. San Antonio, TX: The Psychological Corporation; 2005.

78. Griffiths R. The Abilities of Babies: a Study of Mental Measurement. London: University of London Press; 1954.

79. Griffiths R. The Abilities of Young Children: a Comprehensive System of Mental Measurement for the First Eight Years. London: Child Development Research Center; 1970.

80. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database of Systematic Reviews. 2013;(1).

81. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA G r. o. u. p. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Journal of Clinical Epidemiology. 2009;62(10):1006–12.

82. van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades AE, Welton NJ. Automating network meta-analysis. Res Synth Methods. 2012 Dec;3(4):285–99.

83. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane Handbook for Systematic Reviews of Interventions. 2nd Edition. Chichester (UK): John Wiley & Sons; 2019.

84. Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 2011 Feb;64(2):163–71.

85. Costantini I, Paul E, Caldwell DM, López-López JA, Pearson RM. Protocol for a systematic review and network meta-analysis of randomised controlled trials examining the effectiveness of early parenting interventions in preventing internalising problems in children and adolescents. Systematic Reviews. 2020;9(1):244–244.

86. Baker SG, Kramer BS. The transitive fallacy for randomized trials: if A bests B and B bests C in separate trials, is A better than C? BMC Medical Research Methodology. 2002;2:13–13.

87. Cipriani A, Higgins JPT, Geddes JR, Salanti G. Conceptual and technical challenges in network meta-analysis. Ann Intern Med. 2013 Jul 16;159(2):130–7.

88. Donegan S, Williamson P, Gamble C, Tudur-Smith C. Indirect comparisons: a review of reporting and methodological quality. PLOS One. 2010;5(11):e11054–e11054.

89. White IR, Barrett JK, Jackson D, Higgins JPT. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. Res Synth Methods. 2012 Jun;3(2):111–25.

90. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Stat Med. 2010 Mar 30;29(7–8):932–44.

91. Veroniki AA, Vasiliadis HS, Higgins JPT, Salanti G. Evaluation of inconsistency in networks of interventions. Int J Epidemiol. 2013 Feb;42(1):332–45.

92. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Medical Decision Making: an International Journal of the Society for Medical Decision Making. 2013;33(5):607–17.

93. Lambert PC, Sutton AJ, Burton PR, Abrams KR, Jones DR. How vague is vague? A simulation study of the impact of the use of vague prior distributions in MCMC using WinBUGS. Statistics in Medicine. 2005;24(15):2401–28.

94. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med. 2004 Oct 30;23(20):3105–24.

95. Gelman A, Rubin DB. Inference from Iterative Simulation Using Multiple Sequences. Statist Sci. 1992 Nov;7(4):457–72.

96. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2020.

97. Owen RK, Bradbury N, Xin Y, Cooper N, Sutton A. MetaInsight: an interactive web-based tool for analyzing, interrogating, and visualizing network meta-analyses using R-shiny and netmeta. Research Synthesis Methods. 2019;10(4):569–81.

98. Palmer T, Sterne J, editors. Meta-Analysis in Stata. In: An Updated Collection From the Stata Journal. College Station (TX): Stata Press; 2016.

99. Brignardello-Petersen R, Bonner A, Alexander PE, Siemieniuk RA, Furukawa TA, Rochwerg B, et al. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. Journal of Clinical Epidemiology. 2018;93:36–44.

100. Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ. 2014 Sep 24;349:g5630.

101. Schünemann H, Brozek J, Guyatt G, Oxman A, editors. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. Available from gdt.guidelinedevelopment.org/app/handbook/handbook.html.

102. Yepes-Nuñez JJ, Li SA, Guyatt G, Jack SM, Brozek JL, Beyene J, et al. Development of the summary of findings table for network meta-analysis. J Clin Epidemiol. 2019 Nov;115:1–13.

103. Seok EJ, Kim EJ, Jeon SS, Seo SS. Effect of indomethacin therapy on prevention of intraventricular hemorrhage in very low birth weight infant. Journal of the Korean Society of Neonatal Science. 1998;5(1):27–34.

104. Akbari Asbagh P, Zarkesh MR, Nili F, Nayeri FS, Tofighi Naeem A. Prophylactic teatment with oral paracetamol for patent ductus arteriosus in preterm infants: a randomized clinical trial. Tehran University Medical Journal. 2015;73(2):86–92.

105. Kalani M, Shariat M, Khalesi N, Farahani Z, Ahmadi S. A comparison of early ibuprofen and indomethacin administration to prevent intraventricular hemorrhage among preterm infants. Acta Medica Iranica. 2016;54(12):788–92.

106. Aikio O. Extremely low gestatonal age infants' paracetamol study (Paras). https://clinicaltrials.gov/ct2/show/NCT03641209 (first received 21 August 2018).

107. Rozé JC. Prophylactic treatment of the ductus arteriosus in preterm Infants by acetaminophen (TREOCAPA). https://clinicaltrials.gov/ct2/show/NCT04459117. (first received 7 July 2020).

108. Bada HS, Green RS, Pourcyrous M, Leffler CW, Korones SB, Magill HL, et al. Indomethacin reduces the risks of severe intraventricular hemorrhage. Journal of Pediatrics. 1989;115(4):631–7.

109. Couser R J, Ferrara TB, Wright GB, Cabalka AK, Schilling CG, Hoekstra RE, et al. Prophylactic indomethacin therapy in the first twenty-four hours of life for the prevention of patent ductus arteriosus in preterm infants treated prophylactically with surfactant in the delivery room. Journal of Pediatrics. 1996;128(5 Pt 1):631–7.

110. Couser RJ, Hoekstra RE, Ferrara B, Wright GB, Cabalka AK, Connet JE. Neurodevelopmental follow-up at 36months' corrected age of preterm infants treated withprophylactic indomethacin. Archives of Pediatric and Adolescent Medicine. 2000;154(6):598–602.

111. Hanigan WC, Kennedy G, Roemisch F, Anderson R, Cusack T, Powers W. Administration of indomethacin for the prevention of periventricular-intraventricular hemorrhage in high-risk neonates. Journal of Pediatrics. 1988;112(6):941–7.

112. Jannatdoust A, Samadi M, Yeganehdoust S, Heydarzadeh M, Alikhah H, Piri R, et al. Effects of intravenous indomethacin on reduction of symptomatic patent ductus arteriosus cases and decreasing the need for prolonged mechanical ventilation. Journal of Cardiovascular and Thoracic Research. 2014;6(4):257–9.

113. Krueger E, Mellander M, Bratton D, Cotton R. Prevention of symptomatic patent ductus arteriosus with a single dose of indomethacin. Journal of Pediatrics. 1987;111(5):749–54.

114. Kumar Nair PA, Pai MG, Gazal HA, Da Costa DE, Al Khusaiby SM. Indomethacin prophylaxis for intraventricular hemorrhage in very low birth weight babies. Indian Pediatrics. 2004;41(6):551–8.

115. Mahony L, Caldwell RL, Girod D A, Hurwitz RA, Jansen RD, Lemons JA, et al. Indomethacin therapy on the first day of life in infants with very low birth weight. Journal of Pediatrics. 1985;106(5):801–5.

116. Maruyama K, Fujiu T. Effects of prophylactic indomethacin on renal and intestinal blood flows in premature infants. Pediatrics International. 2012;54(4):480–5.

117. Ment L R, Duncan CC, Ehrenkranz RA, Kleinman CS, Pitt BR, Taylor KJ, et al. Randomized indomethacin trial for prevention of intraventricular hemorrhage in very low birth weight infants. Journal of Pediatrics. 1985;107(6):937–43.

118. Ment LR, Duncan CC, Ehrenkranz RA, Kleinman CS, Taylor K J, Scott DT, et al. Randomized low-dose indomethacin trial for prevention of intraventricular hemorrhage in very low birth weight neonates. Journal of Pediatrics. 1988;112(6):948–55.

119. Ment LR, Oh W, Ehrenkranz RA, Phillip AG, Vohr B, Allan W, et al. Low-dose indomethacin therapy and extension of intraventricular hemorrhage: a multicenter randomized trial. Journal of Pediatrics. 1994;124(6):951–5.

120. Ment LR, Oh W, Ehrenkranz RA, Philip AG, Vohr B, Allan W, et al. Low-dose indomethacin and prevention of intraventricular hemorrhage: a multicenter randomized trial. Pediatrics. 1994;93(4):543–50.

121. Ment LR, Vohr B, Oh W, Scott DT, Allan WC, Westerveld M, et al. Neurodevelopmental outcome at 36 months' corrected age of preterm infants in the Multicenter Indomethacin Intraventricular Hemorrhage Prevention Trial. Pediatrics. 1996;98:714–8.

122. Ment LR, Vohr B, Allan W, Westerveld M, SparrowSS, Schneider KC, et al. Outcome of children in theindomethacin intraventricular hemorrhage prevention trial. Pediatrics. 2000;105:485–91.

123. Vohr BR, Allan WC, Westerveld M, Schneider KC, Katz KH, Makuch RW, et al. School-age outcomes of very low birth weight infants in the indomethacin intraventricular hemorrhage prevention trial. Pediatrics. 2003;111(4 Pt 1):e340–6.

124. Ment LR, Vohr BR, Makuch RW, Westerveld M, Katz KH, Schneider KC, et al. Prevention of intraventricular hemorrhage by indomethacin in male preterm infants. Journal of Pediatrics. 2004;145(6):832–4.

125. Luu TM, Ment LR, Schneider KC, Katz KH, Allan WC, Vohr BR. Lasting effects of preterm birth and neonatal brain hemorrhage at 12 years of age. Pediatrics. 2009;123(3):1037–44.

126. Morales-Suarez M, De Jesus Sanchez-Gil T, Lemus-Varela L, Udaeta-Mora E. Low doses indomethacin for prevention of intraventricular hemorrhage in the preterm newborn infant with mechanical ventilation: final report of a randomized study. Boletin Medico del Hospital Infantil de Mexico. 1994;51(6):389–94.

127. Rennie J M, Doyle J, Cooke RW. Early administration of indomethacin to preterm infants. Archives of Disease in Childhood. 1986;61(3):233–8.

128. Schmidt B, Davis P, Moddemann D, Ohlsson A, Roberts RS, Saigal S, et al. Long-Term Effects of Indomethacin Prophylaxis in Extremely-Low-Birth-Weight Infants. New England Journal of Medicine. 2001 Jun 28;344(26):1966–72.

129. Ohlsson A, Roberts RS, Schmidt B, Davis P, ModdemanD, Saigal S, et al. Male/female differences in indomethacin effects in preterm infants. Journal of Pediatrics. 2005;147:860–2.

130. Schmidt B, Roberts RS, Fanaroff A, Davis P, Kirpalani HM N C, et a. l. Indomethacin prophylaxis, patent ductusarteriosus, and the risk of bronchopulmonary dysplasia:further analyses from the Trial of Indomethacin Prophylaxisin Preterms (TIPP). Journal of Pediatrics. 2006;148:730–4.

131. Zupancic JAF, Richardson DK, O'Brien BJ, Cronin CG, Schmidt B, Roberts R, et al. Retrospective economic evaluation of a controlled trial of indomethacin prophylaxis for patent ductus arteriosus in premature infants. Early Hum Dev. 2006 Feb;82(2):97–103.

132. Bandstra ES, Montalvo BM, Goldberg RN, Pacheco I, Ferrer PL, Flynn J, et al. Prophylactic indomethacin for prevention of intraventricular hemorrhage in premature infants. Pediatrics. 1988;82(4):533–42.

133. Setzer ES M BM, Goldberg RN, Smith M, Bancalari E. Prophylactic indomethacin and intraventricular hemorrhagein the premature. In 1984. p. 345A-345A.

134. Setzer ES, Torres-Arraut E, Gomez-del-Rio M, Young ML P I, Ferrer PL, et a. l. Cardiopulmonary effects of prophylactic indomethacin in the very low birth weight infant. In 1984. p. 346A-346A.

135. Supapannachart S, Khowsathit P, Patchakapati B. Indomethacin prophylaxis for patent ductus arteriosus (PDA) in infants with a birth weight of less than 1250 grams. Journal of the Medical Association of Thailand = Chotmaihet Thangphaet. 1999;82 Suppl 1:S87–92.

136. Vincer M, Allen A, Evans J, Nwaesei C, Stinson D, Rees E, et al. Early intravenous indomethacin prolongs respiratory support in very low birth weight infants. Acta Paediatrica. 1987;76(6):894–7.

137. Vincer M, Allen A. Does prophylactic indomethacin inVLBW (<1500 grams birth weight) infants cause cerebral palsy (CP)? Pediatric Research. 1998;43:232–232.

138. Vogtmann C, Grubbe G, Ruckhäberle KE, Böttcher H, Ockert C. Effects of early therapy with indomethacin on the manifestation of a persistent ductus arteriosus in extremely underweight premature infants. Monatsschrift Kinderheilkund. 1988;136(9):636–9.

139. Dani C, Bertini G, Reali M F, Murru P, Fabris C, Vangi V, et al. Prophylaxis of patent ductus arteriosus with ibuprofen in preterm infants. Acta Paediatrica. 2000;89(11):1369–74.

140. Dani C, Bertini G, Pezzati M, Poggi C, Guerrini P, Martano C, et al. Prophylactic ibuprofen for the prevention of intraventricular hemorrhage among preterm infants: a multicenter, randomized study. Pediatrics. 2005;115(6):1529–35.

141. De Carolis M P, Romagnoli C, Polimeni V, Piersigilli F, Zecca E, Papacci P, et al. Prophylactic ibuprofen therapy of patent ductus arteriosus in preterm infants. European Journal of Pediatrics. 2000;159(5):364–8.

142. Gournay V, Roze J C, Kuster A, Daoud P, Cambonie G, Hascoet J M, et al. Prophylactic ibuprofen versus placebo in very premature infants: a randomised, double-blind, placebo-controlled trial. Lancet. 2004;364(9449):1939–44.

143. Kanmaz G, Erdeve O, Canpolat FE, Oğuz SS, Uras N, Altug N, et al. Serum ibuprofen levels of extremely preterm infants treated prophylactically with oral ibuprofen to prevent patent ductus arteriosus. European Journal of Clinical Pharmacology. 2013;69(5):1075–81.

144. Sangtawesin V, Sangtawesin C, Raksasinborisut C, Sathirakul K, Kanjanapattanakul W, Khorana M, et al. Oral ibuprofen prophylaxis for symptomatic patent ductus arteriosus of prematurity. Journal of the Medical Association of Thailand. 2006;89(3):314–21.

145. Van Overmeire B, Allegaert K, Casaer A, Debauche C, Decaluwé W, Jespers A, et al. Prophylactic ibuprofen in premature infants: a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2004;364(9449):1945–9.

146. van Overmeire B, Casaer A, Allegaert K, Debauche C, Decaluwe W, Jespers A, et al. Multicenter randomized double-blind placebo-controlled trial of ibuprofen prophylaxis in very preterm infants. Pediatric Research. 2002;51(4):379A-379A.

147. Bagheri M. M, Bahman-Bijari B, Torabi-Nejad M. H, Niknafs P, Mousavi H, Sabzevari F, et al. Is prophylactic parenteral paracetamol effective to diminish incidence of PDA in preterm neonates? A randomized trial. Iranian Journal of Pediatrics. 2018;28(4):e11735–e11735.

148. Juujärvi S, Kallankari H, Pätsi P, Leskinen M, Saarela T, Hallman M, et al. Follow-up study of the early, randomised paracetamol trial to preterm infants, found no adverse reactions at the two-years corrected age. Acta Paediatrica. 2019;108(3):452–8.

149. Liebowitz M, Clyman RI. Prophylactic indomethacin compared with delayed conservative management of the patent ductus arteriosus in extremely preterm infants: effects on neonatal outcomes. Journal of Pediatrics. 2017;187:119–26.

150. Varvarigou A, Bardin CL, Beharry K, Chemtob S, Papageorgiou A, Aranda JV. Early ibuprofen administration to prevent patent ductus arteriosus in premature newborn infants. JAMA. 1996 Feb 21;275(7):539–44.

151. Cotts T. Escalating dose indomethacin for prophylactic closure of patent ductus arteriosus does not improve closure rates and is associated with increased complications. Journal of Pediatrics. 2009;154(1):153–153.

152. Hammerman C, Strates E, Valaitis S. The silent ductus: its precursors and its aftermath. Pediatric Cardiology. 1986;7(3):121–7.

153. Kääpä P. Early closure of ductus arteriosus with indomethacin. Klinische Pädiatrie. 1985;197(2):172–172.

154. Rubaltelli F, Bertini G, Reali MF, Vangi V, Dani C. Does early closure of PDA with ibuprofen reduce the severity of RDS in premature infants? Pediatric Research. 1998;43:296A-296A.

155. Schmidt B, Seshia M, Shankaran S, Mildenhall L, Tyson J, Lui K, et al. Effects of prophylactic indomethacin in extremely low-birth-weight infants with and without adequate exposure to antenatal corticosteroids. Archives of Pediatrics and Adolescent Medicine. 2011;165(7):642–6.

156. Valls-i-Soler A, Lopez-de-Heredia J, Roman L, Fernandez-Ruanova MB. Prophylactic indomethacin (INDO) in very low birth weight (VLBW) infants with RDS. A pilot study on the effects of a slow infusion rate. Pediatric Research. 1999;45(6):901–901.

157. Alfaleh K, Smyth JA, Roberts RS, Solimano A, Asztalos EV, Schmidt B; Trial of Indomethacin Prophylaxis in Preterms Investigators. Prevention and 18-month outcomes of serious pulmonary hemorrhage in extremely low birth weight infants: results from the trial of indomethacin prophylaxis in preterms. Pediatrics. 2008;121(2):e233–8.

158. Gregoire N, Gualano V, Geneteau A, Millerioux L, Brault M, Mignot A, et al. Population pharmacokinetics of ibuprofen enantiomers in very premature neonates. Journal of Clinical Pharmacology. 2004;44(10):1114–24.

159. Harma A, Harkin P, Leskinen M, Valkama M, Saarela T, Aikio O, et al. Does intravenous paracetamol offer neonatal brain protection? Study of hemodynamics and cerebral oxygenation in very premature infants. Neonatology. 2018;113(4):417–8.

160. Ment LR, Vohr B, Allan W, Westerveld M, Katz KH, Schneider KC, et al. The etiology and outcome of cerebral ventriculomegaly at term in very low birth weight preterm infants. Pediatrics. 1999;104(2 Pt 1):243–8.

161. Naulaers G, Delanghe G, Allegaert K, Debeer A, Cossey V, Vanhole C, et al. Ibuprofen and cerebral oxygenation and circulation. Archives of Disease in Childhood Fetal Neonatal Edition. 2005;90(1):F75–6.

162. Pleacher MD, Vohr BR, Katz KH, Ment LR, Allan WC. An evidence-based approach to predicting low IQ in very preterm infants from the neurological examination: outcome data from the indomethacin Indomethacin Intraventricular Hemorrhage Prevention Trial. Pediatrics. 2004;113(2):416–9.

163. Vohr B, Allan WC, Scott DT, Katz KH, Schneider KC, Makuch RW, et al. Early-onset intraventricular hemorrhage in preterm neonates: incidence of neurodevelopmental handicap. Seminars in Perinatology. 1999;23(3):212–7.

164. Domanico RS, Waldman JD, Lester LA, McPhillips HA, Catrambone JE, Covert RF. Prophylactic indomethacin reduces the incidence of pulmonary hemorrhage and patent ductus arteriosus in surfactant-treated infants. Pediatric Research. 1994;35:331A-331A.

165. Gutierrez NG, Lapasset M. Prophylactic indomethacin and the incidence of patent ductus arteriosus in preterm neonates. Proceedings of the 3rd Argentinian Congress of Perinatology, Buenos Aires. 1987;62.

166. Puckett CG, Cox MA, Haskins KS, Fisher DJ. Prophylactic indomethacin (I) for the prevention of patent ductus arteriosus (PDA). Pediatric Research. 1985;19:358–358.

167. Zarkesh MR, Nili F, Akbari Asbagh P, Nayeri FS, Naeem A. Prophylactic treatment with oral paracetamol for patent ductus arteriosus in preterm infants admitted in Nicu Vali-Asr Hospital In 2012. Iranian Journal Of Pediatrics. 2013;23(Suppl 1):54–5.

168. Meau-Petit V. Prophylactic ibuprofen vs placebo in very premature infants: a randomised, double blind, placebo-controlled trial. Archives de Pédiatrie. 2005;12:605–8.

169. Ment LR. Randomized low-dose indomethacin trial for the prevention of intraventricular hemorrhage in very low birth weight neonates. Annals of Neurology. 1987;22(3):406–7.

170. Morales-Suarez M, Lemus-Varela L, Udaeta-Mora E, Cardiel-Marmolejo L, Rodríguez-Balderrama I, Liz-Cedillo RE. Indomethacin in the prevention of subependymal-intraventricular hemorrhage in preterm newborns with conventional mechanical ventilation. Boletín Médico del Hospital Infantil de México. 1992;49(4):217–24.

171. Roze JC, Gournay V, Daoud P, Cambonie G, Chamboux C, Hascoet JM, et al. Multicenter double blind randomized placebo-controlled study comparing prophylactic versus curative ibuprofen treatment in premature infants less than 28 weeks of gestation. Pediatric Research. 2003;53:386A-386A.

172. Barrington KJ, Finer NN, Ment LR. Indomethacin for prevention of intraventricular hemorrhage. Journal of Pediatrics. 1986;109(2):396–8.

173. Hammerman C, Kaplan M. Prophylactic ibuprofen in premature infants: a multicentre, randomised, double-blind, placebo-controlled trial. Journal of Pediatrics. 2005;146(5):709–10.

174. McGuire W, Fowlie PW. Treating extremely low birthweight infants with prophylactic indomethacin. Evidence for short term benefits only. BMJ. 2002;324(7329):60–1.

175. Ment LR, Westerveld M, Makuch R, Vohr B, Allan WC. Cognitive outcome at 4 1/2 years of very low birth weight infants enrolled in the multicenter indomethacin intraventricular hemorrhage prevention trial. Pediatrics. 1998;102(1 Pt 1):159–60.

176. Schmidt B, Wright LL, Davis P, Solimano A, Roberts RS; Indomethacin Prophylaxis in Preterms Investigators. Ibuprofen prophylaxis in preterm neonates. Lancet. 2002;360(9331):492–492.

177. Tyson JE. Does indomethacin prophylaxis benefit extremely low birth weight infants? Results of a placebo-controlled multicenter trial. Pediatric Research. 2002;51(1):1–1.

178. Hamrick SEG, Sallmon H, Rose AT, Porras D, Shelton EL, Reese J, et al. Patent Ductus Arteriosus of the Preterm Infant. Pediatrics. 2020 Nov;146(5):e20201209.

179. Ryan M, Lacaze-Masmonteil T, Mohammad K. Neuroprotection from acute brain injury in preterm infants. Paediatr Child Health. 2019 Jul;24(4):276–90.

180. Santesso N, Glenton C, Dahm P, Garner P, Akl EA, Alper B, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. Journal of Clinical Epidemiology. 2020;119:126–35.

181. Brignardello-Petersen R, Guyatt GH, Mustafa RA, Chu DK, Hultcrantz M, Schünemann HJ, et al. GRADE guidelines 33: Addressing imprecision in a network meta-analysis. Journal of Clinical Epidemiology. 2021;139:49–56.

182. Sangtawesin C, Sangtawesin V, Lertsutthiwong W, Kanjanapattanakul W, Khorana M, Ayudhaya JK. Prophylaxis of symptomatic patent ductus arteriosus with oral ibuprofen in very low birth weight infants. Journal of the Medical Association of Thailand. 2008;91(Suppl 3):S28–34.

183. Zeng L, Brignardello-Petersen R, Hultcrantz M, Siemieniuk RA, Santesso N, Traversy G, et al. GRADE guidelines 32: GRADE offers guidance on choosing targets of GRADE certainty of evidence ratings. Journal of Clinical Epidemiology. 2021;137:163–75.

184. Weiss EM, Xie D, Cook N, Coughlin K, Joffe S. Characteristics Associated With Preferences for Parent-Centered Decision Making in Neonatal Intensive Care. JAMA Pediatr. 2018 May 1;172(5):461–8.

185. Soltys F, Philpott-Streiff SE, Fuzzell L, Politi MC. The importance of shared decision-making in the neonatal intensive care unit. Journal of Perinatology. 2020 Mar;40(3):504–9.

186. Webbe JWH, Duffy JMN, Afonso E, Al-Muzaffar I, Brunton G, Greenough A, et al. Core outcomes in neonatology: development of a core outcome set for neonatal research. Arch Dis Child Fetal Neonatal Ed. 2020;105(4):425-431.

187. Alonso-Coello P, Ebrahim S, Guyatt GH, Tikkinen KAO, Eckman MH, Neumann I, et al. Evaluating patient values and preferences for thromboprophylaxis decision making during pregnancy: a study protocol. BMC Pregnancy Childbirth. 2012 May 30;12:40.

188. Eckman MH, Alonso-Coello P, Guyatt GH, Ebrahim S, Tikkinen KAO, Lopes LC, et al. Women's values and preferences for thromboprophylaxis during pregnancy: a comparison of direct-choice and decision analysis using patient specific utilities. Thromb Res. 2015 Aug;136(2):341–7.

189. Boyatzis RE. Transforming qualitative information: thematic analysis and code development. 1998.

190. Applied Thematic Analysis [Internet]. SAGE Publications Inc. 2020 [cited 2020 Oct 28]. Available from: https://us.sagepub.com/en-us/nam/applied-thematic-analysis/book233379

191. Vandvik PO, Brandt L, Alonso-Coello P, Treweek S, Akl EA, Kristiansen A, et al. Creating clinical practice guidelines we can trust, use, and share: a new era is imminent. Chest. 2013 Aug;144(2):381–9.

192. Agoritsas T, Heen AF, Brandt L, Alonso-Coello P, Kristiansen A, Akl EA, et al. Decision aids that really promote shared decision making: the pace quickens. BMJ. 2015 Feb 10;350:g7624.

193. Kandraju H, Kanungo J, Lee KS, Daspal S, Adie MA, Dorling J, et al. Association of Co-Exposure of Antenatal Steroid and Prophylactic Indomethacin with Spontaneous Intestinal Perforation. J Pediatr. 2021 Aug;235:34-41.e1.

194. Bellini C, Campone F, Serra G. Pulmonary hypertension following L-lysine ibuprofen therapy in a preterm infant with patent ductus arteriosus. CMAJ. 2006 Jun 20;174(13):1843–4.

195. Sehgal A, Kumarshingri PSN. Pulmonary hypertension in an infant treated with ibuprofen. Indian J Pediatr. 2013 Aug;80(8):697–9.

196. Mitra S, Weisz D, Jain A, Jong G 't. Management of the patent ductus arteriosus in preterm infants. Paediatrics & Child Health. 2022 Mar 1;27(1):63–63.

197. Moberg J, Alonso-Coello P, Oxman AD. GRADE Evidence to Decision (EtD) Frameworks Guidance. Version 1.1 [updated May 2015] [Internet]. The GRADE Working Group; 2015. Available from: https://ietd.epistemonikos.org/#/help/guidance

198. Piggott T, Brozek J, Nowak A, Dietl H, Dietl B, Saz-Parkinson Z, et al. Using GRADE evidence to decision frameworks to choose from multiple interventions. J Clin Epidemiol. 2021 Feb;130:117–24.

199. Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. BMJ [Internet]. 2016 Jun 28 [cited 2019 Dec 4];353. Available from: https://www.bmj.com/content/353/bmj.i2016

200. Qaseem A, Wilt TJ, Clinical Guidelines Committee of the American College of Physicians. Disclosure of Interests and Management of Conflicts of Interest in Clinical Guidelines and Guidance Statements: Methods From the Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med. 2019 03;171(5):354–61.

201. Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiol. 2011 Apr;64(4):395–400.

202. Lynn MR. Determination and quantification of content validity. Nurs Res. 1986 Dec;35(6):382–5.

203. Mitra S, Gardner CE, MacLellan A, Disher T, Styranko DM, Campbell-Yeo M, et al. Prophylactic cyclo-oxygenase inhibitor drugs for the prevention of morbidity and mortality in preterm infants: a network meta-analysis. Cochrane Database Syst Rev. 2022 Apr 1;4:CD013846.

204. Santesso N, Glenton C, Dahm P, Garner P, Akl EA, Alper B, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. J Clin Epidemiol. 2020 Mar;119:126–35.

205. Kelleher J, Salas AA, Bhat R, Ambalavanan N, Saha S, Stoll BJ, et al. Prophylactic Indomethacin and Intestinal Perforation in Extremely Low Birth Weight Infants. Pediatrics. 2014 Nov;134(5):e1369–77.

206. Brignardello-Petersen R, Izcovich A, Rochwerg B, Florez ID, Hazlewood G, Alhazanni W, et al. GRADE approach to drawing conclusions from a network meta-analysis using a partially contextualised framework. BMJ. 2020 Nov 10;371:m3907.

207. Neumann I, Brignardello-Petersen R, Wiercioch W, Carrasco-Labra A, Cuello C, Akl E, et al. The GRADE evidence-to-decision framework: a report of its testing and application in 15 international guideline panels. Implement Sci. 2016 Jul 15;11:93.

208. Qureshi M, Shah PS, Abdelgadir D, Ye XY, Afifi J, Yuen R, et al. Gestational Age-Dependent Variations in Effects of Prophylactic Indomethacin on Brain Injury and Intestinal Injury. J Pediatr. 2021 Aug;235:26-33.e2.

209. Singh R, Gorstein SV, Bednarek F, Chou JH, McGowan EC, Visintainer PF. A predictive model for SIVH risk in preterm infants and targeted indomethacin therapy for prevention. Sci Rep. 2013;3:2539.

210. Evans P, O'Reilly D, Flyer JN, Soll R, Mitra S. Indomethacin for symptomatic patent ductus arteriosus in preterm infants. Cochrane Database Syst Rev. 2021 Jan 15;1:CD013133.

211. Doyle LW, Cheong JL, Hay S, Manley BJ, Halliday HL. Late (≥ 7 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. Cochrane Database Syst Rev. 2021 Nov 11;11:CD001145.

212. Mitra S, Campbell-Yeo M, Kuhle S, Dorling J, Johnston BC. Exploring health-related values and preferences of former preterm infants and families of preterm infants on use of prophylactic cyclo-oxygenase inhibitor drugs for patent ductus arteriosus: a cross-sectional mixed-methods study. Manuscript in preparation.

213. Baud O, Maury L, Lebail F, Ramful D, El Moussawi F, Nicaise C, et al. Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMILOC): a double-blind, placebo-controlled, multicentre, randomised trial. Lancet. 2016 Apr 30;387(10030):1827–36.

214. Turck CJ, Marsh W, Stevenson JG, York JM, Miller H, Patel S. Pharmacoeconomics of Surgical Interventions vs. Cyclooxygenase Inhibitors for the Treatment of Patent Ductus Arteriosus. J Pediatr Pharmacol Ther. 2007;12(3):183–93.

215. Moya MP, Goldberg RN. Cost-effectiveness of prophylactic indomethacin in very-low-birth-weight infants. Ann Pharmacother. 2002 Feb;36(2):218–24.

216. Gournay V, Roze JC, Kuster A, Daoud P, Cambonie G, Hascoet JM, et al. Prophylactic ibuprofen versus placebo in very premature infants: a randomised, double-blind, placebo-controlled trial. Lancet. 2004 Dec 27;364(9449):1939–44.

217. Sehgal A, Kumarshingri PSN. Pulmonary hypertension in an infant treated with ibuprofen. Indian J Pediatr. 2013 Aug;80(8):697–9.

218. Avella-Garcia CB, Julvez J, Fortuny J, Rebordosa C, García-Esteban R, Galán IR, et al. Acetaminophen use in pregnancy and neurodevelopment: attention function and autism spectrum symptoms. Int J Epidemiol. 2016 01;45(6):1987–96.

219. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ. 1996 Jan 13;312(7023):71–2.

220. Schünemann HJ, Santesso N, Brozek JL. Interactive Summary of Findings tables: the way to present and understand results of systematic reviews. JBI Database of Systematic Reviews and Implementation Reports. 2019 Mar;17(3):259.

221. Webbe JWH, Ali S, Sakonidou S, Webbe T, Duffy JMN, Brunton G, et al. Inconsistent outcome reporting in large neonatal trials: a systematic review. Arch Dis Child Fetal Neonatal Ed. 2020;105(1):69-75

222. van Veenendaal NR, van der Schoor SRD, Broekman BFP, de Groof F, van Laerhoven H, van den Heuvel MEN, et al. Association of a Family Integrated Care Model With Paternal Mental Health Outcomes During Neonatal Hospitalization. JAMA Netw Open. 2022 Jan 24;5(1):e2144720.

223. Cheng C, Franck LS, Ye XY, Hutchinson SA, Lee SK, O'Brien K. Evaluating the effect of Family Integrated Care on maternal stress and anxiety in neonatal intensive care units. J Reprod Infant Psychol. 2021 Apr;39(2):166–79.

224. Lakshminrusimha S, Kinsella JP, Krishnan US, Van Meurs K, Edwards EM, Bhatt DR, et al. Just Say No to iNO in Preterms-Really? J Pediatr. 2020 Mar;218:243–52.

225. Benitz WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? J Perinatol. 2010 Apr;30(4):241–52.

226. Steinhorn RH. Adding to the controversy of postnatal steroids for preterm infants. J Pediatr. 2019 Aug;211:1–3.

227. Bynum JP, Barre L, Reed C, Passow H. Participation of Very Old Adults in Healthcare Decisions. Med Decis Making. 2014 Feb;34(2):216–30.

228. Davidson JE, Aslakson RA, Long AC, Puntillo KA, Kross EK, Hart J, et al. Guidelines for Family-Centered Care in the Neonatal, Pediatric, and Adult ICU. Crit Care Med. 2017 Jan;45(1):103–28.

APPENDIX A: JOURNAL COPYRIGHT FORMS

JOHN WILEY AND SONS LICENSE
TERMS AND CONDITIONS

Apr 13, 2022

This Agreement between Dr. Souvik Mitra ("You") and John Wiley and Sons ("John Wiley and Sons") consists of your license details and the terms and conditions provided by John Wiley and Sons and Copyright Clearance Center.

License Number	5287300968870
License date	Apr 13, 2022
Licensed Content Publisher	John Wiley and Sons
Licensed Content Publication	Cochrane Database of Systematic Reviews
Licensed Content Title	Prophylactic cyclo-oxygenase inhibitor drugs for the prevention of morbidity and mortality in preterm infants: a network meta-analysis
Licensed Content Author	Souvik Mitra, Courtney E Gardner, Abigale MacLellan, et al
Licensed Content Date	Dec 31, 1969
Licensed Content Pages	1

Type of use	Dissertation/Thesis
Requestor type	Author of this Wiley article
Format	Print and electronic
Portion	Full article
Will you be translating?	No
Title	Prophylactic Cyclo-oxygenase Inhibitor Drugs for the Prevention of Morbidity and Mortality in Extremely Preterm Infants: A Clinical Practice Guideline Incorporating Family Values and Preferences
Institution name	Dalhousie University
Expected presentation date	Jul 2022
Requestor Location	Dr. Souvik Mitra 5980 University Avenue P.O. Box 9700 Halifax, NS B3K 6R8 Canada Attn: Dr. Souvik Mitra
Publisher Tax ID	EU826007151
Total	0.00 CAD

Terms and Conditions

TERMS AND CONDITIONS

This copyrighted material is owned by or exclusively licensed to John Wiley & Sons, Inc. or one of its group companies (each a"Wiley Company") or handled on behalf of a society with

which a Wiley Company has exclusive publishing rights in relation to a particular work (collectively "WILEY"). By clicking "accept" in connection with completing this licensing transaction, you agree that the following terms and conditions apply to this transaction (along with the billing and payment terms and conditions established by the Copyright Clearance Center Inc., ("CCC's Billing and Payment terms and conditions"), at the time that you opened your RightsLink account (these are available at any time at http://myaccount.copyright.com).

Terms and Conditions

- The materials you have requested permission to reproduce or reuse (the "Wiley Materials") are protected by copyright.

- You are hereby granted a personal, non-exclusive, non-sub licensable (on a stand-alone basis), non-transferable, worldwide, limited license to reproduce the Wiley Materials for the purpose specified in the licensing process. This license, **and any CONTENT (PDF or image file) purchased as part of your order,** is for a one-time use only and limited to any maximum distribution number specified in the license. The first instance of republication or reuse granted by this license must be completed within two years of the date of the grant of this license (although copies prepared before the end date may be distributed thereafter). The Wiley Materials shall not be used in any other manner or for any other purpose, beyond what is granted in the license. Permission is granted subject to an appropriate acknowledgement given to the author, title of the material/book/journal and the publisher. You shall also duplicate the copyright notice that appears in the Wiley publication in your use of the Wiley Material. Permission is also granted on the understanding that nowhere in the text is a previously published source acknowledged for all or part of this Wiley Material. Any third party content is expressly excluded from this permission.

- With respect to the Wiley Materials, all rights are reserved. Except as expressly granted by the terms of the license, no part of the Wiley Materials may be copied, modified, adapted (except for minor reformatting required by the new Publication), translated, reproduced, transferred or distributed, in any form or by any means, and no derivative works may be made based on the Wiley Materials without the prior permission of the respective copyright owner.**For STM Signatory Publishers clearing permission under the terms of the STM Permissions Guidelines only, the terms of the license are extended to include subsequent editions and for editions in other languages, provided such editions are for the work as a whole in situ and does not involve the separate exploitation of the permitted figures or extracts,** You may not alter, remove or suppress in any manner any copyright, trademark or other notices displayed by the Wiley Materials. You may not license, rent, sell, loan, lease, pledge, offer as security, transfer or assign the Wiley Materials on a stand-alone basis, or any of the rights granted to you hereunder to any other person.

- The Wiley Materials and all of the intellectual property rights therein shall at all times remain the exclusive property of John Wiley & Sons Inc, the Wiley Companies, or their respective licensors, and your interest therein is only that of having possession of and the right to reproduce the Wiley Materials pursuant to Section 2 herein during the continuance of this Agreement. You agree that you own no right, title or interest in or to the Wiley Materials or any of the intellectual property rights therein. You shall have no rights hereunder other than the license as provided for above in Section 2. No right, license or interest to any trademark, trade name, service mark or other branding ("Marks") of WILEY or its licensors is granted hereunder, and you agree that you

shall not assert any such right, license or interest with respect thereto

- NEITHER WILEY NOR ITS LICENSORS MAKES ANY WARRANTY OR REPRESENTATION OF ANY KIND TO YOU OR ANY THIRD PARTY, EXPRESS, IMPLIED OR STATUTORY, WITH RESPECT TO THE MATERIALS OR THE ACCURACY OF ANY INFORMATION CONTAINED IN THE MATERIALS, INCLUDING, WITHOUT LIMITATION, ANY IMPLIED WARRANTY OF MERCHANTABILITY, ACCURACY, SATISFACTORY QUALITY, FITNESS FOR A PARTICULAR PURPOSE, USABILITY, INTEGRATION OR NON-INFRINGEMENT AND ALL SUCH WARRANTIES ARE HEREBY EXCLUDED BY WILEY AND ITS LICENSORS AND WAIVED BY YOU.

- WILEY shall have the right to terminate this Agreement immediately upon breach of this Agreement by you.

- You shall indemnify, defend and hold harmless WILEY, its Licensors and their respective directors, officers, agents and employees, from and against any actual or threatened claims, demands, causes of action or proceedings arising from any breach of this Agreement by you.

- IN NO EVENT SHALL WILEY OR ITS LICENSORS BE LIABLE TO YOU OR ANY OTHER PARTY OR ANY OTHER PERSON OR ENTITY FOR ANY SPECIAL, CONSEQUENTIAL, INCIDENTAL, INDIRECT, EXEMPLARY OR PUNITIVE DAMAGES, HOWEVER CAUSED, ARISING OUT OF OR IN CONNECTION WITH THE DOWNLOADING, PROVISIONING, VIEWING OR USE OF THE MATERIALS REGARDLESS OF THE FORM OF ACTION, WHETHER FOR BREACH OF CONTRACT, BREACH OF WARRANTY, TORT, NEGLIGENCE, INFRINGEMENT OR OTHERWISE (INCLUDING, WITHOUT LIMITATION, DAMAGES BASED ON LOSS OF PROFITS, DATA, FILES, USE, BUSINESS OPPORTUNITY OR CLAIMS OF THIRD PARTIES), AND WHETHER OR NOT THE PARTY HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES. THIS LIMITATION SHALL APPLY NOTWITHSTANDING ANY FAILURE OF ESSENTIAL PURPOSE OF ANY LIMITED REMEDY PROVIDED HEREIN.

- Should any provision of this Agreement be held by a court of competent jurisdiction to be illegal, invalid, or unenforceable, that provision shall be deemed amended to achieve as nearly as possible the same economic effect as the original provision, and the legality, validity and enforceability of the remaining provisions of this Agreement shall not be affected or impaired thereby.

- The failure of either party to enforce any term or condition of this Agreement shall not constitute a waiver of either party's right to enforce each and every term and condition of this Agreement. No breach under this agreement shall be deemed waived or excused by either party unless such waiver or consent is in writing signed by the party granting such waiver or consent. The waiver by or consent of a party to a breach of any provision of this Agreement shall not operate or be construed as a waiver of or consent to any other or subsequent breach by such other party.

- This Agreement may not be assigned (including by operation of law or otherwise) by you without WILEY's prior written consent.

- Any fee required for this permission shall be non-refundable after thirty (30) days from receipt by the CCC.

- These terms and conditions together with CCC's Billing and Payment terms and conditions (which are incorporated herein) form the entire agreement between you and WILEY concerning this licensing transaction and (in the absence of fraud) supersedes all prior agreements and representations of the parties, oral or written. This Agreement may not be amended except in writing signed by both parties. This Agreement shall be binding upon and inure to the benefit of the parties' successors, legal representatives, and authorized assigns.

- In the event of any conflict between your obligations established by these terms and conditions and those established by CCC's Billing and Payment terms and conditions, these terms and conditions shall prevail.

- WILEY expressly reserves all rights not specifically granted in the combination of (i) the license details provided by you and accepted in the course of this licensing transaction, (ii) these terms and conditions and (iii) CCC's Billing and Payment terms and conditions.

- This Agreement will be void if the Type of Use, Format, Circulation, or Requestor Type was misrepresented during the licensing process.

- This Agreement shall be governed by and construed in accordance with the laws of the State of New York, USA, without regards to such state's conflict of law rules. Any legal action, suit or proceeding arising out of or relating to these Terms and Conditions or the breach thereof shall be instituted in a court of competent jurisdiction in New York County in the State of New York in the United States of America and each party hereby consents and submits to the personal jurisdiction of such court, waives any objection to venue in such court and consents to service of process by registered or certified mail, return receipt requested, at the last known address of such party.

WILEY OPEN ACCESS TERMS AND CONDITIONS

Wiley Publishes Open Access Articles in fully Open Access Journals and in Subscription journals offering Online Open. Although most of the fully Open Access journals publish open access articles under the terms of the Creative Commons Attribution (CC BY) License only, the subscription journals and a few of the Open Access Journals offer a choice of Creative Commons Licenses. The license type is clearly identified on the article.

The Creative Commons Attribution License

The Creative Commons Attribution License (CC-BY) allows users to copy, distribute and transmit an article, adapt the article and make commercial use of the article. The CC-BY license permits commercial and non-

Creative Commons Attribution Non-Commercial License

The Creative Commons Attribution Non-Commercial (CC-BY-NC)License permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.(see below)

Creative Commons Attribution-Non-Commercial-NoDerivs License