ON THE ROLE OF SUB-ANESTHETIC KETAMINE FOR POST-OPERATIVE ANALGESIA FOLLOWING THIRD MOLAR SURGERY

by

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Dedication

I dedicate this thesis to my loving wife Catherine for all her support and care throughout my studies and training. I also dedicate this manuscript to my parents for their love and kindness throughout the years of my education.

And I also dedicate this work to my three cats for keeping me company as I prepare this thesis.

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Abstract

The role of ketamine in post-operative pain following third molar surgery is unclear. Therefore, one hundred and thirty-four patients were enrolled into a randomized double-blinded clinical trial to investigate if patients undergoing third molar surgery who receive a sub-anesthetic pre-operative dose of intravenous ketamine will experience less post-operative pain. The primary outcome was post-operative pain intensity as determined by 10-point visual analogue scales (VAS) during the first 48-hours post-op. The secondary outcome was post-operative non-opioid and opioid consumption. Data analysis involved descriptive statistics, multivariate analysis, and regression analysis. There was a small, yet statistically significant ($P<0.05$) difference in median pain score at 6-hours post-operatively with the ketamine group experiencing more pain. However, no further differences were detected at any post-operative time between groups. Overall, this study did not find evidence that pre-operative sub-anesthetic ketamine reduced pain following third molar surgery, nor had any effects on non-opioid or opioid analgesic consumption.

List of Abbreviations Used

OMFS – Oral and maxillofacial surgery

PSA – Procedural sedation anesthesia

CT – Computed tomography

MANOVA – Multivariate analysis of variance

NMDA – N-methyl D-aspartate

NSAID – Non-steroidal anti-inflammatory drug

VAS – Visual analogue scale

MICE - multivariate imputation by chained equations

GEE – Generalized estimating equations

IQR – Interquartile range

IV – Intravenous

ASA – American Society of Anesthesiologists

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Chapter 1: Introduction

1.1 Third Molars and the Rationale for Removal

The typical human dentition contains thirty-two teeth, four of which are wisdom teeth or third molars. Wisdom teeth are usually the last to develop, and ideally erupt into proper function and alignment within the dental arch. Unfortunately, not every individual has adequate space in their jaws to accommodate for full and functional eruption of wisdom teeth. Therefore, given space limitations and in finding a path of least resistance, wisdom teeth tend to erupt malpositioned or remain impacted. Impacted wisdom teeth can remain fully covered by soft tissue or hard tissue, and the adjacent second molar tooth may often be an obstacle towards successful eruption as well. It is also common for wisdom teeth to become partially erupted, with the exposed tooth surfaces being susceptible to plaque build-up. Theperiodontal tissues can become prone to food trapping with subsequent inflammation and possible infection. Given the location of wisdom teeth (partial or fully erupted), appropriate oral hygiene for these teeth can be difficult to achieve and therefore they are subject to tooth decay and/or periodontal disease [1]. Even if a wisdom tooth is impacted, there is still a possibility that an open communication can develop between the oral cavity and the unerupted third molar just behind the second molars due to a breakdown in the integrity (and presence of disease) of the periodontal tissues in this area. Furthermore, the presence of caries or periodontal disease on wisdom teeth may even affect neighbouring molars and vice versa [1]. Moreover, it is suggested that the absence of symptoms do not equate to absence of disease. For example, 25-60% and 28-77% (depending on age and gender) of asymptomatic wisdom teeth show clinical signs of periodontal disease and caries, respectively [1]. Should a patient decide on

keeping their wisdom teeth due to the absence of symptoms or disease, active monitoring of these teeth should be performed at recall appointments as the behavior, eruption position, and onset of disease patterns can often be unpredictable [1]. However, evidence has shown that removal of wisdom teeth often improves the periodontal health of adjacent teeth (with the reduction of localized inflammation) as well as improving the quality of life of patients that are suffering from symptomatic periodontal pathology (or pericoronitis). In certain rare circumstances, unerupted wisdom teeth may even develop associated cysts and tumors [2], and therefore prophylactic removal of such wisdom teeth may be considered beneficial under these scenarios as well. Therefore, the surgical removal of wisdom teeth is a beneficial procedure towards restoring and maintaining the health of the oral cavity (whether or not symptoms exist), as well as having beneficial outcomes to the quality of life of the patient.

1.2 Procedural Sedation Anesthesia

The surgical removal of wisdom teeth is a routine outpatient service provided by oral and maxillofacial surgeons. For this procedure, patients are offered three different routes of anesthesia including local anaesthetic only, procedural sedation and analgesia (PSA), or general anesthesia. At our institution, PSA is the most commonly selected method owing to its safety, convenience, and ability to provide a comfortable procedural experience. To achieve safe and effective PSA, oral and maxillofacial surgeons commonly use a combination of intravenous medications including midazolam, fentanyl, propofol, and ketamine [3]. Medications are titrated to effect but generally reach a level of moderate to deep conscious sedation. During the provision of PSA, the patient's vital

signs are actively monitored and recorded in terms of heart rate, blood pressure, heart rhythm, oxygen saturation, and end tidal carbon dioxide. Supplemental oxygen at a low flow rate is also provided through a nasal canula. The exact sedation regimen is often a matter of surgeon preference with regards to the depth of desired sedation, medical comorbidities of the patient, medication availability, familiarity with medication, and consideration for post-operative recovery and analgesia. The surgeons are trained with respect to the pharmacology and administration of the sedative drugs, patient monitoring, management of airway emergencies, and advanced cardiac life support. The registered nurses or dental assistants, who are present in the operatory unit, are also trained in advanced cardiac life support and/or basic life support. Appropriate recovery room nurses continue to monitor patient vital signs and airway status during the post-operative period for at least 30 minutes prior to discharge.

1.3 Ketamine

Ketamine, an N-methyl-D-aspartate (NMDA)-receptor antagonist, is a drug of particular interest due to its dissociative anesthetic properties and wide-ranging physiological effects including cardio-respiratory stability. As an anesthetic agent, ketamine provides analgesia, transient amnesia, and sedation. Ketamine is commonly used for inducing general anesthesia, or even acting as the sole anesthetic agent for children undergoing minor procedures [4]. Ketamine has an onset time of 30 seconds through an intravenous route with an approximate duration of anesthetic effect that lasts 25 minutes. Its terminal elimination half-life is approximately 3 hours. The physiologic

benefits of using ketamine as a component of sedation include the drug having minimum effects on respiratory depression and the patient's own protective airway reflexes being preserved. Patients are also unlikely to experience a decreases in blood pressure as the drug stimulates the circulatory system. Although rare, side effects of the medication include agitation, confusion, headaches, hallucinations, fluctuations in heart rate and rhythm, and nausea/vomiting. These side effects are more common when used at dosages appropriate for general anaesthesia (greater than 1 mg/kg). However, at sub-anaesthetic dosages (0.1-0.5 mg/kg), these side effects are highly unlikely and transient at worst [5-7]. In fact, ketamine when used in conjunction with midazolam in PSA have further decreased side effects and a marked decrease in emergence delirium [8]. Beyond its utility as an anesthetic, other documented pharmacological uses include treating depression, alcohol addiction, heroin addiction, severe asthma, complex regional pain syndrome, and cancer pain [9]. An intriguing and debatable pharmacological effect of ketamine in the literature has been its ability to provide extended post-operative pain relief when given at sub-anesthetic dosages (at 0.1-0.5 mg/kg) [4, 9, 10]. At sub-anesthetic dosages, it is thought that ketamine provides anti-hyperalgesia, anti-allodynia, and "preventive analgesia" for patients having undergone surgery [9]. Among the surgery literature, the peri-operative administration of ketamine has demonstrated a post-operative analgesic phenomenon and this has been well reported in many studies involving cleft palate repair [11], tonsillectomies [12], spinal surgeries [13] [14], orthopedic surgery [15], thoracic surgery [16], and major abdominal surgeries [17]. In addition to reporting less post-operative pain, patients who received peri-operative ketamine often showed a reduction in the amount of post-operative opioids consumed. The latter finding would imply less risk towards undesirable side effects from post-operative analgesics such as

non-steroidal inflammatory agents (NSAIDs) or opioids. However, several studies found no effect of ketamine on post-operative analgesia when ketamine was given perioperatively in studies involving ophthalmological surgery [18], gynecological surgery [19], caesarean sections [20], or prostate surgery [21]. Therefore, whether sub-anesthetic ketamine truly has an effect on post-operative analgesia remains widely debated and leaves experts in anesthesia and pain medicine divided on the issue [5-7, 10].

1.4 The Role of Ketamine in Analgesia for Third Molar Surgery

In terms of third molar surgery, there have been several studies that examined the effects of pre-operative sub-anesthetic ketamine on post-operative analgesia. Of note, a number of studies have suggested a positive effect on post-operative pain relief [22-28] while one study suggested a lack of effect [29] following third molar surgery. Like other surgical studies involving ketamine and post-operative analgesia, there also appears to be conflicting evidence in the area of third molar surgery. Part of this may stem from studies employing different routes of ketamine administration ranging from topical application [22], injection into surgical sites [23, 26-28], oral route [25], or via intravenous route [24, 29]. Therefore, differences in routes of drug administration and dosing regimen (i.e. single, multiple, or infusion) may lead to alterations in the pharmacological action of ketamine at sub-anesthetic doses. Another limitation amongst studies published thus far is small sample sizes and thus a reduced external validity of results. As such, conclusions from multiple studies have called for trials involving a greater number of participants.

1.5 Study Purpose, Hypothesis and Aims

The purpose of this study is to determine whether a single pre-operative sub-anesthetic dose of intravenous ketamine can provide post-operative analgesia to patients undergoing third molar surgery. We hypothesize that ketamine administered at a sub-anesthetic intravenous dose would confer a post-operative analgesic benefit, as had been previously shown in the literature. We aim to demonstrate this by assessing visual analogue pain scores during the immediate post-operative period and tabulating post-operative analgesic consumption. These results will be further analyzed amongst variables including age, gender, and difficulty of surgery, with the hope of definitively characterizing the role of "pre-emptive analgesia" for ketamine in third molar surgery.

Chapter 2: Materials and Methods

2.1 Study Design

The study was a prospective, randomized, double-blinded clinical trial, designed by the investigators at the Department of Oral and Maxillofacial Surgery at Dalhousie University, Halifax, Nova Scotia. The study population was composed of patients presenting with impacted wisdom teeth for removal (see reasons for removal below under Study Sample) between July 2017 to June 2018. The treatment group consisted of patients receiving a single bolus (dose and timing) of IV ketamine as part of their procedural sedation anesthesia (in combination with midazolam and fentanyl). The control group received an IV bolus of 0.9% saline in place of IV ketamine. The study was reviewed and approved by the institutional ethics committee (Nova Scotia Health Authority Research Ethics Board) and all participants signed an informed consent agreement. The clinical trial was registered on www.isrctn.com on April 2017 (with study identifier ISRCTN13624724).

2.2 Study Sample

The study participants included adolescent and adult patients who were initially seen in our outpatient clinics for consultation regarding surgical extraction of third molars under procedural sedation anesthesia. The inclusion criteria for our study consisted of patients at ages 16 to 25 years old inclusive, American Society of Anesthesiologists (ASA) physical status class I or II health status, and presence of at least three third molars. The third molars were either impacted, and would not predictably erupt into function, and/or were associated with diseases such as caries or periodontal disease.

Patients were excluded from the study if they: were younger than 16 or older than 25 years of age, had fewer than three third molar teeth, were noted on clinical or radiographic exam to have pathology (i.e. cysts or tumors) associated with a third molar, were pregnant or lactating, had an ASA physical status of III or above, had a known allergy to any of the sedation agents, or were being treated with central nervous system depressants or chronic pain medications.

Participants were recruited into the study at the consultation appointments at our institution's outpatient clinic. The advertisement on www.isrctn.com also provided an additional source of patient recruitment. Each surgical consultation included a comprehensive medical history review, oral examination of the third molars in question, radiographic examination, and discussion of the nature, risks, and benefits of the procedure and accompanying anesthesia. Upon confirming the decision to proceed with surgery, potential participants were provided with details of this study and full verbal and written consent for participation was obtained at that time.

2.3 Variables and Outcome Measures

The primary outcome measure was post-operative pain intensity measured on a visual analogue scale (VAS) marked with intervals from 1 to 10, with extreme limits set at 1 being "no pain" and 10 being "worst pain imaginable". This would be assessed at 6-hour intervals within the initial 48-hour post-operative period. The secondary outcome measure included the total amount of post-operative analgesics (standardized as 600 mg Ibuprofen and/or 325 mg Acetaminophen + 30 mg Codeine) consumed within the immediate 48-hour post-operative period. Tertiary outcomes included time to first opioid dose, patient satisfaction, surgeon satisfaction, and procedure time. Additional variables

measured included patient age, gender, number and type of third molars removed, and surgeon's grading of procedural difficulty or extent of surgery (Table 1).

2.4 Study Randomization

Patients were randomly assigned to one of the two study groups by using a random number generator. The generated number was placed inside a sealed envelope by one of the study investigators and then given to a pre-operative registered nurse who was not involved in the study. After the nurse completed their pre-operative assessment, the nurse would open the sealed envelope and reveal to the surgeon which treatment group the patient belonged to. The surgeon was then provided with either a labelled 5 ml syringe containing 2 ml of 1% ketamine or a labelled 5 ml syringe containing 2 ml of 0.9% normal saline. Both solutions appeared identical in terms of fluid appearance, colour, and clarity. Due to ethical and safety reasons, the surgeons were unable to inject unlabelled medications. However, the patient, accompanying friends or family members, and the study investigator were unaware of the treatment group assignments. Therefore, the study was double-blinded. The pre-operative nurse kept a master list of patient assignments that was not revealed to the investigators until the conclusion of the study.

2.5 Surgery and Procedural Sedation Anesthesia

A total of 4 staff oral and maxillofacial surgeons performed the third molar surgery and provided the procedural sedation anesthesia for this study. All participants received a dose of 600 mg ibuprofen and 2 grams of amoxicillin pre-operatively. Clindamycin, 600 mg, was provided to those with reported penicillin allergies. Intravenous access was established in all patients and a Ringer's Lactate infusion was

established. All patients were provided with supplemental oxygen via nasal cannula at 2-3L/min. Vital signs, including blood pressure, heart rate, oxygen saturation, and end tidal CO_2 were recorded during each procedural sedation. Sedation medications consisted of a combination of midazolam, fentanyl and either ketamine or placebo depending on which study cohort the patient had been randomly assigned to. In all cases, the desired sedation effect was targeted to a Ramsay sedation scale score of -2 to -3. Midazolam (in the form of a 5 mg/mL solution) was administered via IV access at 0.05-0.1 mg/kg was titrated to the desired effect with a maximum dose of 10 mg. Fentanyl (in the form of a 50 mcg/ml solution) was administered via IV access at 0.5-2 mcg/kg and titrated to the desired effect with a maximum dose of 100 mcg. For the experimental group, ketamine at a sub-anesthetic dosage of 0.1-0.5 mg/kg, to a maximum of 20 mg, was given via IV access 30 – 60 seconds prior to administration of local anaesthetic. The dosing range of ketamine chosen allowed surgeons the liberty of providing a single weight-appropriate dose at a sub-anesthetic level without the worry of providing a single fixed dose to all participants, which may risk over-sedation. Alternatively, 0.9% normal saline was given via IV access instead to placebo patients. Up to 5 ml of 2% lidocaine with 1:100000 epinephrine was provided as local anaesthetic per wisdom tooth via nerve blocks and infiltration. Additional local anaesthetic was provided if the patient demonstrated pain up to a maximum dose of 7mg/kg. After the onset of the desired sedation, 10 mg of dexamethasone was also given intravenously. A trained dental assistant, who was not involved in the study, acted as the surgical assistant. The total surgery time, from initial incision to final suture, was recorded for each case. Third molars were removed using a combination of elevators, forceps, and surgical handpieces as needed. Soft tissue flaps and bone removal was performed as needed. The amount of IV fluids infused, the doses

and timing of medication administered, were recorded by the surgeon. At the end of the procedure, the surgeons completed their post-operative survey to document the difficulty of each tooth extracted, and their overall satisfaction with the case with consideration for sedation quality and ease of the overall procedure. Patient's vital signs (blood pressure, heart rate, and oxygen saturation) were regularly measured in the post-operative recovery area for at least 30 minutes. When deemed stable, patients were discharged home with appropriate accompaniment.

2.6 Data Collection

Immediately after surgery, each surgeon completed a post-operative survey which rated their overall satisfaction with the case which took into consideration both the surgical procedure experience as well as the adequacy of the procedural sedation. This was ranked on a scale of 1 to 4 with 1 being "not satisfied" and 4 being "very satisfied". Surgeons also graded each wisdom tooth removed in terms of extraction difficulty: this allowed for a subjective clinical measure of the actual difficulty of the surgery rather than relying on the clinical and radiographic predictors of the case, which are sometimes not truly reflective. Each tooth extraction was graded by the surgeon as follows: "no incision", "incision", "incision plus bone removal", and "incision plus bone removal and tooth sectioning". A patient case would be considered "difficult" if soft tissue incision and bone removal had been required for extraction of at least two teeth. The distribution of tooth extraction difficulty is detailed in Table 1.

All participants were provided with a standardized medication package upon discharge. This package consisted of 30 tablets of ibuprofen 600 mg (to be taken every 6

hours as needed for pain), 10 tablets of acetaminophen 325 mg + codeine 30 mg (to be taken every 4-6 hours for breakthrough pain relief), and a bottle of 0.12% chlorhexidine oral rinse (to be used as instructed every 12 hours for two weeks post-operatively). All participants were also given a post-operative questionnaire containing the pain intensity VAS scales to be assessed at 6-hour intervals for the first 48 hours. Patients were also requested to record their medication consumption dosage and timing on the questionnaire. Pain was first assessed at the 6-hour mark to ensure that the effect of local anesthesia was no longer a confounding variable in the patient's subjective assessment of their pain. After 48 hours, patients were asked to rank their satisfaction with the entire experience with consideration for the anesthesia, surgical experience, and recovery on a single 10-point VAS. Participants were asked to mail back the survey using a self-addressed envelope provided with the survey. Phone calls to the participants were made at 24 hours and again at 48 hours post-op to check on their status and to remind them of completing and mailing in their post-operative questionnaire.

2.7 Data Analysis

The sample size estimation for this study was performed by considering detection of medium effect size, setting α to 0.05, power of 80%, and a standard deviation of 2 on the VAS scale. According to Cohen et al. (1992) and in consultation with a biomedical statistician, sample size estimation under these parameters yielded at least 128 participants to detect a statistically significant difference [30].

Descriptive statistics for categorical variables (sex and extent of surgery) were reported as numbers and percentages. Continuous variables (age and patient satisfaction)

were reported as medians with interquartile range (IQR). Cramer's V test was employed to measure the strength of the association between categorical variables. Pearson chi-square (χ^2) was used to test whether there was an association between the nominal variables. A Kruskal-Wallis test—with a null hypothesis that the observations per treatment group came from the same population with the equal median—was used to determine whether the samples were from different populations: the Kruskal Wallis test was used to compare continuous and categorical variables[31].

Multivariate analysis of variance (MANOVA) was performed to determine the effect of treatment on VAS scores, using Wilks' lambda (λ) as the omnibus test statistic. A one-way MANOVA was performed with only treatment group indicator as the predictor; a two-way MANOVA with treatment group and the extent of surgery; and an N-way MANOVA with sex and age as additional predictors. Data on the extent of surgery per tooth (tooth: 1.8, 2.8, 3.8 and 4.8) were collected on a scale that ranged from one (no incision) to four (incision plus bone removal and tooth sectioning). A binary variable was created for the extent of surgery that equals one if the rating on any of the tooth was less than or equal to two, and zero otherwise. Also, the age variable was binary: equals one if age was less than or equal to 18, and zero otherwise (18 was the average age). Box's M test, a likelihood ratio statistic, was used to test the equality of covariance matrices for the two groups.

A generalized estimating equation (GEE) population-averaged model with an identity link, Gaussian family, and an exchangeable correlation was used to analyze the effect of treatment group on the outcome [32], utilizing the longitudinal nature of the data. The study variables included in the model include the extent of surgery, sex, age, the interaction between treatment group indicator and the extent of surgery, and seven-time

dummy variables to capture any potential temporal (time) effects. Also, a mixed-effects and a random-effects generalized least squares regression models were also estimated as part of sensitivity analysis. Covariates were deemed statistically significant if $p < 0.05$. In a further sensitivity analysis, the analyses were repeated using data from a multivariate imputation by chained equations (MICE) procedure to account for missing data [33].

For the analysis and comparison of post-operative medication usage between groups, the D'Agostino-Pearson omnibus test was used to evaluate the normality of the data. In instances where data assumed Gaussian distribution, the unpaired Student's T-test was used to detect any statistically significant differences. In cases of data that are not normally distributed, the Mann-Whitney *U* test was used to compare groups for the same purpose. The relative risks of opioid and non-opioid pain medication use after surgery between the two treatment groups was estimated using a generalized linear model with a binomial family and a log link function. Three binary variables were created: individuals who had any pain medication within the first 24 hours post-surgery get a value of one and zero otherwise. A similar approach was adopted for 48 hours, and overall.

All statistical analyses were performed using Stata (version 15.1) software (StataCorp. 2017) and GraphPad Prism version 7.04 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com. Graphical illustration was performed using the latter software.

Chapter 3: Results

3.1 Patient Characteristics

A total of 148 patients were initially recruited into the study. Twelve patients were lost to follow-up or did not return their post-operative pain questionnaires. Two additional patients were disqualified from the study since an intra-operative decision was made to only remove two wisdom teeth. This resulted in 134 total participants as the final study sample, of which 74 (55.2%) participants were randomly enrolled into the ketamine group while 60 (44.8%) participants were randomly assigned into the placebo group. The overall participant retention was 90.5%. Table 1 shows the summary and descriptive statistics of the study variables and against the primary predictor variable. The table shows the frequencies, the results of Cramer's V, Kruskal-Wallis, and the Pearson chi-square tests. Overall, there were no statistically significant associations (p values > 0.05).

Out of the ketamine group, 41 (55.4%) participants were females and 33 (44.6%) participants were males. From the placebo group, 38 (63.3%) participants were females and 22 (36.7%) participants were males. There were no differences in age (p-value =0.62) or gender (p-value =0.35) amongst both groups (Table 1). For the post-operative survey of surgeons, there was a 100% (74/74) survey completion rate for the ketamine group and a 96.6% (58/60) survey completion rate for the placebo group. The ketamine group displayed a tendency for a greater number of difficult surgeries requiring "incision + bone removal ± tooth sectioning" but this difference did not reach statistical significance (p-value =0.07). There was also no statistical difference (p-value =0.35) in patient satisfaction, which took into account the surgical experience, anesthesia experience, and

post-operative recovery period for the first 48 hours. The median VAS score was 8 for both groups, with IQR of 7-10 and 7-9 for ketamine and placebo, respectively.

Table 1. Study Variables versus Predictor Variables

Variable	Ketamine	Placebo	Test statistic	P-value
Sample size, n (%)	74 (55.2%)	60 (44.8%)		
Sex, n (%)			-0.08‡	0.35ǀ
Female	41 (55.4%)	38 (63.3%)		
Male	33 (44.6%)	22 (36.7%)		
Age, median (IQR),	17 (17 – 19)	18 (16 – 20)	0.25†	0.62†
Patient satisfaction, median (IQR),	8 (7 – 10)	8 (7 – 9)	0.89†	0.35†
Extent of surgery scale, n (%)				
Tooth: 1.8			0.18‡	0.14ǀ
No incision	13 (18.6%)	12 (20.7%)		
Incision	42 (60%)	41 (70.7%)		
Incision plus bone removal	15 (21.4%)	5 (8.6%)		
Incision plus bone removal and tooth sectioning	-	-		
Tooth: 2.8			0.12‡	0.42ǀ
No incision	14 (19.72%)	11 (19.0%)		
Incision	44 (62.0%)	41 (70.7%)		
Incision plus bone removal	13 (18.3%)	6 (10.3%)		
Incision plus bone removal and tooth sectioning	-	-		
Tooth: 3.8			0.18‡	0.23ǀ
No incision	1 (1.4%)	2 (3.5%)		
Incision	18 (25.0%)	19 (33.3%)		
Incision plus bone removal	11 (15.3%	3 (5.3%)		
Incision plus bone removal and tooth sectioning	42 (58.3%)	33 (57.9%)		
Tooth: 4.8			0.14‡	0.44ǀ
No incision	1 (1.4%)	2 (3.5%)		
Incision	16 (21.9%)	15 (26.3%)		
Incision plus bone removal	11 (15.1%)	4 (7.0%)		
Incision with bone removal and tooth sectioning	45 (61.6%)	36 (63.2%)		

Table 1. Study Variables versus Predictor Variables (*Continued*)

Variable	Ketamine	Placebo	Test statistic	P-value
Extent of surgery, overall, n (%)			-0.15‡	0.07ʃ
Simple (± incision)	20 (27%)	25 (41.7%)		
Difficult (incision + bone removal ± tooth sectioning)	54 (73%)	35 (58.3%)		

‡ Cramer's V test: equals 0 when there is no relationship between the two variables; † Kruskal-Wallis test; ʃ Pearson χ^2 test.

3.2 Primary Outcome: Post-operative Pain

The average dose of ketamine received by each participant in the ketamine group was 0.18 (± 0.06) mg/kg. This was selected by the surgeons from a range of 0.1-0.5 mg/kg which is known to be the analgesic range of ketamine.

The post-operative VAS score (outcome variable) were initially analyzed against the study variables (sex and extent of surgery), irrespective of patient group assignment. The median VAS scores for females for 30, 42 and 48 hours after surgery were statistically significantly different from those of men (p-value <= 0.05), based on a Kruskal-Wallis test. Patients with "difficult" operations (incision plus bone removal ± tooth sectioning) had statistically significant higher median VAS scores at 12, 30, and 48 hours post-surgery compared to those who had simple surgeries (Table 2).

Table 2. Study Variables versus Primary Outcome Variable

VAS score (hrs)	Sex				Extent of surgery			
	Female, Median (IQR)	Male Median (IQR)	Test Statistic†	P-value†	Simple,§ Median (IQR)	Difficult,§ Median (IQR)	Test Statistic†	P-value†
6	3 (1 – 5) N = 78	3 (1 – 5) N = 54	0.17	0.68	3 (1 – 5) N = 45	3 (1 – 5) N = 87	0.003	0.95
12	3 (1 – 5) N = 62	3 (2 – 4) N = 44	0.52	0.47	2 (1 – 4) N = 36	3 (2 – 5) N = 70	3.70	0.05
18	3 (1 – 5) N = 65	3 (1.5 – 4.5) N = 44	0.07	0.80	2 (1 – 4) N = 37	3 (2 – 5) N = 72	1.71	0.19
24	3 (1 – 5) N = 78	2 (1 – 4) N = 55	1.82	0.18	2 (1 – 4) N = 45	3 (1.5 – 4) N = 88	1.38	0.24
30	3 (1 – 5) N = 79	2 (1 – 3) N = 54	3.76	0.05	2 (1 – 3) N = 45	3 (2 – 5) N = 88	7.22	0.01
36	4 (1 – 6) N = 63	2 (1 – 4) N = 44	2.20	0.14	2 (1 – 4) N = 34	3 (1 – 6) N = 73	2.55	0.11
42	4 (2 – 6) N = 69	2 (1 – 4) N = 44	4.50	0.03	2 (1 – 5) N = 38	4 (2 – 5) N = 78	2.56	0.11
48	3 (2 – 5) N = 76	2 (1 – 4) N = 55	4.08	0.04	3 (1 – 3) N = 45	3 (2 – 5) N = 86	3.68	0.05

† Kruskal-Wallis test

§ Simple (± incision)

§ Difficult (incision + bone removal ± tooth sectioning in at least two out of four extractions)

In terms of the association between post-operative VAS scores and treatment groups, there was a statistically significant difference in median VAS score at 6 hours post-surgery (p-value = 0.03) (Table 3). There were no other statistical differences in post-operative pain intensity at any other time interval over 48 hours. Table 4 reports the results of the MANOVA. The estimated Wilks' lambda (λ) associated with the one-way MANOVA was 0.85, F (8, 65) = 1.46, p-value =0.18; there was no statistically significant difference between the treatment groups on the combined VAS scores. Adding the extent of surgery as an additional predictor did not change the conclusion (λ = 0.85, F (8, 64) = 1.43, p-value = 0.20). The further addition of sex and age also did not change the conclusions (λ = 0.85, F (8, 62) = 1.35, p-value = 0.24).

Table 3. Association Between VAS Score and Predictor Variables

VAS score	Ketamine, Median (IQR)	Placebo, Median (IQR)	Test Statistic[†]	P-value
6 hours	4 (2 – 5) N = 73	2 (1 – 4) N = 59	4.85	0.03
12 hours	3 (2 – 5) N = 62	3 (1 – 4) N = 44	0.58	0.45
18 hours	3 (1.5 – 5) N = 60	3 (1 – 4) N = 49	1.07	0.30
24 hours	3 (1 – 4) N = 74	2 (1 – 4) N = 59	0.12	0.73
30 hours	3 (1 – 4) N = 74	2 (1 – 4) N = 59	0.15	0.70
36 hours	2.5 (1 – 6) N = 62	3 (1 – 5) N = 45	0.11	0.74
42 hours	3 (1 – 5) N = 65	3 (2 – 5) N = 51	0.01	0.94
48 hours	3 (1 – 5) N = 73	3 (2 – 4) N = 58	0.34	0.56

[†] Kruskal-Wallis test

Table 4. Multivariate Analysis of Variance (MANOVA)

Variable	Wilk's lamda (λ)	F	P-value
Case 1: One-way MANOVA			
Treatment group (Ketamine = 1)	0.85	1.46	0.18
Case 2: Two-way MANOVA			
Overall	0.67	1.78	0.04
Treatment group (Ketamine = 1)	0.85	1.43	0.20
Extent of surgery (Simple = 1)[§]	0.78	2.09	0.05
Case 3: N-way MANOVA			
Overall	0.41	1.96	< 0.00
Treatment group (Ketamine = 1)	0.85	1.35	0.24
Extent of surgery (Simple = 1)[§]	0.79	2.08	0.05
Sex (Female = 1)	0.68	3.64	< 0.00
Age (<= 18 = 1, 0 otherwise)	0.90	0.88	0.54
Test of equality of covariance matrices across the two samples:			
Modified likelihood ratio χ^2	= 41.54		
Box F(36,11115.3)	= 1.00	P-value = 0.46	
Box $\chi^2_{(36)}$	= 36.27	P-value = 0.46	

[§] Simple (± incision): Difficult (incision + bone removal ± tooth sectioning in at least two out of four extractions)

Table 5 reports the results of the regression analysis using longitudinal data models. In all three models, the treatment effect was not statistically different from zero (p-value > 0.05). Additional sensitivity analysis based on the imputed data (not reported) did not yield different results. These results were consistent with the results from the MANOVA.

Table 5. Regression Results Based on Longitudinal Data Models

Variable	Random-effects GLS model[1]		Mixed-effects model[2]		Generalized estimation equation model[3]	
	Coefficient, (95% CI)	P-value	Coefficient, (95% CI)	P-value	Coefficient, (95% CI)	P-value
Treatment (Ketamine = 1)	0.20 (-0.60 to 1.00)	0.63	0.20 (-0.58 to 0.98)	0.61	0.20 (-0.59 to 0.99)	0.62
Extent of surgery (Simple = 1) [§]	-0.33 (-1.29 to 0.64)	0.51	-0.32 (-1.27 to 0.62)	0.49	-0.33 (-1.21 to 0.55)	0.47
Sex (Female = 1)	0.40 (-0.25 to 1.05)	0.23	0.40 (-0.24 to 1.03)	0.21	0.40 (-0.20 to 1.00)	0.20
Age (<= 18 = 1, 0 otherwise)	0.37 (-0.30 to 1.05)	0.28	0.37 (-0.29 to 1.04)	0.26	0.37 (-0.26 to 1.01)	0.25
Treatment & extent of surgery	-0.51 (-1.88 to 0.86)	0.46	-0.51 (-1.27 to 0.62)	0.45	-0.51 (-1.76 to 0.74)	0.42
Intercept	2.77 (1.88 to 3.65)	0.01	2.77 (1.91 to 3.63)	< 0.00	2.77 (2.00 to 3.52)	< 0.00
Time controls[¥]	Yes		Yes		Yes	

[§] Simple (± incision): Difficult (incision + bone removal ± tooth sectioning in at least two out of four extractions)
[1] Random-effects generalized least square regression
[2] Mixed-effects maximum likelihood regression
[3] Generalized estimation equation population-averaged model with identity link, Gaussian family with an exchangeable correlation
[¥] We included seven time dummy variables in the model to account for any potential temporal effects (6 hours = base).

3.3 Secondary Outcome: Post-operative Medication Usage

Both groups did not show a statistical difference (p-value =0.78) in the number of ibuprofen 600 mg tablets consumed over a 48-hour post-operative period with both groups showing a median of 7 tablets (IQR 6-8) (Figure 1a). When considering "difficult" cases only, there was still no statistical difference between both groups (p-value =0.49) in terms of tablets of ibuprofen consumed after 48 hours (Figure 1b). Neither group displayed a difference in the number of acetaminophen/codeine combination tablets consumed over a 24-hour (P=0.48) or 48-hour post-operative period (p-value =0.97) (Figure 2). At 24 hours post-operatively, the placebo and ketamine groups both consumed a mean of 1.3 and 1.4 tablets of the breakthrough acetaminophen/codeine combination analgesic respectively (Figure 2a). At 48 hours post-operatively, placebo and ketamine groups consumed a mean of 2.5 and 2.6 tablets (Figure 2b), respectively. Similarly, when examining "difficult" cases only, there was again no statistical difference at 24 hours (p-value =0.48) or 48 hours (p-value =0.93) post-operatively for the mean number of acetaminophen/codeine tablets consumed (Figure 3). Lastly, we examined the elapsed time since surgery until the first dose of acetaminophen/ codeine combination tablet was taken and found no statistical differences among all data (p-value =0.35) or when only "difficult" cases were analyzed (p-value =0.76) (Figure 4).

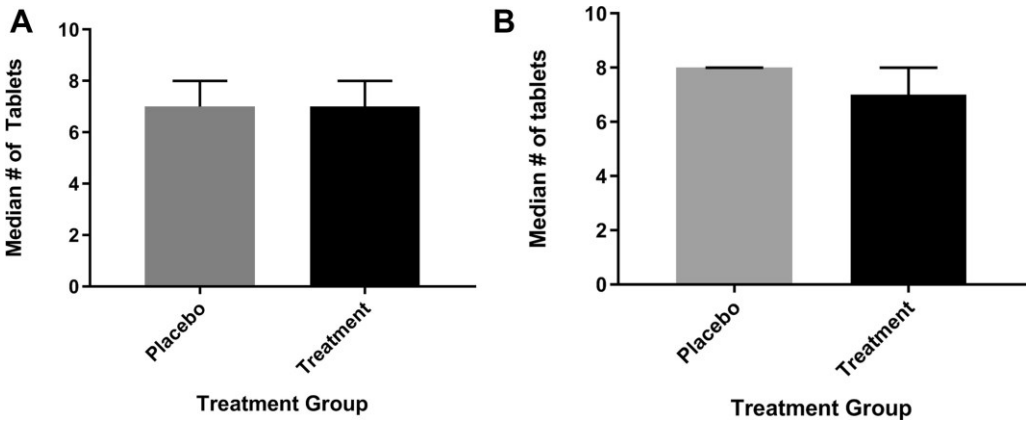


Figure 1. Post-operative consumption of ibuprofen over 48 hours among all cases (**A**) and in "difficult" cases only (**B**). Error bars represent median, interquartile range.

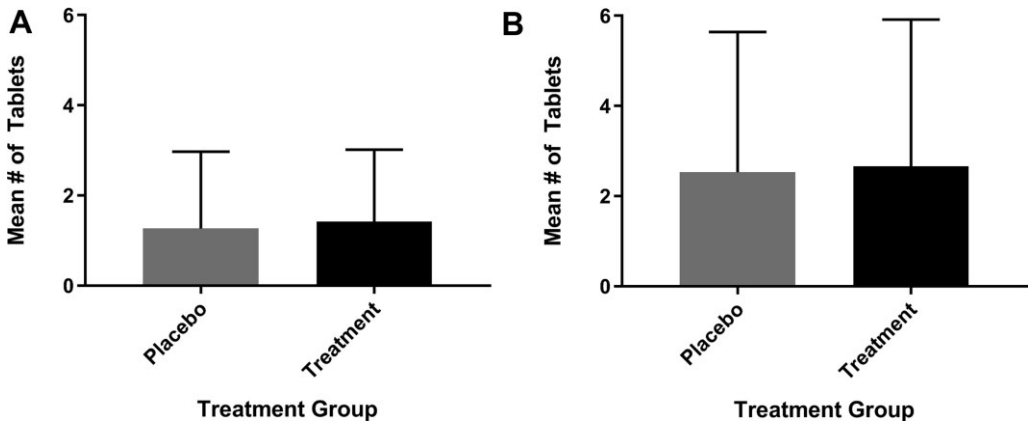


Figure 2. Post-operative consumption of acetaminophen/codeine combination tablets among all cases over 24 (**A**) and 48 hours (**B**). Error bars represent the standard deviation from the mean.

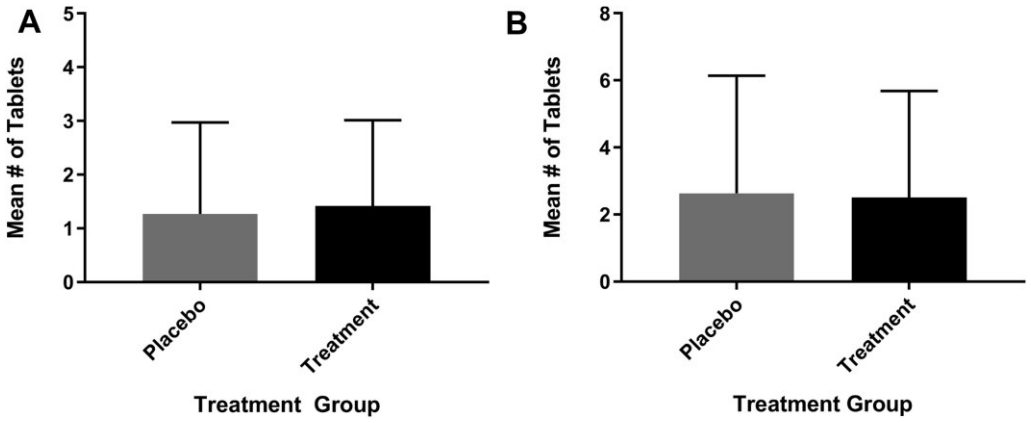


Figure 3. Post-operative consumption of acetaminophen/codeine combination tablets over 24 hours **(A)** and 48 hours **(B)** in "difficult" cases only. Error bars represent the standard deviation from the mean.

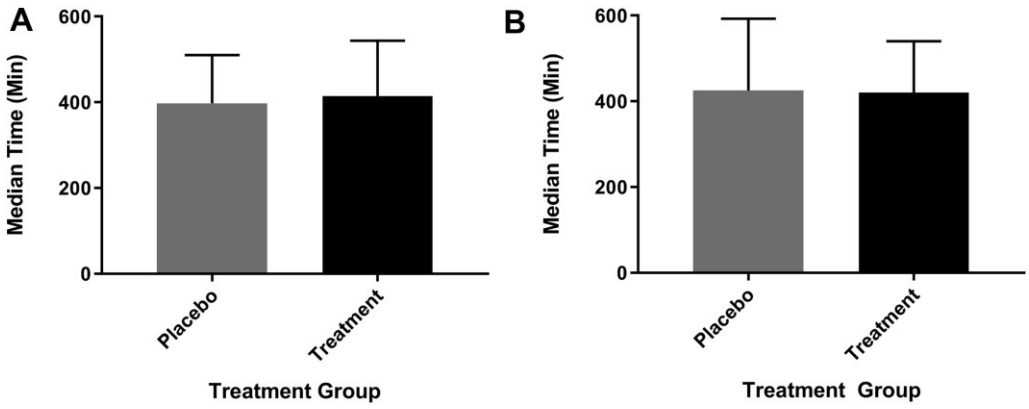


Figure 4. Elapsed post-operative time until first dose of acetaminophen + codeine combination tablets consumed (**A**) and among "difficult" cases only (**B**). Error bars represent median, interquartile range.

Table 6 reports the relative risks of any opioid and non-opioid medication use, estimated using generalized linear models with a binomial family and a log link function, controlling for the extent of surgery, sex, age, and the interaction between the extent of surgery and treatment group. In all three cases (24 hours, 48 hours, and overall), there were no statistically significant differences in relative risks (p-values > 0.05) for use of any type of pain medication when comparing the ketamine group to the placebo group.

Table 6. Relative Risk of Pain Medication Use: Ketamine Group versus Placebo Group

Variable	Relative risk, (95% CI)	P-value
Pain medication use at 24 hours	1.27 (0.85 to 1.89)	0.25
Pain medication use at 48 hours	0.99 (0.73 to 1.36)	0.98
Overall: Pain medication use at any time during the 48 hours	1.23 (0.81 to 1.85)	0.33

Relative risks estimated using generalized linear models with a binomial family and a log link function, controlling for the extent of surgery, sex, age, and the interaction between extent of surgery and treatment group

3.4 Other Outcomes

There was no statistical difference in the mean operating time (p-value =0.899) between both groups with the mean duration of the surgery being 15.92 (±7.1) minutes for the ketamine group and 16.08 (±7.7) minutes for the control group. In terms of the surgeon's satisfaction of the case, which took into account both the surgery and the procedural sedation anesthesia, there was no statistical difference (p-value =0.951) detected between both groups as the mean satisfaction scores were 1.42 for both groups (Figure 5a).

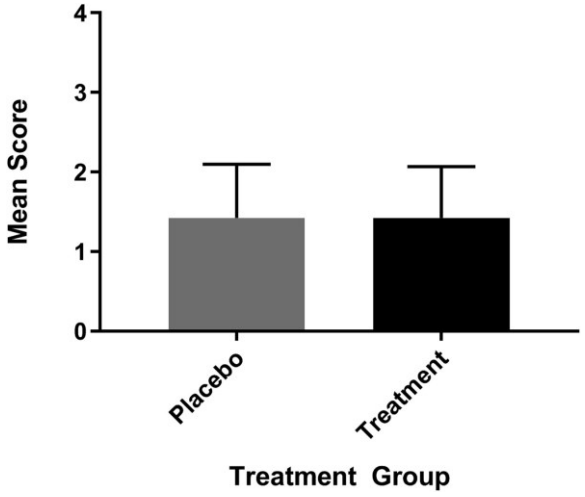


Figure 5. Overall surgeon satisfaction in regard to surgical experience, anesthesia experience, and overall ease of procedure. Surgeon's satisfaction on a scale of 1 to 4 with 1 being "very satisfied" and 4 being "very unsatisfied". Error bars represent the standard deviation from the mean.

3.5 Adverse Events

There were no adverse events reported in either treatment group during the first 48-hour post-operative. No patients required an emergency follow-up visit, experienced excessive bleeding, or infection during the study's timeframe. There were also no incidences of prolonged sedation or episodes of hallucinations or emergence delirium during the study. Reversal agents for sedation were never required.

Chapter 4: Discussion

4.1 Post-operative Pain Intensity and Medication Consumption

This study was undertaken to assess if a single pre-operative intravenous dose of ketamine can provide decreased post-operative pain following third molar surgery with procedural sedation. We hypothesized that the provision of ketamine in this manner would reduce post-operative pain, and in effect reduce the consumption of post-operative non-opioid and opioid analgesics. To assess this, study participants recorded their pain intensities over a 48-hour period as well as their use of standardized analgesic medications through a post-operative questionnaire. In the present study, we did not detect any improvement in post-operative pain when ketamine was used pre-operatively as part of the sedation regiment. However, at 6 hours post-operatively, we did detect a small yet statistically significant difference in which the ketamine group reported experiencing more pain than the placebo group (Table 3). This was certainly an unexpected finding given the reported analgesic effects of ketamine in the literature, and the true clinical significance of such a small difference (VAS of 2 versus 4) remains unknown. There may still be little impact on the post-operative recovery period when the reported pain intensities are in the 2-4 range within a 10-point VAS scale. A further explanation of this unexpected finding is that there were a greater proportion of more difficult extractions in the ketamine group compared to the placebo group. In addition, there was also a higher proportion of female participants in the ketamine group, and as demonstrated by the MANOVA, the variables of gender and extent of surgery each have statistically significant effects on the outcome variable whether alone, or together (Table 4). Therefore, it is at least reasonable to expect that extracted teeth that required more

extensive surgery will likely produce more discomfort in the immediate post-operative period. Furthermore, we were unable to detect a difference in the amount of post-operative opioid and non-opioid analgesic consumption between both groups. Overall, there were no differences in the key outcomes between both groups.

4.2 Minor Outcome Variables

Pre-operative classification of third molars according to radiographic evidence alone may not accurately correlate with the clinical difficulty of the surgery or the patient's post-operative course. Therefore, we employed an approach in which the surgeon's classified the individual difficulty of each tooth extracted and this information helped formulate the overall surgical difficulty of each participant. As such, post-operative pain reported in previous studies could be potentially influenced by the extent of surgical involvement (regardless of exposure to sub-anesthetic ketamine or not) but had not been characterized. Alternatively, it may also be beneficial to use an integrated approach in which the extent of surgical difficulty and an established radiographical standard (such as the Pell-Gregory classification) to be used in conjunction. In the present study, the extent of surgery did not influence the key outcomes, but participants who endured more extensive surgery (regardless of treatment group) demonstrated increased pain in the immediate post-operative period (at 12 hours) and during the peak inflammatory period (30 and 48 hours) (Table 2). There was also no difference between both groups for the "time to first dose" of acetaminophen/codeine combination tablets, since an earlier time would have been an indication of a more rapid onset of pain, or increased intensity of pain in the early post-operative period. On a rather interesting note, despite providing our participants with 10 acetaminophen/codeine combination tablets as

part of their standardized post-operative analgesic package, the mean number of tablets consumed after 48 hours post-operatively was only 2.6 tablets. This may suggest that in terms of prescription analgesics, adequate pain control following third molar surgery can be mostly achieved with ibuprofen and only a few tablets of opioid-containing medications for immediate post-operative breakthrough pain. There was also no difference in terms of patient or surgeon satisfaction between both groups in regard to the anesthesia, surgical experience, and/or recovery.

4.3 The Relationship of This Study to Central Sensitization

Central sensitization arises from surgical tissue trauma and inflammation with activation of peripheral nocireceptors and subsequent transmission of pain signals toward the dorsal horn of the spinal cord where methyl-D-aspartate (NMDA) receptors are located. Initially, the NMDA receptors are normally occupied by magnesium but repetitive nociceptive afferent stimulation from the periphery (or surgical site) will cause membrane depolarization to displace this magnesium inhibition from the NMDA receptor. This allows for the excitatory neurotransmitter glutamate to bind to the NMDA receptor with subsequent transmission of pain signals to the brain [34]. Therefore, repeated stimulation of the wound leads to a state of hyperalgesia or reduced pain sensitivity threshold (or otherwise known as the "wind-up" phenomenon) as facilitated by the NMDA receptors. Overall, central sensitization initiates a state of increased sensitivity to painful stimuli with implications for chronic pain symptoms from surgical sites [34, 35]. As such, this hyperalgesic effect can be a cause of increased post-surgical discomfort for patients. Therefore, it is with hopes that an NMDA receptor antagonist such as ketamine would inhibit or suppress the activation of central sensitization, and by

extension provide more post-operative pain relief and a reduction in analgesic consumption [36]. Indeed, several studies have already shown a post-operative analgesic effect for ketamine when the medication itself was mixed into local anaesthetic prior to injection as infiltration or provision of nerve blocks [23, 26-28]. The oral route [25] and topical application of ketamine into the extraction socket [22] also showed positive effects on analgesia versus control groups. Only two studies have examined the effect of pre-operative IV ketamine on post-operative analgesia following third molar surgery and that both studies have shown conflicting results with each other [24, 29]. While Garip et al. (2011) showed a post-operative analgesic effect of IV ketamine when given pre-operatively, Lebrun et al. (2005) did not reach the same findings. However, there may be an explanation as to why the present study and Lebrun et al. (2005) did not observe any post-operative analgesic effects of IV ketamine. As mentioned previously, noxious peripheral surgical stimuli can lead to central sensitization via activation of NMDA receptors. However, if there is already abundance of peri-operative analgesia then NMDA receptor activation may be suppressed, and as such the opportunity for central sensitization to occur becomes attenuated. The current study utilized a pre-operative dose of ibuprofen, lidocaine for local anaesthesia as well as fentanyl for intra-operative analgesia. Additionally, dexamethasone was also provided pre-operatively, which may further aid in reducing any pain as well as post-operative swelling. This analgesia regimen may be enough to blunt NMDA receptor activation and central sensitization, which would render ketamine as non-effective for pain management amongst patients in the current study. Therefore, the presence of sufficient peri-operative analgesia can lead to a Type II statistical error in studies that are examining for post-operative analgesic effects of ketamine. Certainly, a commonality between the present study and Lebrun et al.

(2005) include intra-operative opioid administration of fentanyl and alfentanil, respectively, whereas neither medications were used by Garip et al. (2011).

4.4 Study Limitations

The present study has several limitations. The first is the potential of bias in recall, which is an inherent risk with the use of take-home questionnaires, VAS scales, and medication diaries. A second limitation of the study is that the strict age range (16-25 years of age) for inclusion may mean that extrapolation of the results to other age groups is not possible. The same concept applies to patients with other medical comorbidities beyond ASA class I or II, which is a third limitation to the study. The fourth limitation was the absence of a pre-operative pain assessment in relation to any of the third molars prior to their removal. Pre-existing pain or discomfort may have potentially influenced post-operative VAS scores or analgesic consumption. Lastly, our average dose of ketamine was 0.18 (± 0.06) mg/kg, but this still falls within the acceptable sub-anesthetic and analgesic dosage of ketamine ranging from 0.1-0.5 mg/kg [4, 9, 10]. However, one can suggest that perhaps this cumulative average dose can be too low to detect a post-operative analgesic effect. This may be especially true when 10-50% of ketamine is bound to plasma proteins in the circulation, and therefore the bioavailability may be limited [37]. Although having a single fixed and higher dosage of ketamine among all participants may allow for a more equal (and perhaps more detectable) comparison of outcomes, there is always the risk of subjecting participants to deeper levels of anaesthesia than appropriately desired.

Chapter 5: Conclusion

Under the present study conditions, I was unable to demonstrate that a sub-anesthetic pre-operative dose of intravenous ketamine can convincingly provide post-operative analgesia following the surgical removal of third molars. There was also no measurable impact on the reduction of post-operative analgesic consumption. A pre-operative dose of intravenous ketamine was unable to confer pre-emptive analgesia for the participants in this study. Future studies can directly compare different routes of ketamine administration (and/or different dosing regimens) to examine their effects on post-operative analgesia following third molar surgeries. Despite the findings in this study, ketamine remains a valuable medication for oral and maxillofacial surgeons to achieve excellence in anesthesia, comfort, and safety for their patients undergoing procedures in an ambulatory setting.

Note on contribution to manuscript: Most of this thesis is based on a recent manuscript published in the Journal of Oral & Maxillofacial Surgery. The publication status is In Press at the time of the thesis defense. I was involved in the ethics application, study design, enrollment of patients, conducting the clinical trial, collecting the data, performing the statistical analyses, and writing of the manuscript:

Cheung J, Alashi A, Koto P, Brady J, Davis B, Does sub-anesthetic ketamine provide post-operative analgesia for third molar surgery?, Journal of Oral and Maxillofacial Surgery (2019), doi:https://doi.org/10.1016/j.joms.2019.05.009

Appendix 1: Surgeon Post-operative Survey

Date of Surgery: _____ Patient #:_____
Age: _____
Sex: M/F

Extent of Surgery Scale:

1 = Simple (No Incision)
2 = Simple (With Incision)
3 = Incision + Bone Removal
4 = Incision + Bone Removal + Tooth Sectioning

Please rate the extent surgery per tooth:
(Consider also difficulty of removal, duration of surgery, and patient cooperation)

Tooth: 1.8 = _____
2.8 = _____
3.8 = _____
4.8 = _____

Surgery Start Time: _____
Surgery End Time: _____

Remarks:

_____
_____
_____
_____
_____

Surgeon Level of Satisfaction:

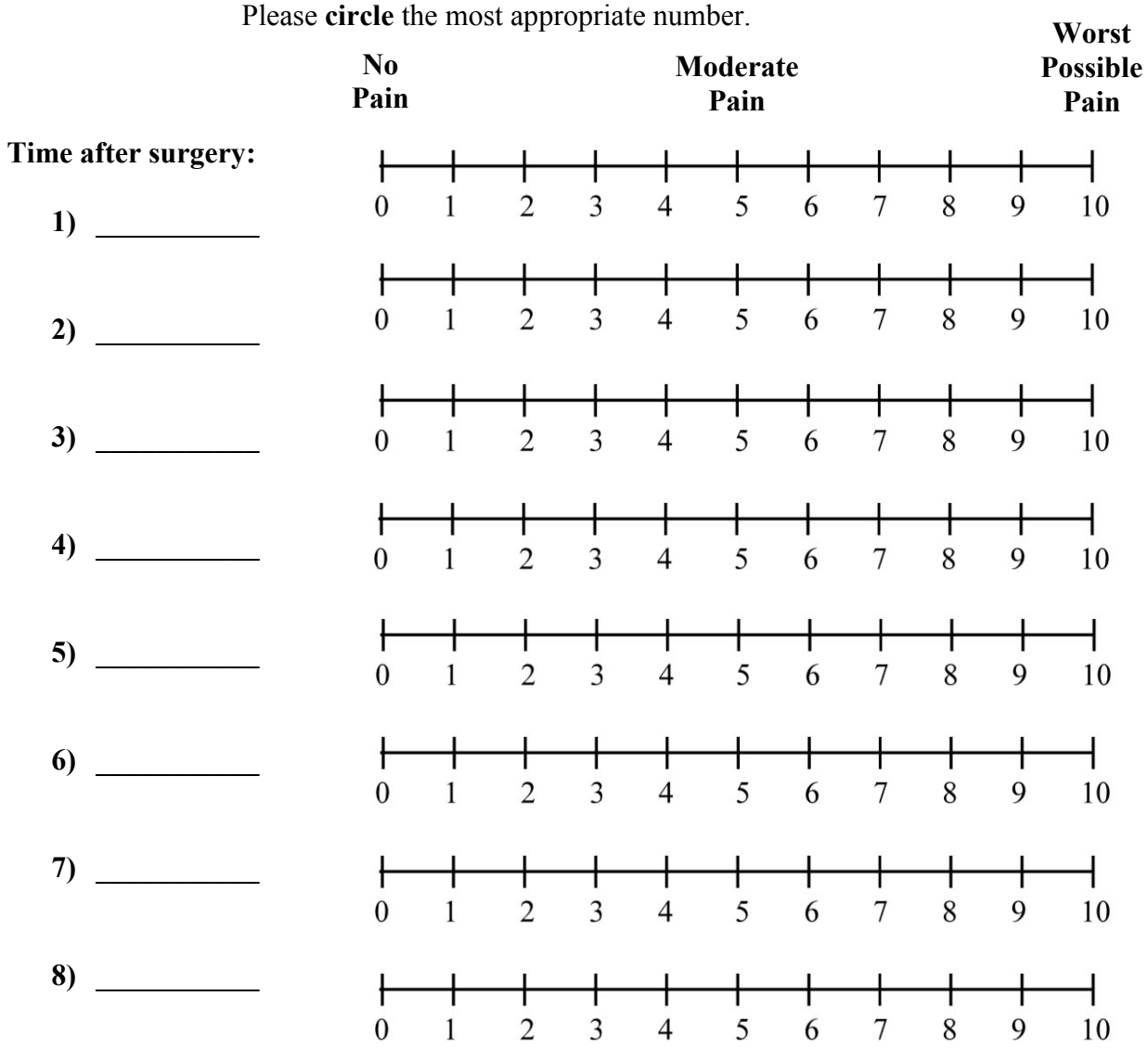
1. Very Satisfied
2. Satisfied
3. Neutral
4. Unsatisfied
5. Very Unsatisfied

**Note: The surgeon's satisfaction level considers the entire procedure experience including sedation, administration of local anaesthesia, and the surgery itself.*

Appendix 2: Patient Take Home Pain and Medication Survey

For each time slot below, please indicate the intensity of pain you are experiencing.
Please **circle** the most appropriate number.

Time after surgery:



Please see reverse side for tracking pain medication use. →

Thank you very much for completing this survey and for your participation in this research study. Once completed, please mail this survey using the self-addressed and stamped envelope to the Department of Oral and Maxillofacial Surgery.

Appendix 2: Patient Take Home Pain and Medication Survey (Continued)

Please indicate what pain medication you used at each time slot, and also indicate the dosage (*in **milligrams** for Ibuprofen and Tylenol (Regular), and in **number of tablets** for Tylenol #3*).
Please check all that apply.

Time after surgery:

1) _____	☐ Ibuprofen Dose: _____	☐ Tylenol (Regular) Dose: _____	☐ Tylenol #3 Tablets: ____	☐ None
2) _____	☐ Ibuprofen Dose: _____	☐ Tylenol (Regular) Dose: _____	☐ Tylenol #3 Tablets: ____	☐ None
3) _____	☐ Ibuprofen Dose: _____	☐ Tylenol (Regular) Dose: _____	☐ Tylenol #3 Tablets: ____	☐ None
4) _____	☐ Ibuprofen Dose: _____	☐ Tylenol (Regular) Dose: _____	☐ Tylenol #3 Tablets: ____	☐ None
5) _____	☐ Ibuprofen Dose: _____	☐ Tylenol (Regular) Dose: _____	☐ Tylenol #3 Tablets: ____	☐ None
6) _____	☐ Ibuprofen Dose: _____	☐ Tylenol (Regular) Dose: _____	☐ Tylenol #3 Tablets: ____	☐ None
7) _____	☐ Ibuprofen Dose: _____	☐ Tylenol (Regular) Dose: _____	☐ Tylenol #3 Tablets: ____	☐ None
8) _____	☐ Ibuprofen Dose: _____	☐ Tylenol (Regular) Dose: _____	☐ Tylenol #3 Tablets: ____	☐ None

Please indicate your overall satisfaction with your surgery and recovery.
Please circle the most appropriate number**.**

Appendix 3: Publishing Agreement

Appendix 3: Publishing Agreement (Continued)

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