THE PROSPECTIVE EVALUATION OF PERIOPERATIVE STEROID DOSING ON POSTSURGICAL EDEMA IN ORTHOGNATHIC SURGERY

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ABSTRACT

Problem:

While there exists good evidence to support steroid use, there is no consensus on the optimal dose of methylprednisolone to be used in orthognathic surgery. The purpose of this study is to investigate the postoperative effects of two perioperative doses of methylprednisolone in orthognathic surgery.

Methods:

A double-blinded randomized control evaluating 250 orthognathic surgery patients was conducted. Patients were randomized 1:1 to receive either a 1000mg dose or a 125mg dose of methylprednisolone perioperatively. Postoperative facial swelling was measured and secondary postoperative outcomes were recorded.

Results:

No significant difference in facial swelling was found between steroid groups (P= 0.42). Other than for mood (P= 0.05), no secondary outcomes differed between groups (all P > 0.05). In our study, younger age, male gender and BSSO procedures were associated with increased facial swelling.

Conclusion:

A perioperative dose of 125mg of methylprednisolone can be used as effectively as a 1000mg dose for the control of postoperative facial edema.

LIST OF ABBREVIATIONS USED

3D	Three Dimensional
ACTH	Adrenocorticotropic Hormone
ANOVA	Analysis of Variance
BMI	Body Mass Index
BSSO	Bilateral Sagittal Split Osteotomy
cGCR	Cytosolic Glucocorticoid Receptor
cm^3	Cubic Centimeter
CAOMS	Canadian Oral and Maxillofacial |Surgeons
CRH	Corticotropin Releasing Hormone
CT	Computed Tomography
CYP450	Cytochrome P450
DNA	Deoxyribonucleic Acid
FG	Functional Genioplasty
GA	General Anesthetic
GC	Glucocorticoids
GC-GCR complex	Glucocorticoid-Glucocorticoid Receptor Complex
GCR	Glucocorticoid Receptors
HPA axis	Hypothalamic-Pituitary-Adrenal Axis
ICC	Intraclass Correlation Coefficient
IV	Intravenous
kg	Kilograms
LF	Lefort 1
LOS	Length of Stay
mGCR	Membrane Glucocorticoid Receptor
mg	Milligrams
mm	Millimeter
MP	Methylprednisolone
MRI	Magnetic Resonance Imaging
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
NSD	Neurosensory Disturbance
NSHA	Nova Scotia Health Authority
NSHA REB	Nova Scotia Health Authorities Research Ethics Board
OMF	Oral Maxillofacial
OMFS	Oral Maxillofacial Surgery
OQLQ	Orthognathic Quality of Life Questionnaire
PCA	Patient Controlled Analgesia
POD	Post-Operative Day
PONV	Post-Operative Nausea and Vomiting
RANK	Receptor Activator of Nuclear Factor
RMS	Root Mean Squared
SD	Standard Deviation
SION	Steroid-Induced Osteonecrosis
SSI	Surgical Site Infection
TNF-α	Tumor Necrosis Factor Alpha
VAS	Visual Analog Scale

ACKNOWLEDGEMENTS

CHAPTER 1.   INTRODUCTION

Orthognathic surgery is a commonly performed procedure to correct functional and esthetic dentofacial deformities. As the face is richly vascularized, intense postoperative edema is a recognized consequence of soft tissue incisions, subperiosteal dissection, and bony osteotomies required for the manipulation of the facial skeleton. Swelling of the face can be concerning to both patients and clinicians and can contribute to lengthened hospital stays, increased delays in return of function and poorer surgical outcomes[1–3]. Since the 1970's, systemic glucocorticoid therapy has been used to reduce postoperative edema[1].

Despite being a mainstay in clinical practice for over forty years, limited high-quality evidence exists to support the use of a particular dose or type of glucocorticoid for orthognathic surgery[4–6]. Early trials were placebo controlled and demonstrated that intravenous administration of glucocorticoids in orthognathic surgery produces a significant decrease in facial edema in the postoperative period. Over the years, very high doses of steroids have been used. Glucocorticoids are a useful class of medications with dose-dependent adverse effects including hyperglycemia, adrenal insufficiency, immunosuppression, avascular necrosis of the hip, acne, as well as sleep and mood disorders[7]. While the majority of the literature in orthognathic surgery has shown short-term, high-dose steroid use in patients undergoing orthognathic surgery to be safe, a number of case studies have highlighted steroid-related adverse consequences[8–10].

With the advent of three-dimensional technologies, we are now able to quantify facial swelling and quantify its resolution accurately[11,12]. This has allowed researchers to better assess edema after surgery and evaluate the efficacy of commonly employed interventions used to minimize postoperative swelling. This study will describe a method of quantifying swelling and

compare the anti-edema effects of two different glucocorticoid doses used in orthognathic

surgery.

CHAPTER 2.   REVIEW OF THE LITERATURE

2.1 ORTHOGNATHIC SURGERY

Orthognathic surgery refers to the surgical procedures used for manipulation of the facial skeleton in the correction of dentofacial deformities. This includes maxillary, mandibular and chin (or genioplasty) procedures of the bony face. The first of these procedures was described by Hullihan in 1849, where he used a subapical mandibular osteotomy to correct apertognathia[13]. Nearly 50 years later, Blair described a mandibular body osteotomy to correct mandibular horizontal excess[14]. Over the next 80 years, the mandibular osteotomy was modified by several surgeons until the mandibular sagittal split osteotomy was refined and popularized by Trauner and Obwegeser in 1955[15]. Hofer described the first horizontal osteotomy of the anterior mandible, performed from an external approach in 1942. Trauner and Obwegeser later performed the same surgery from an intraoral approach, which is still used today[15].

In 1901, Rene Lefort classically described the natural planes of fracture of the maxilla[16] and subsequently in 1927, Wassmund described the Lefort 1 osteotomy to correct maxillary hypoplasia. In his surgery, he used elastic traction to mobilize the maxilla. Schuchardt later described pterygomaxillary separation in 1942. Obwegeser later described complete maxillary mobilization and stabilization in 1965, leading to improved long-term stability of maxillary movements[17].

Today, orthognathic surgery is used primarily for the correction of dentofacial deformities of the lower and mid face. Proffit was one of the first to define the term dentofacial deformity as "facial and dental disproportions great enough to affect the individual's quality of life"[18]. Dentofacial deformities are primarily anomalies of the upper and lower jaws and the dentition of one or both of these jaws. Several studies have shown that patients with these

skeletal discrepancies often suffer from decreased biting efficiency, limited mandibular

movement, abnormal chewing patterns, temporomandibular joint (TMJ) dysfunction and low

self-esteem[19,20]. The term orthognathic surgery is rooted in Greek: orthos meaning straight and

gnathos meaning jaw. Therefore, the goal of orthognathic surgery is to correct the skeletal

deformity by harmonizing the position of the jaws with one another and with the rest of the face.

To determine which jaw or jaws require correction, a complete clinical and radiographic

examination of the craniofacial structures must be performed. This involves examining the

vertical, horizontal and transverse position of the maxilla and mandible with respect to the

features of the face and the dentition. Special attention should be taken to evaluate the soft tissue

envelope of the facial structures both at rest and when animated. An ideal occlusal scheme of the

teeth would be considered an angle class 1 relationship of the molar and cuspid teeth, with

maxillary and mandibular midlines coincident with the middle of the face.

Cephalometric analysis of the face is an important part of characterizing the anomalies of

the craniomaxillofacial skeleton. Several different analyses exist, measuring the patients' bony

and dental proportions and comparing these to population norms[21,22]. The problem with these

methods is defining the "normal" population for comparison[23]. The Delaire structural and

architectural cephalometric analysis is based on the balance of cranial and facial bony structures

(Figure 1). It uses the patient's own cranial parameters to assess the position of the jaws. This

avoids the use of "population norms" and statistical averages, and makes the patient their own

"control" in defining the ideal facial structure[24].
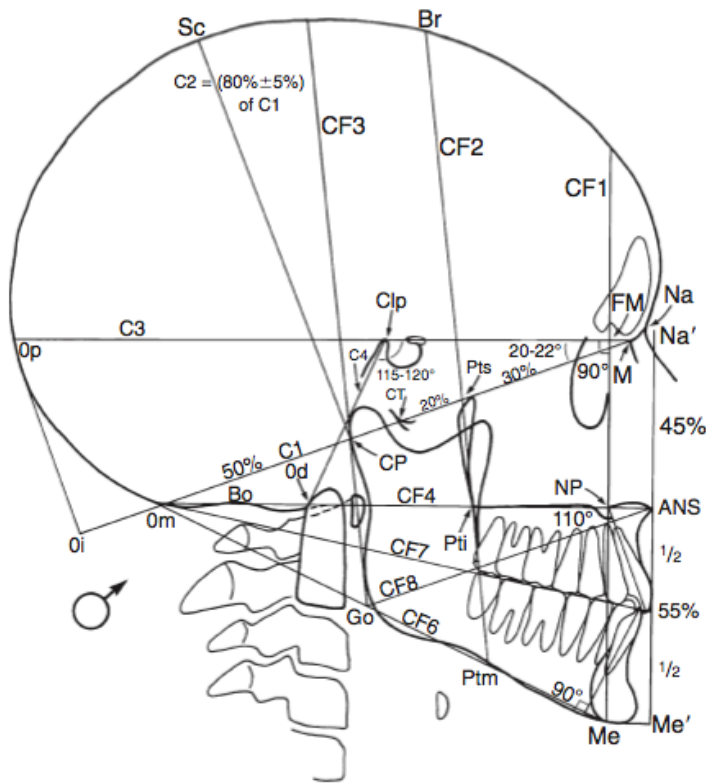
Figure 1. Delaire's Architectural and Structural Craniofacial Cephalometric Analysis. In: Fonseca RJ, Marciani RD, Turvey TA: Oral and maxillofacial surgery. St. Louis, Mo.: Saunders/Elsevier, 2009.

Optimizing the relationship of the bony facial skeleton has been shown to have beneficial effects on chewing, speech, TMJ function and masticatory muscle pain, as well as dental and periodontal health[25]. The added benefit of this new, harmonious position of the jaws is usually a more aesthetic facial profile. Several studies using the validated Orthognathic Quality of Life Questionnaire (OQLQ) have proven that patient satisfaction with facial appearance and self-confidence improves after orthognathic surgery[26–29].

2.2. COMPLICATIONS AND SEQUALLAE OF ORTHOGNATHIC SURGERY

Orthognathic surgery is safe and predictable, with a litany of literature to support its use in the correction of dentofacial deformities. Despite this, there are a number of undesirable events that can arise after surgery. For the purpose of this manuscript we will differentiate between post-operative complications and sequelae. A sequela is an "after-effect" of a surgery that is inherent to that procedure, whereas a complication is defined as any alteration to the normal procedure or postoperative course.

Complications in orthognathic surgery can be divided into intraoperative and postoperative events. Intraoperative complications include acute bleeding, observed nerve damage, unfavorable osteotomies and damage to teeth or adjacent soft tissues. Postoperative complications include permanent neurosensory disturbances, temporomandibular joint dysfunction, condylar resorption, malocclusion, relapse, late bleeding and infection. Immediate postoperative sequelae generally occur, to some degree, in all orthognathic surgery patients. These include, but are not limited to, swelling, pain, nausea and vomiting.

2.2.1 SWELLING AFTER ORTHOGNATHIC SURGERY

Celsius, in the 1st century A.D., was credited with describing swelling among the four main signs of inflammation. Galen later noted in the 3rd century A.D. that inflammation was an inescapable reaction to tissue injury. We now understand inflammation to be the initial phase by which injured tissues heal.

Initially, vasodilation and increased vascular permeability in the area of injury accounts for the majority of the four main signs of inflammation: redness, heat, pain and swelling (Figure

2). Various chemical mediators, including histamine, bradykinin, complement and prostaglandins, are released or synthesized by injured cells (Figure 3). These chemical mediators sensitize sensory nerve cells, playing a major role in nociception and pain transmission. They also play a chemotactic role for the cellular players in the inflammatory process.
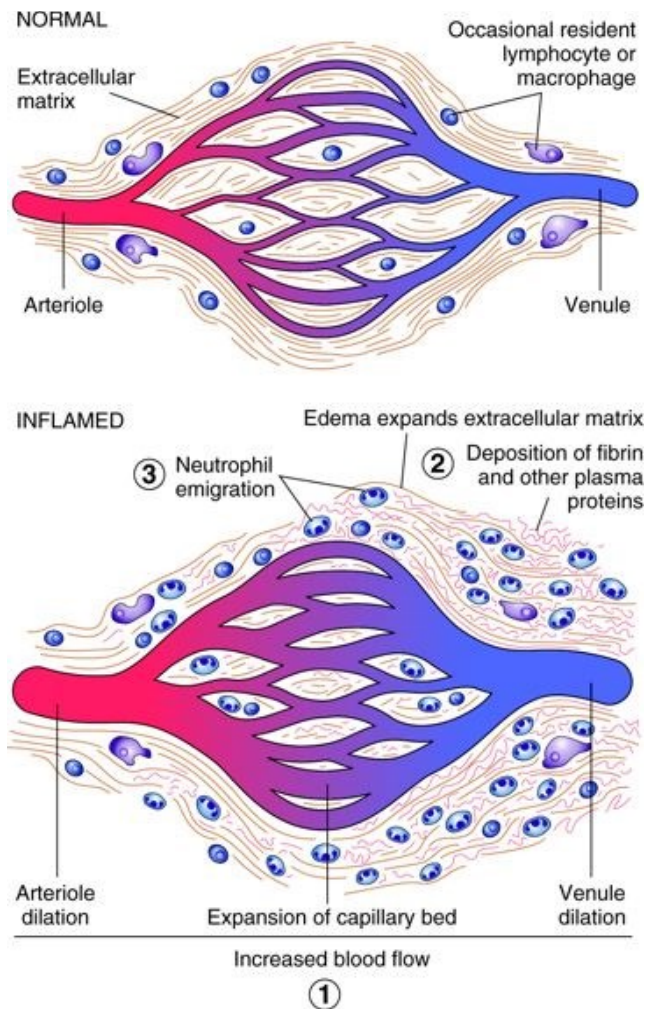
Figure 2. The major local manifestations of acute inflammation compared to normal. (1) Vascular dilation and increased blood flow (causing erythema and warmth), (2) extravasation and deposition of plasma fluid and proteins (edema), and (3) leukocyte emigration and accumulation in the site of injury. In: Kumar V, Abbas AK, Aster JC eds: Robbins and Cotran pathologic basis of disease. Ninth edition. Philadelphia, PA: Elsevier/Saunders, 2015.
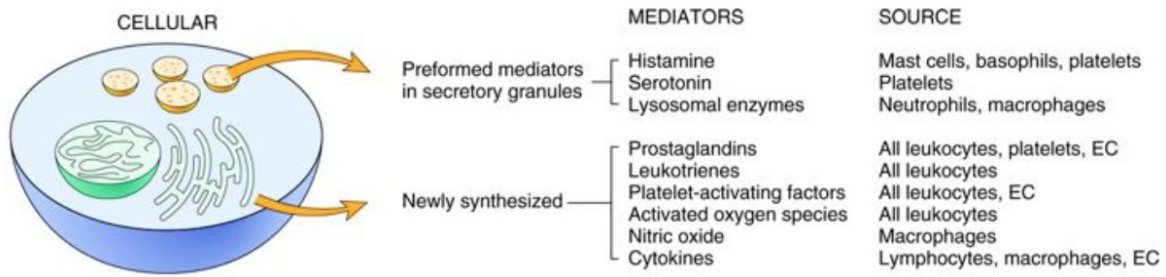
Figure 3. A list of major chemical inflammatory mediators and their sources. In: Kumar V, Abbas AK, Aster JC eds: Robbins and Cotran pathologic basis of disease. Ninth edition. Philadelphia, PA: Elsevier/Saunders, 2015.

Next, in the cellular phase of inflammation, margination of leukocytes occurs in blood vessels and they move through vessel walls to the site of injury. Once there, inflammatory cells perform phagocytosis and initiate the repair process[30]. As the head and neck is richly vascularized, significant facial edema occurs to some extent to all patients after undergoing orthognathic surgery.

Postoperative swelling is a problematic result of orthognathic surgery for patients, caregivers, nurses and surgeons. Swelling is commonly reported by patients as the one of the most difficult post-operative symptoms to tolerate[3,31]. Swelling of the cheeks and lips affects their ability to coordinate stomatognathic function, leading to difficulties with speech and oral nutritional intake after surgery [32]. The latter point can lead to increased length of stay in hospital. Despite preoperative counselling, Zhou found that immediately after surgery more than nearly three-quarters of patients had more swelling than expected[33]. Facial swelling and resulting loss of function of the oral apparatus is a recognized factor in the development of depressive symptoms after orthognathic surgery. Cunningham et al. found that over 80% of patients who underwent orthognathic surgery reported low mood states in the immediate period following surgery[34].

Pain and swelling often go hand in hand after a surgical insult, as they both are among the cardinal signs of inflammation. Several key inflammatory mediators are known to play important

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roles in pain pathways. Numerous studies have shown that patients with more swelling after facial surgery have more discomfort in the immediate postoperative period[35–39]. Whether swelling is a cause of postoperative pain after oral surgery is not clear[40-43] . It follows that the more tissues swell, that more inflammatory mediators will be present, causing a greater tension on fascial planes and irritation of their associated nerve fibers.

Pronounced swelling of the face can occur after facial surgery. Obstruction of the airway and the need for reintubation or prolonged intubation after surgery is also a concern[44]. Case reports have described the need for reintubation after surgery[45]. This concern has been evaluated by Jean et al., who found no studies assessing airway compromise after orthognathic surgery[46].

2.2.2 PAIN AFTER ORTHOGNATHIC SURGERY

Nearly half (48%) of respondents in a 2016 U.K. study complained of moderate to severe pain after undergoing orthognathic surgery[47]. Pain can be expected after periosteal and muscular stripping, stretching of soft tissues and bony osteotomy, all which are inherent to orthognathic surgical procedures. Pain has also been rated by orthognathic surgery patients as one of the most difficult symptoms to tolerate in the postoperative period[31,3] and has been found to increase length of stay in hospital and contribute to readmissions[47]. The orthognathic surgery patient's age and naivety to surgical insults, as well as a decreased ability to communicate after surgery and maxillomandibular fixation may also contribute to worsened pain states[48].

Pain is often managed with multimodal therapy in the post-operative period[49]. Non-steroidal anti-inflammatory drugs (NSAIDS), acetaminophen and various narcotic agents have been described in the literature[3, 49-53]. Today, surgeons are prescribing less opioid medications and rely more heavily on non-narcotic analgesics[54]. Multimodal analgesia with NSAIDS has been shown

to reduce opioid consumption after orthognathic surgery[55]. Precious et al. found that discomfort after orthognathic surgery was managed as well with naproxen as with morphine patient-controlled analgesia (PCA). Both analgesic regimens were better than oral codeine alone and resulted in fewer drug-related side effects, such as nausea and vomiting[48].

2.2.3 NAUSEA AND VOMITING AFTER ORTHOGNATHIC SURGERY

Post-operative nausea and vomiting (PONV) is the most common side-effect of general anesthesia (GA). Although rates of PONV have decreased dramatically over the last twenty years, its prevalence is still estimated to be 20-30% for all patients undergoing GA. In a review of the literature Silva found rates of PONV after orthognathic surgery to be significantly higher at 40.1%, when looking at the first 48 hours postoperatively[56]. Phillips found a rate higher of 67% in his cohort of patients after surgery[57].

Several patient, anesthetic, and surgical factors have been identified which contribute to the development of PONV in the general population[58]. These can be found in Table 1.

Table 1. Patient, anesthetic and surgical risk factors for PONV.

Patient Factors	Anesthetic Factors	Surgical Factors
Female	Use of perioperative opioids	Duration of surgery
Non-smoker	Use of volatile anesthetics	Type of surgery including
History of motion sickness or PONV	Use of nitrous oxide	abdominal, ear/nose/throat/, gynecologic, laparoscopic,
Family history of motion sickness or PONV		ophthalmologic, orthopedic, plastic

In the orthognathic surgery population, Silva showed that important risk factors for PONV include young age (15-25 years old), maxillary surgery, surgical duration of over 1 hour, use of inhalational agents and the use of post-operative opioids. It is also important to note that the literature shows the majority of patients undergoing orthognathic surgery are non-smoking females of an average age of 20 years old[32,56,57,59].

Beyond the discomfort and anxiety it can cause for patients, surgical consequences of PONV include dehydration, electrolyte disturbance, development of hematoma, wound dehiscence and aspiration events[60,32]. PONV is a common cause for increased LOS and readmission to hospital[50,51] and is estimated to account for $1.2 billion per year in extra health care costs in the United States[60]. In patients having undergone intraoral procedures PONV can lead to prolonged bleeding and swallowing of blood, which can then worsen PONV. Insertion of a nasogastric tube for suctioning of ingested blood has been employed by maxillofacial surgeons to limit this emetogenic stimulus. Evidence to support this practice is limited[61]. Patients are routinely in maxillomandibular fixation after orthognathic surgery and have facial swelling and numbness, which leads to discoordination of the oral apparatus. This can make PONV especially distressing for these patients.

2.2.4 INFECTION AFTER ORTHOGNATHIC SURGERY

Surgical site infection (SSI) can negatively affect surgical outcome, increase postoperative discomfort and worsen the burden on the health care system[62]. In orthognathic surgery, this can lead to additional procedures for incision and drainage or fixation hardware removal, readmission to hospital and increased costs and complications associated with

prolonged antibiotic use[63]. Intraoral wounds are considered clean-contaminated and carry an

expected infection rate of 10-15%[64]. In a large, retrospective review of 2,268 patients who

underwent orthognathic surgery, Davis et al. found that longer operating time and bimaxillary

surgery were risk factors for the development of SSI. They did not find a correlation between

patient factors such as age, gender, medical history or smoking status and SSI[65].

2.3 GLUCOCORTICOIDS

Corticosteroids is a term to describe the steroid hormones normally produced in the

adrenal cortex. Their synthesis begins with cholesterol and ends in the production of

glucocorticoids (GC), mineralocorticoids and androgen hormones. Glucocorticoids have several

anti-inflammatory and immunosuppressive properties and perform a number of metabolic

functions in the body that are essential for life. Aldosterone is the chief mineralocorticoid

produced by the adrenal glands and is responsible for salt retention and water balance.

2.3.1 GLUCOCORTICOIDS MECHANISM OF ACTION

Cortisol is the main glucocorticoid in the human body. Its synthesis and secretion take

place in the zona fasciculata of the adrenal cortex. Cortisol is released into the bloodstream in

response to stimulation from the hypothalamic-pituitary-adrenal axis (HPA axis)(Figure 4). The

HPA axis is responsible for the body's neural and endocrine response to stress. Normally,

cortisol is secreted in a diurnal pattern with serum levels highest in the morning, shortly after

waking. Levels decrease throughout the day as cortisol exerts an inhibitory effect back on the

anterior pituitary gland and hypothalamus. In response to stress, the neural inputs to the

hypothalamus stimulate the anterior pituitary and eventually the adrenal cortex raising

circulating levels of cortisol.
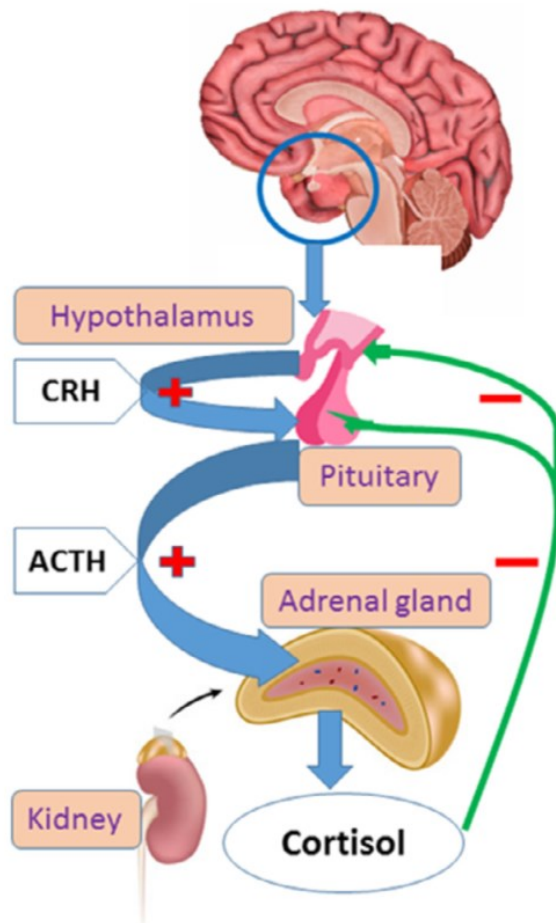
Figure 4.The hypothalamic-pituitary-adrenal axis. Cortisol release from the adrenal gland is regulated by ACTH. CRH (corticotropin-releasing hormone) is the principal factor causing ACTH release from the anterior pituitary. Cortisol feeds back negatively on the pituitary and hypothalamus inhibiting ACTH and CRH release. In: Deng J, Chalhoub NE, Sherwin CM, Li C, Brunner HI: Glucocorticoids pharmacology and their application in the treatment of childhood-onset systemic lupus erythematosus. Seminars in Arthritis and Rheumatism, 2019.

In general, glucocorticoids play a major role in metabolism and in the maintenance of

homeostasis in the cardiovascular, immune, muscular, renal, endocrine and nervous systems.

They also have powerful anti-inflammatory and immunoregulatory properties. Glucocorticoids

affect nearly all cells in the human body. This is due to the presence of glucocorticoid receptors (GCR), which are ubiquitous in nearly all cell types[66].

Glucocorticoids act on cells by either genomic or non-genomic mechanisms (Figure 5). In the genomic pathway, the steroid hormone passes through the plasma membrane to bind with cytosolic GCR. This complex then enters the nucleus of the cell and either turns on DNA transcription (transactivation) or inhibits it (transrepression). The GC-GCR complex alters gene expression by binding specific DNA promoter elements or other transcription factors[67]. Classically, it is thought that transrepression leads to many of the desirable anti-inflammatory and immunosuppressive effects of glucocorticoids whereas transactivation is responsible for many of their adverse effects[68,69]. As it takes time to organize DNA and protein synthesis, genomic mechanisms are slow. Cell changes due to genomic mechanisms occur no sooner than 30 minutes after glucocorticoid binding, and often take several hours to days before their effects become clinically relevant[70].

Non-genomic mechanisms do not directly influence gene transcription, and therefore occur quickly. They can either be specific, occurring via the binding of GC to cytosolic or membrane bound glucocorticoid receptors or by nonspecific mechanisms, which do not require GC-GCR binding. Non-specific nongenomic effects are seen at higher steroid doses, greater than 100mg equivalent of prednisone, as glucocorticoid receptors become saturated[71]. Non-genomic effects are numerous and not yet fully understood. Several non-genomic pathways lead to an intracellular signaling cascade which has been shown downstream to inhibit phospholipase A2 activity and impair arachidonic acid release, suppressing inflammation[72]. As these effects are not reliant on DNA synthesis, glucocorticoid non-genomic effects occur quickly with effects seen within seconds to minutes of drug administration[73].
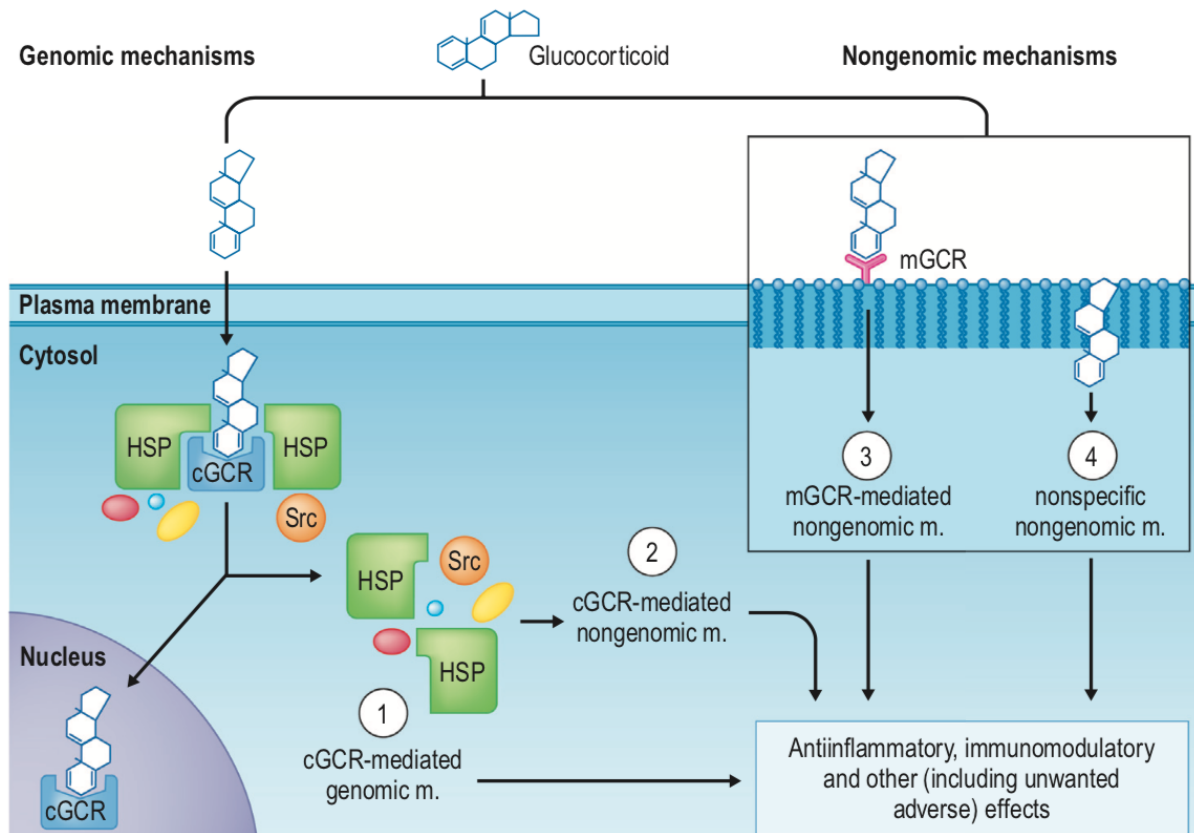
Figure 5.Genomic and nongenomic glucocorticoid mechanisms. Glucocorticoids are lipophilic and easily cross the plasma membrane and can bind cytosolic glucocorticoid receptors (cGCR). The GC bound cGCR can then move into the nucleus and affect gene transcription and protein synthesis (either by transactivation or transrepression) (1). These mechanisms are slow. Conversely, the GC-cGCR may dissociate quickly before crossing into the nucleus and the altered cGCR complex will participate in non-genomic mechanisms (2). Glucocorticoids can also bind membrane glucocorticoid receptors (mGCR) (3) or bind directly into the plasma membrane and participate in nongenomic mechanisms (4). These mechanisms are fast. In: Rich RR: Clinical immunology: principles and practice. 4. ed. Philadelphia, Pa: Elsevier Saunders, 2013.

2.3.2 SYNTHETIC GLUCOCORTICOIDS

Kendall, Hench and Reichstein received the Nobel Prize in 1950 for their research isolating cortisone and successfully using it to treat patients with rheumatoid arthritis[74]. It was quickly realized that prolonged treatment with cortisone caused several unwanted effects, and research began for novel corticosteroids to circumvent these effects[75,76]. All glucocorticoids share a similar structure, with additions made to specific positions of the central carbon ring which enhance or reduce certain properties. Researchers quickly devised methods to modify glucocorticoids, minimizing the mineralocorticoid effect of new compounds and limiting salt and water retention. A challenge still faced today is separating the catabolic and most untoward effects of glucocorticoids from the desired anti-inflammatory and immunomodulatory ones[69,77].

The chemical modification of glucocorticoids also yielded steroids with different pharmacokinetic and pharmacodynamic properties. Pharmacokinetic parameters, including the elimination half-life, greatly alter the duration of glucocorticoid action. Clinically this affects the need for drug re-dosing. Pharmacodynamic properties influence the intensity of the glucocorticoid effects and will dictate the dose of steroid required to achieve clinical effectiveness[77]. Classically, bioassays measuring the ability of synthetic glucocorticoids to suppress inflammatory cells, their mediators and their effect on glycogen storage in hepatocytes have been used to estimate relative glucocorticoid potency[77,78]. Ranking the relative potencies of different synthetic glucocorticoids depends on the experimental design and type of assay used. Table 2 highlights the relative potencies of synthetic GCs and their duration of action.

Table 2. Relative potencies and equivalent doses of representative glucocorticoids. Duration of action is marked S- short (8-12 hour biological half-life), I- intermediate (12-36 hour biological half-life), L- long (36-72 hour biological half-life). Equivalent dose is only for oral and intravenously administered steroids. In: Goodman LS, Brunton LL, Chabner B, Knollmann BC: Goodman & Gilman's pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011.

COMPOUND	ANTIINFLAMMATORY POTENCY	Na$^+$-RETAINING POTENCY	DURATION OF ACTION*	EQUIVALENT DOSE,[†] MG
Cortisol	1	1	S	20
Cortisone	0.8	0.8	S	25
Fludrocortisone	10	125	I	[‡]
Prednisone	4	0.8	I	5
Prednisolone	4	0.8	I	5
6α-Methylprednisolone	5	0.5	I	4
Triamcinolone	5	0	I	4
Betamethasone	25	0	L	0.75
Dexamethasone	25	0	L	0.75

There is growing evidence to show that the classical estimates of glucocorticoid potencies are not entirely accurate, given the developing understanding of the difference between the slower acting genomic effects and fast-acting non-genomic ones[73]. Buttgreit et al. developed a model to evaluate the non-genomic effects of five commonly used synthetic glucocorticoids. They found a significant difference between the genomic (classical) and non-genomic potencies for the glucocorticoids studied. The non-genomic potencies for these drugs can be found in Figure 6[70].
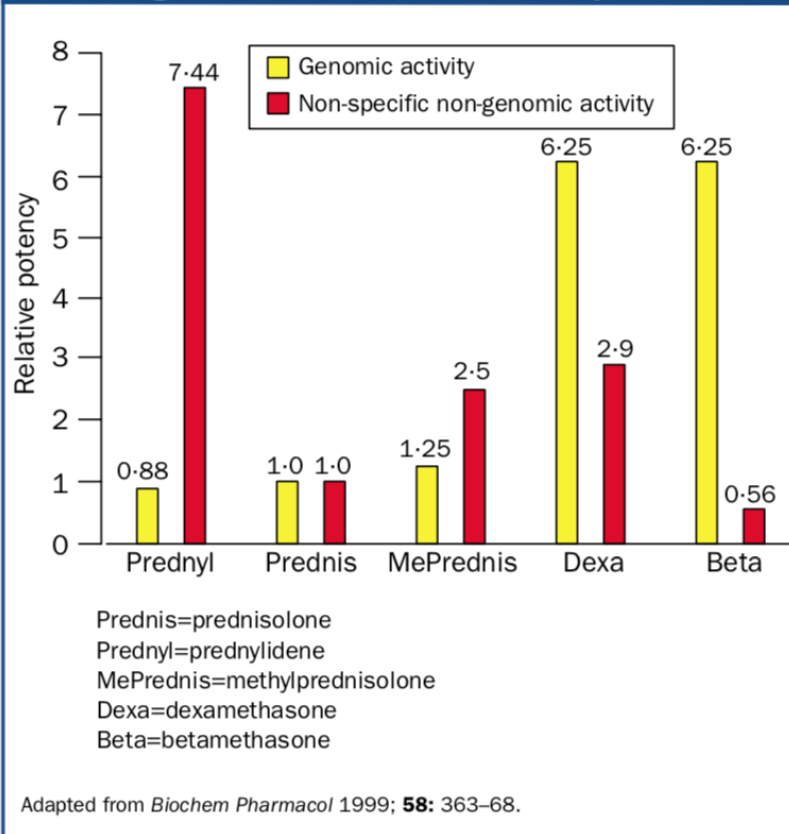
Figure 6. Relative potencies of synthetic glucocorticoids to produce genomic and nongenomic effects. All potencies are indexed to prednisone. Yellow bars represent the relative genomic activity and red bars represent the nongenomic potencies. In: Lipworth BJ: Therapeutic implications of non-genomic glucocorticoid activity. The Lancet 356: 87, 2000.

These differences between genomic and non-genomic effects may be especially pertinent given the indication for steroid use. Genomic effects may be more important if using steroids for the management of chronic inflammatory conditions, whereas non-genomic effects may be more relevant if treating rapidly progressing traumatic or allergy-mediated swelling.

2.4 ADVERSE EFFECTS OF GLUCOCORTICOIDS

Less than a month after starting his first patient with rheumatoid arthritis on glucocorticoid therapy, Hench noted that she had developed facial puffiness, hirsutism and severe acne. She began complaining of myalgias and was found to have worsening agitation and low mood[75]. It was quickly realized that while glucocorticoids may be beneficial tools in the management of inflammatory and immune mediated conditions, their use is fraught with unwanted side effects. Table 3 provides an overview of the adverse effects of exogenous glucocorticoid use.

Table 3. Side effects of glucocorticoids.

Affected System	Undesirable Effect
Cardiovascular	Hypertension
	Congestive Heart Failure
Gastrointestinal	Esophagitis, gastritis
	Peptic ulcer
Neuropsychiatric	Mood swings, depression, psychosis
Ophthalmic	Glaucoma
	Cataracts
Musculoskeletal	Osteoporosis
	Avascular necrosis of bone
	Myopathies
Endocrine/ metabolic	Hyperglycemia
	Cushing's Syndrome
	Electrolyte disturbances
Immune	Immunosuppression
	Increased risk of infection
Cutaneous	Acne
	Delayed wound healing

Glucocorticoids play an integral role in glucose and protein metabolism. During periods of stress, cortisol levels rise, mobilizing stores of glucose in order to protect glucose dependent organs (e.g. the brain and heart) from starvation. Gluconeogenesis and both glycogenolysis and storage at the level of the liver increases and serum glucose spikes. Glucocorticoids decrease the peripheral use of glucose and stimulate protein and lipid breakdown, further mobilizing sources for gluconeogenesis[79]. Glucocorticoids also bind mineralocorticoid receptors and at high circulating concentrations, mineralocorticoid effects can be seen in the body.

Overall many steroid-related adverse effects seem to be both dose and duration dependent, however no safe maximum dose of glucocorticoid has been established to avoid these complications. Care should be taken in interpreting literature on steroid-related complications. A strong selection bias for glucocorticoid use exists, as patients with more severe diseases and more medical comorbidities are often on higher doses of steroids for longer durations. These patients may be more prone to adverse GC-related effects.

2.4.1 ENDOCRINE SYSTEM

Elevated blood glucose and insulin resistance is commonly seen in patients receiving even short term doses of steroid therapy[80,81]. This is a transient phenomenon and blood glucose quickly returns to normal after glucocorticoid administration[7]. Glucocorticoid administration may make glycemic control in the diabetic patient even more difficult, predisposing them to diabetic ketoacidosis[82]. Corticosteroid administration has been shown to be a risk factor in the development of diabetes, with steroid dose and duration shown to be risk factors. Despite this association, neither the dose or duration of steroid therapy required for the development of diabetes is known[7,80,82,83].

Adrenal insufficiency is a recognized consequence of prolonged exogenous glucocorticoid therapy and has been shown to occur with as little as 5mg equivalent of prednisone daily. This roughly equates to physiological levels of cortisol produced by the adrenal glands[84]. The duration of therapy required to produce adrenal insufficiency is controversial and is as variable as the proposed regimens for additional perioperative stress doses of steroids[85,86]. Adrenal insufficiency can deteriorate into adrenal crisis, which manifests as altered mental status, gastrointestinal symptoms, electrolyte abnormalities, hypotension and death. Studies have demonstrated the safety of pulse dosed steroids (up to 2g methylprednisolone daily) for short courses, without the development of adrenal insufficiency[87,88].

There are no reports of patients developing adrenal insufficiency after steroid administration for orthognathic or dental surgeries[4]. Despite these studies, a recent systematic review found adrenal insufficiency can present in patients receiving cumulative steroid doses less than 5mg prednisone equivalent and those receiving short steroid courses[89]. This highlights the need to be vigilant of adrenal insufficiency and adrenal crisis even with lower cumulative doses and shorter treatment regimens commonly used for orthognathic surgery.

2.4.2 MUSCULOSKELETAL SYSTEM

A stereotypical "Cushingoid" appearance is a well-recognized consequence of prolonged hypercortisolism or exogenous steroid use. Characteristic features include facial rounding, upper dorsal fat pad, central obesity, peripheral muscle weakness, myalgias, osteoporosis and hirsutism[7]. These findings are primarily attributable to the metabolic redistribution of energy sources (glucose, amino acids and lipids), as described earlier. The dose and duration of exogenous steroids to cause Iatrogenic Cushing's Syndrome is not known, but it is recognized

that high dose steroids for prolonged periods (>4 weeks) is a risk factor[90,91]. In reviewing the available literature, the development of Iatrogenic Cushing's Syndrome has not been described after steroid administration for orthognathic surgery or with perioperative single-dose steroids in other surgeries[88].

Osteoporosis is another complication of prolonged steroid use and is dose and duration dependent. No consensus on a safe minimum dose or duration of steroid exists[92]. Glucocorticoids decrease calcium absorption in the gut, suppress osteoblast function and promote osteoclast function through the RANK ligand pathways, leading to bone resorption and fracture.

Steroid-induced osteonecrosis (SION) is a well-recognized consequence of high-dose steroid use. Its pathogenesis is not fully understood, but several theories owing to the catabolic effects of glucocorticoids exist[93]. Roughly 2/3 of patients who develop steroid-induced osteonecrosis are between 30 and 60 years old and a strong male predilection exists[94,95]. Like other adverse steroid-related adverse effects, dose and duration of therapy are important factors in the development of SION and a safe minimal dose has not been established. In multiple reviews of the literature pertaining to steroid-related osteonecrosis, no cases of SION in otherwise healthy patients were discussed[93–95]. Patients in these reviews had pre-existing connective tissue, inflammatory or hematologic conditions, or were recipients of solid organ transplants, and were presumed to be receiving pulsed high-dose steroids for treatment of their disease. Precious et al. showed that SION in the patients receiving high-dose steroids for orthognathic surgery is very uncommon. None of the 1276 patients who underwent orthognathic surgery in his retrospective cohort study went on to develop osteonecrosis of the hip and subsequent hip replacement. Furthermore, he looked at 1497 patients who underwent hip replacement during the same study period. None of these patients had previous orthognathic

surgery. From this large cohort review, Precious concluded that high-dose steroids used for orthognathic surgery was not related to SION and the need for hip replacement[96].

2.4.3 DERMATOLOGIC SYSTEM

Glucocorticoids have a number of adverse effects on fibroblasts, including a reduction in their mitotic events causing reduced cell size. The effect of reduced fibroblast function leads to thinning and fragile skin, as well as ecchymoses and striae. These changes are again seen only with prolonged courses of systemic or topical steroids and, with the exception of striae, resolve after steroid discontinuation[7,79].

Acne is also a recognized steroid-related phenomenon. The exact pathogenesis is unclear, but a preponderance for white females under the age of 30 and treatment with high-dose steroids has been shown[97]. Steroid-related acneiform lesions typically present several weeks after steroid treatment and are predominantly located on the trunk and extremities, instead of the face as is common in acne vulgaris. Discontinuation of the steroid is enough for these lesions to resolve without additional treatment[97,98]. Precious et al. highlighted the development of steroid-induced acne in eight patients following high-dose steroid administration for orthognathic surgery. These patients were all females, without prior history of acne, between the ages of 24 and 36 years old. The acneiform lesions resolved slowly, without scarring[99].

2.4.4 IMMUNE SYSTEM

The most beneficial effect of glucocorticoids is on cells of the immune system. These cells and their mediators are central to the inflammatory response. Glucocorticoids limit

leukocyte migration to the site of injury, decrease neutrophil and macrophage function, suppress immunoglobulin production in B-cells and prevent the release of pro-inflammatory cytokines such as interleukin-1 and tumor necrosis alpha[100]. Use of supraphysiologic doses for long term treatment causes immunosuppression. These patients are predisposed to infection from both typical and atypical pathogens and are at risk for reactivation of latent infections, such as tuberculosis[7,30,79,84].

The inflammatory phase is also the initial stage of wound healing. Patients with prolonged immunosuppression from glucocorticoid use are at increased risk of delayed wound healing, wound dehiscence and surgical site infections. Recent systematic reviews investigating adverse effects of perioperative steroids in cardiac and orthopedic surgery demonstrated no increased risk of wound problems or infection with routine use of perioperative steroids[88,101,102]. No increased risk of infection was found in a similar meta-analysis in the orthognathic surgery literature[4].

2.4.5 CENTRAL NERVOUS SYSTEM, MOOD AND PSYCHIATRIC EFFECTS

Cortisol is an important hormone involved in the maintenance of sleep patterns and homeostasis of the central nervous system. Exogenous steroids disrupt normal cortisol diurnal secretion and its feedback on the HPA axis, which has been shown to have negative effects on sleep, mood, behavior and memory.

Characteristic sleep pattern changes are seen in patients with Cushing's Disease and those receiving high dose exogenous steroids. These changes include increased sleep latency, decreased REM sleep and increased arousals during sleep[103–105]. In some studies, complaints of sleep disturbance rank second only to issues with weight gain among patients receiving

steroids[106]. As with many other steroid-related effects, dose and duration of treatment required to affect sleep is not known. Studies have shown that acute high dose glucocorticoid administration has little effect on sleep EEG patterns[103].

Labile mood, excitability and mild euphoria, panic attacks, mania and acute psychoses have all been described with even single dose administrations of glucocorticoids. Depressive symptoms and suicidal ideation are more common with chronic steroid use[104]. Several instances of steroid-induced psychosis have been documented in the oral and maxillofacial surgery literature[8,9,107,108]. Legal precedence exists for steroid-induced "intoxication". A man in England attempted to murder his fiancée after receiving glucocorticoids for an orthognathic surgery procedure and was found to be acting under the influence of a medication and was acquitted[10]. Although a prior history of psychiatric disease does not seem to predispose patients to steroid-related psychiatric disturbances, these effects appear to increase with greater cumulative steroid doses[7].

2.5 METHYLPREDNISOLONE

Methylprednisolone was developed in the United States in the late 1950s when researchers added a methyl group to the 6th carbon position of the basic steroid structure in hopes of potentiating or increasing the glucocorticoid effects of prednisolone. Addition of 6-α methyl group confers slightly greater glucocorticoid effect and less mineralocorticoid activity than prednisolone. Methylprednisolone sodium succinate, sold in North America as Solumedrol, is administered intravenously and is rapidly absorbed and distributed after injection. Methylprednisolone is considered an intermediate acting steroid, with a biologic half-life of 12-36 hours[109]. Its onset of action is rapid, within the first hour of IV administration, but this is difficult to precisely quantify given the lack of concrete understanding of its genomic and non-genomic actions[70,110]. Unlike many older glucocorticoids, methylprednisolone does not bind to transcortin, a steroid binding protein. This leads to linear pharmacokinetics with no dose-dependency, meaning that with increased doses of methylprednisolone there will be increased glucocorticoid receptor binding until all glucocorticoid receptors are bound[110]. Methylprednisolone is first oxidized then conjugated in the liver and the hydrophilic inactive moiety is excreted in the urine. Excretion of an administered IV dose is nearly complete in twelve hours, making it necessary to re-dose methylprednisolone every 4-6 hours to maintain high blood levels. Hepatic and renal dysfunction does not significantly impact methylprednisolone pharmacokinetics[110] and no dosing adjustments are recommended for patients with hepatic or renal impairment[111]. Like other glucocorticoids, methylprednisolone is metabolized in the liver by the CYP450 enzyme family. Medications that induce the CYP450 enzymes, such as barbiturates, carbamazepine, phenytoin and rifampicin will increase methylprednisolone clearance and decrease its half-life. Coadministration of drugs that inhibit

CYP450 enzymes, such as ketoconazole and clarithromycin, will increase methylprednisolone half-life[76,77,110,111].

Solumedrol is recommended for clinical situations where rapid and intense anti-inflammatory action is required. Indications for use include anaphylaxis, shock, severe asthma, urticaria and dermatologic conditions such as exfoliative dermatitis and erythema multiforme. Methylprednisolone can be used for a number of immune mediated conditions such as systemic lupus erythematosus, acute rheumatic fever or ulcerative colitis. Immunomodulation required for the prevention of solid organ rejection is another indication for its use. The use of Solumedrol for the mitigation of facial swelling or post-operative nausea and vomiting, or for managing upper airway edema is considered off-label use[111].

Methylprednisolone, like other glucocorticoids, is a pregnancy category C drug and is excreted into breastmilk. Use of the medication in pregnant or breastfeeding women is not advised, unless the benefits outweigh the risks of use[111].

2.6 GLUCOCORTICOID USE IN ORTHOGNATHIC SURGERY

Systemic glucocorticoid use in orthognathic surgery has a history dating back to the early 1970's when Guernesy and DeChamplain documented their experience and complications in sagittal split osteotomies of the mandible. They described using systemic dexamethasone as an anti-inflammatory agent in the mitigation of facial swelling which occurred universally in all surgical patients[1]. After over a decade of use in orthognathic surgery, Schaberg et al. were the first to quantify the effect of methylprednisolone versus placebo on swelling in orthognathic surgery patients. They used CT scans taken at 24 and 72 hours postoperatively to determine that the steroid treatment cut facial swelling after surgery nearly in half[112]. Since these studies, systemic glucocorticoid administration has become commonplace in orthognathic surgical practices. Besides its benefit as an antiedema agent, steroids have been advocated for the mitigation of several common sequalae of orthognathic surgery, such as post-operative pain and post-operative nausea and vomiting. Perioperative administration of steroids has also been advocated for improved patient outcomes such as decreased hospital length of stay and neurosensory regeneration.

An optimal steroid regimen for orthognathic surgery, which balances adverse steroid-related effects and their desired anti-inflammatory ones, has not been determined. Studies show the choice of steroid type and dose varies considerably among surgeons performing orthognathic surgery.

2.6.1 EFFECT OF GLUCOCORTICOIDS ON SWELLING AFTER SURGERY

Several studies have examined the value of glucocorticoids as an antiedema agent in orthognathic surgery. Four double-blinded randomized control trials exist evaluating the use of perioperative glucocorticoids in orthognathic surgery[113–116].

Widar et al. evaluated the effect of varying doses of betamethasone (no steroid, 8mg and 16mg) given perioperatively to patients undergoing bilateral sagittal split osteotomy (BSSO). Facial edema was measured using a string spanning between the earlobes going underneath the chin. They found less swelling in the both test groups (8mg and 16mg) than the control group (P= 0.017) measured on post-operative day one[113].

Abukawa et al. measured swelling of the masseters and the overlying soft tissue using CT scan in patients undergoing BSSO. They randomized 24 patients in a double blinded fashion between a no steroid control group and treatment groups receiving 8mg and 16mg of dexamethasone perioperatively. They found decreased swelling between the 16mg treatment group and the control group 24 hours postoperatively (P <0.05). There was no difference between the control group and the 8mg group in facial swelling (P>0.05). They postulated that doses of dexamethasone of at least 16mg were required to affect surgery-induced facial swelling and proposed further studies using higher doses of dexamethasone[114].

Weber and Griffin randomized 23 BSSO patients into groups receiving placebo, a single 16mg dose of dexamethasone perioperatively and a group receiving 16mg of dexamethasone at induction of general anesthesia and 3 subsequent 8mg doses, spaced every 6 hours. They showed the treatment groups had significantly less swelling (P <0.05) than the placebo group. No difference was found between treatment groups, which led them to conclude that there may be a cumulative steroid dose threshold above which additional steroid may not be beneficial[115].

Munro et al. found no benefits in using steroids for orthognathic surgical procedures for his cohort of patients. They randomized patients into a control and treatment group, the latter receiving 0.5mg/kg of dexamethasone at surgery and 0.25mg/kg/day of dexamethasone divided into 4 doses postoperatively. Their group quantified facial swelling as: 1) the duration of intubation in ICU postoperatively, 2) the patient's ability to resume full oral fluid intake, and 3) observed facial swelling. No difference was found between treatment and control groups for any of these 3 measures, however no statistical analysis was performed. These findings lead Munro and his associates to conclude that there was no therapeutic benefit to steroid use in bony facial surgery[116].

Three systematic reviews examining the use of systemic glucocorticoids for orthognathic surgery exist[4,5,46]. All three papers state independently that, given the available literature, steroids reduce facial swelling after orthognathic surgery. They all agree that more clinical trials are required and that an "ideal" therapeutic dose of steroids cannot presently be determined.

2.6.2 EFFECT OF GLUCOCORTICOIDS ON PAIN AFTER SURGERY

Various inflammatory mediators play a major role in the maintenance and perception of pain[117]. It follows that by limiting inflammation, the duration and intensity of post-surgical pain can also be lessened. Glucocorticoids are used in multimodal pain control after various surgeries[118].

Widar et al. performed the only study in the orthognathic surgery literature looking at the effect of different perioperative glucocorticoid doses on post-operative pain. They looked at post-operative pain as an outcome after BSSO which was evaluated by patients using a visual analog scale (VAS). No difference was found between groups (no steroid, 8mg and 16mg

betamethasone) at any time point during their study (POD 1, 7, 2 months and 6 months) (P >0.05 for all)[113].

Support for the administration of systemic glucocorticoids for pain management after orthognathic surgery is largely taken from studies evaluating the analgesic effects of steroids used during and after extraction of third molars[4,5]. This evidence will be discussed later.

2.6.3 EFFECT OF GLUCOCORTICOIDS ON OTHER OUTCOMES AFTER SURGERY

Two studies have determined that the administration of systemic glucocorticoids prior to orthognathic surgery is a factor in decreasing length of stay in hospital after surgery[50,119]. These studies employed a multiple regression model but were unable to identify a steroid dose used.

Widar et al. evaluated length of stay in hospital as a secondary outcome measure and found that patients who received 8mg of betamethasone perioperatively and an additional two 4mg doses postoperatively had a shorter LOS than the no steroid group (P= 0.049)[113]. The effect of steroids on neurosensory regeneration after orthognathic surgery has been evaluated and shows mixed results. Widar evaluated sensation of the lower lip at POD 1, 7, 2 months and 6 months and found no difference between groups that were administered 0mg, 8mg and 16mg of betamethasone (P >0.05)[113]. Similar results were found by Abukawa when evaluating escalating doses of dexamethasone[114]. Seo et al. administered a fixed steroid regimen after orthognathic surgery for patients who presented on follow-up with neurosensory impairment. They found steroid administration accelerates neurosensory recovery after orthognathic surgery (P <0.05)[120]. Retrospectively looking at his cohort of patients who underwent BSSO, Al-Bishri et al. evaluated neurosensory disturbance (NSD) by way of patient survey at least one year after surgery. They found that patients who were administered

perioperative steroids had a rate of long-lasting (>1 year) neurosensory disturbance of 15% compared to the non-steroid group who reported long-lasting NSD at 30%[121].

2.7 GLUCOCORTICOID USE IN 3RD MOLAR SURGERY

Surgical removal of 3rd molars often requires the elevation of a submucoperiosteal flap and drilling of bone. As in orthognathic surgery, facial swelling, pain and trismus occur commonly afterwards, although not necessarily to the same extent. Glucocorticoids have been used to limit these unpleasant after-effects. There is more evidence on the effects of steroids after removal of 3rd molars, likely since this procedure is more commonly performed than orthognathic surgery. Given the similarities in post-operative sequalae, the effects of steroids in 3rd molar surgery can be generalized to orthognathic surgery. For the purpose of this review, studies using only intravenous steroids will be discussed.

2.7.1 EFFECT OF GLUCOCORTICOIDS ON SWELLING IN 3RD MOLAR SURGERY

Several studies have assessed the use of perioperative glucocorticoids and their effect on postoperative facial swelling after 3rd molar removal. A 2019 systematic review and meta-analysis by Nagori et al. reviewed ten studies measuring the effect of intravenous (IV) methylprednisolone (MP) administration on facial edema after 3rd molar removal[122]. Nine of them demonstrated a significant reduction in facial swelling seen in the early postoperative period ($P < 0.05$). Only four of these studies evaluated swelling in the late postoperative period. None of them reported a statistically significant difference between treatment and control (no steroid) groups. Nagori's conclusion was that methylprednisolone significantly reduces facial

edema in the early post-operative period but has no effect on late facial swelling after 3rd molar removal.

2.7.2 EFFECT OF GLUCOCORTICOIDS ON PAIN IN 3RD MOLAR SURGERY

Several studies exist that evaluate the effects of intravenous steroids on post-operative pain in 3rd molar surgeries. The systematic review by Nagori et al. highlighted three studies showing significantly reduced pain in the steroid group in the early post-operative period. Six other studies evaluated did not show a difference between treatment and control (no steroid) groups in post-operative pain scores. Nagori concluded that IV methylprednisolone has no effect on post-operative pain after 3rd molar surgery[122]. Dan et al. supported the use of perioperative steroids for pain reduction in their systematic review and meta-analysis of the 3rd molar literature. They found a statistically significant reduction in pain after 3rd molar surgery when perioperative steroids were used (P <0.0001)[4]. Their study did not differentiate between routes of administration or type of steroid given.

2.7.3 EFFECT OF GLUCOCORTICOID REGIMEN ON OUTCOMES AFTER 3RD MOLAR SURGERY

Ustun et al. conducted a double blinded cross-over study evaluating the effects of different doses of methylprednisolone on pain and swelling after 3rd molar surgery. They selected 26 patients based on bilateral symmetry of their impacted 3rd molars. Patients presented on two separate days for surgery by the same surgeon, receiving a different dose of IV methylprednisolone each time. For one side they were given 1.5mg/kg IV MP and the other side a 3mg/kg dose. Swelling as measured by linear facial measurements at 48 hours and 7 days

postoperatively was not found to differ based on steroid dose (P= 0.541). Pain as measured by VAS and by post-operative analgesic requirements was also not different between groups (P= 0.793). They concluded that there was no clinical benefit with the higher MP dose[123].

Three studies exist evaluating the difference between methylprednisolone and dexamethasone for the reduction of swelling and pain after 3rd molar surgery[124–126]. Lim et al. evaluated the effects of placebo, methylprednisolone and dexamethasone injected submucosally at the time of surgery on postoperative swelling and pain. They found both steroid groups had significantly reduced swelling compared to the control group at POD 1, 2, 5 and 7 ($P < 0.05$). Pain was significantly less in only the MP group versus the control groups on POD 1 and 2 ($P < 0.05$)[126]. Studies by Alcantra et al. and Darawade et al. evaluated oral doses of MP (40mg) and dexamethasone (8mg) on postoperative outcomes after 3rd molar surgery. No control group was used in either study. Both studies found less swelling in the dexamethasone group ($P = 0.002$[124] and $P < 0.05$[125] respectively). Neither study found a significant difference in analgesic qualities of either dose of steroid.

2.8 PERIOPERATIVE GLUCOCORTICOID USE IN OTHER SURGERIES

Systemic glucocorticoids are used in a multitude of surgical specialties. They have been shown in a number of systematic reviews and meta-analyses to mitigate multiple adverse postoperative outcomes such as pain, PONV and ecchymosis. Intraoperative steroid use has been shown to decrease LOS in hospital after various surgeries.

A meta-analysis of 8 randomized control trials showed that a single perioperative dose of dexamethasone is effective for reducing pain after tonsillectomy (P= 0.01)[127]. Two large reviews of the orthopedic literature show grade-A evidence supporting intraoperative intravenous steroids as a part of post-operative multimodal analgesia[102,118]. The authors of these studies also highlight the efficacy of perioperative steroids in decreasing opioid requirements after surgery, contributing to lower rates of PONV in these patients.

Two systematic reviews of cosmetic facial surgeries concluded that steroid administration significantly reduces PONV as well as swelling and ecchymosis after rhinoplasty. Despite these findings, one author supports the use of intraoperative steroids for rhinoplasty, while the other advocates steroid use only for prevention of PONV and not for "transient edema"[128,129].

Finally, two large orthopedic studies, one looking at arthroplasty patients and the other at spinal surgery patients, found LOS was significantly reduced in patients receiving perioperative glucocorticoids (P< 0.05[130] and P= 0.0025[101]). The reduction in hospital length of stay in the steroid groups in both studies was roughly one day.

2.9 SURGICAL AND PATIENT FACTORS IN POSTOPERATIVE SWELLING

A multitude of studies have examined the effects of different treatments (including glucocorticoids) on facial swelling after orthognathic surgery. The majority of these studies have controlled for surgical and patient factors between treatment groups. Relevant surgical factors include both procedure type and duration of surgery. Patient factors related to facial swelling include gender, age and body mass index (BMI). Some studies have evaluated the effect these factors have on facial swelling.

2.9.1 EFFECT OF PROCEDURE TYPE ON FACIAL SWELLING

Six studies evaluated the effect of procedure (i.e. Lefort, BSSO, etc.) on facial swelling[116,131–135]. This was a secondary outcome measure in all six articles. Yamamoto et al., Kau et al., and Van der Vlis all looked to quantify facial swelling with different facial scanning techniques. No intervention or treatment groups were used in these studies.

Kau et al. found less overall swelling in patients undergoing surgery on a single jaw versus patients who underwent bimaxillary surgery. A faster rate of reduction in swelling was also seen in seen in the bimaxillary group; however, a statistical analysis was not performed. Van der Vlis demonstrated that patients undergoing Lefort only surgery had less overall swelling than patients undergoing bimaxillary surgery (P= 0.004)[134]. Yamamoto et al. did not find a significant difference in swelling based on procedure type or duration of surgery in their orthognathic surgery patients (P >0.05)[133].

The Munro et al. craniomaxillofacial study involved a treatment group receiving dexamethasone perioperatively and a placebo group. They observed that patients who underwent

LF only had a decreased duration of intubation postoperatively, which was one of their measures of postoperative facial swelling. No statistical analysis was performed[116]. Semper-Hogg et al. also found the LF only group to have less swelling than the BSSO and bimaxillary surgery groups when patients received either a 5mg "antiemetic" dose of dexamethasone or a 40mg treatment dose. No formal analysis was done[135].

Gasperini et al. did not find an effect of procedure type on post-operative swelling (P= 0.394) in their study evaluating the effects of low-level laser therapy on facial edema after orthognathic surgery[131].

2.9.2 EFFECT OF GENDER, AGE AND BMI ON FACIAL SWELLING

In their evaluation of 49 patients undergoing orthognathic surgery, Van der Vlis et al. found the amount of facial swelling and rate of resolution did not vary significantly by gender or age (P >0.05). They also found that patients with higher BMI had a greater amount of swelling and the fastest rate of resolution following operation[134].

2.10 ANALYSIS OF FACIAL SWELLING

2.10.1 MEASUREMENT OF FACIAL SWELLING

Several methods have been employed in the measurement of facial swelling. Early studies by Habal and Powell used "qualified observers" and standardized photographs to measure swelling created in an experimental piglet model when looking at the effect of 1 gram of methylprednisolone versus placebo on facial swelling. Observers gave a grade out of 4 for swelling, basing their estimate of facial swelling caused by coronal flap elevation on eyelid function and periorbital edema[136]. Munro used 3 criteria to evaluate swelling after his craniomaxillofacial surgery procedures. He used an aggregate of postoperative intubation duration, return to full oral feeding and "observed facial swelling" as measured by pre and postoperative clinical photographs rated by three trained observers[116]. Use of standardized clinical photographs was popular in early days of evaluating swelling after orthognathic and 3rd molar surgery[115,137,138], but this later gave way to more objective measurements of facial swelling.

Linear measurements of facial swelling using strings, metal wires bent to the face and calipers is an easy, low-cost way to quantify swelling after surgery and has been well used. A method popularized by Ustun et al. used a string between the lateral canthus and angle of the mandible as well as measurements from the tragus to the corner of the mouth and pogonion to quantify swelling after 3rd molar surgery (Figure 7).
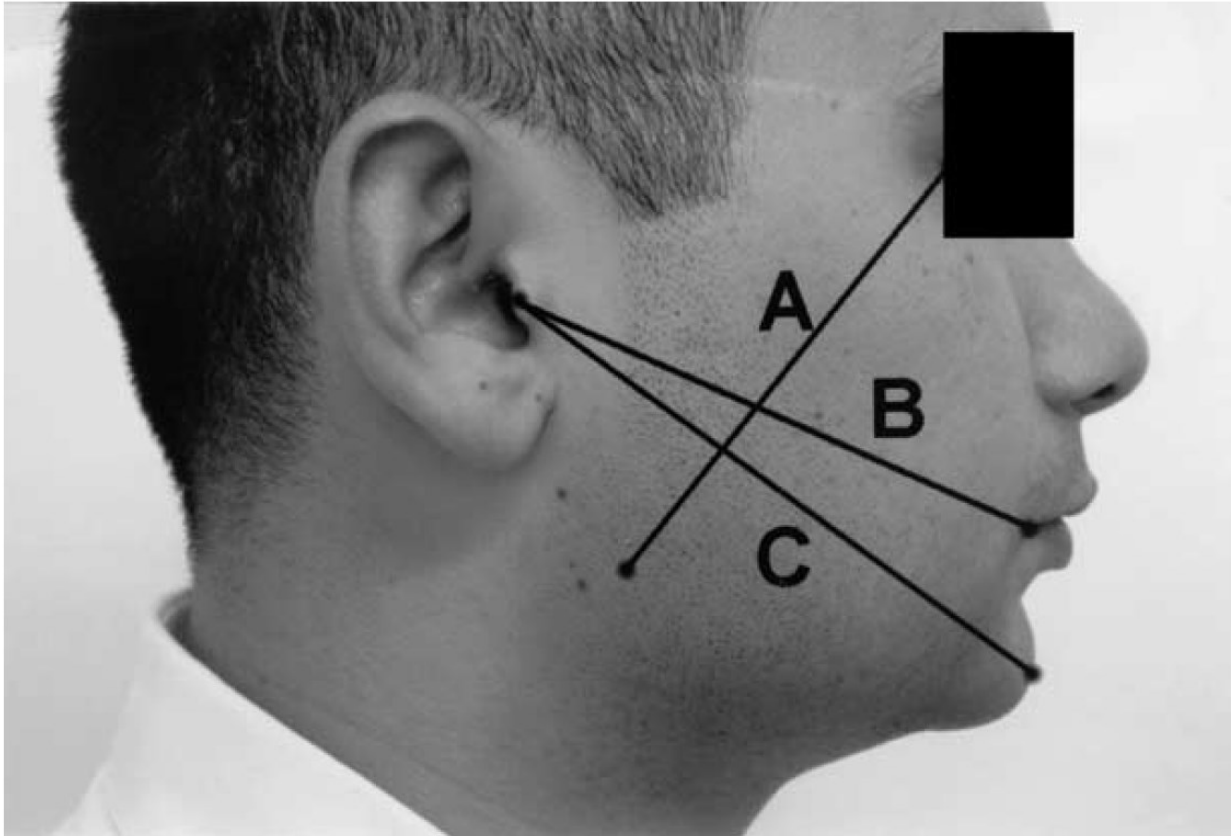
Figure 7. A linear measurement method developed by Ustun et al. A) The distance between the lateral canthus and angle of the mandible, B) tragus to corner of the mouth, C) tragus to pogonion. These measurements were taken prior to surgery, 48 hours and seven days postoperatively to assess change in facial swelling. In: Üstün Y, Erdoğan Ö, Esen E, Karsli ED: Comparison of the effects of 2 doses of methylprednisolone on pain, swelling, and trismus after third molar surgery. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology 96: 535, 2003.

Linear measurements using CT scans, MRI and ultrasonography have also been described. In axial CT slices, Schaberg et al. measured the difference in scan area at defined levels using soft tissue anatomic references[112]. Abukawa et al. performed a similar analysis using bony landmarks for reference in the axial plane[114]. MRI scans have also been used[139].

2.10.2 THREE-DIMENSIONAL ANALYSIS OF FACIAL SWELLING

Measurement of swelling in three-dimensions provides the most accurate evaluation of volume and volume changes. MRI and CT scans are radiation dose intensive and costly. Three-dimensional surface scanners and cameras provide a quick, reproducible and radiation-free method of assessing facial swelling.

The study by Kau et al. provides a model for measuring 3D facial swelling (Figure 8). They described a method for measuring facial swelling after orthognathic surgery using a 3D laser scanning device. He and his team obtained 3D facial photographs, smoothed the surfaces and removed "extraneous data" to create a facial shell. Extraneous data was defined as hair and the neck area which could vary from timepoint to timepoint based on the patient's hairstyle or posture while obtaining the scan. Three-dimensional photographs were taken at time points T1 (preoperative), T2 (1 day), T3 (1 week), T4 (1 month), T5 (3 months) and T6 (6 months) and 3D facial shells were created for each time point. Using five anatomic points (inner and outer canthi of each eye and the tip of the nose), the shells were superimposed and the difference in volume between the shells was calculated using an algorithm built into their software. Assuming that no swelling was present at the 6 month timepoint, they compared the volume of all other timepoints (T2-T5) to T6. They further calculated the rate of swelling change. Kau later used this method to evaluate the facial swelling of twelve patients requiring orthognathic surgery[132]. Van der Vlis et al. validated this method using a 3D camera instead of laser surface scanner to evaluate swelling in orthognathic surgery in 49 patients[134].
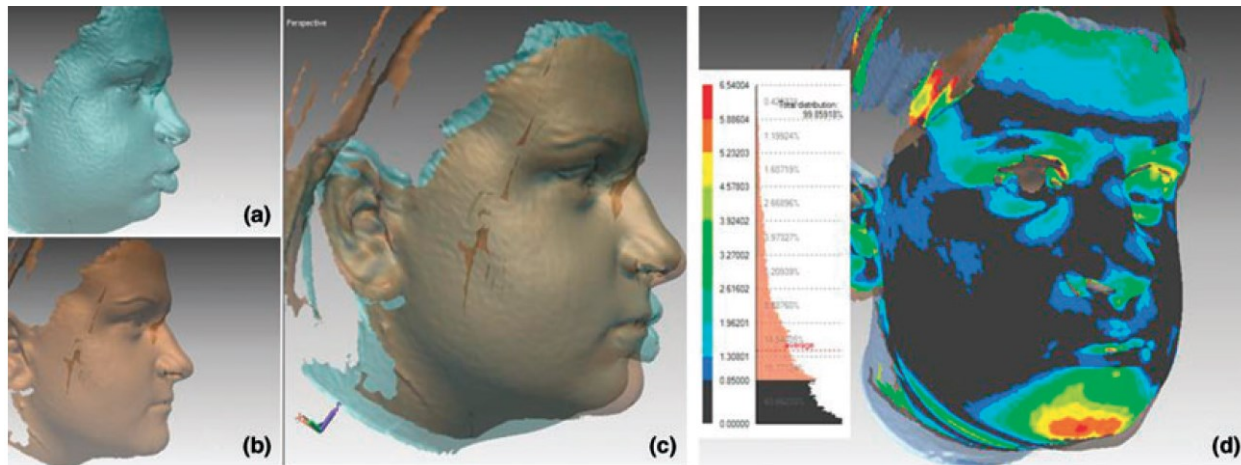
Figure 8. 3-Dimensional measurement of facial swelling. A) Post-operative facial scan. B) A facial scan taken at 6 months post-operatively. C) Alignment of facial scans based on a best fit algorithm. D) A shell deviation map showing areas of greatest difference between the two facial shells. In: Kau C, Cronin A, Durning P, Zhurov A, Sandham A, Richmond S: A new method for the 3D measurement of postoperative swelling following orthognathic surgery. Orthodontics and Craniofacial Research 9: 31, 2006

2.10.3 ACCURACY OF FACIAL SCANNING TECHNOLOGIES

Since the introduction of three-dimensional scanners into clinical use, much work has been done to verify the accuracy and precision of these instruments[140]. Van der Meer et al. assessed the validity and reliability of the 3DMD facial scanner in measuring facial swelling. They artificially created facial swellings using dental putty pressed into the buccal vestibule and onto the teeth of 24 volunteers. 3D photos were taken of the subjects with and without the swelling at two different times of day. The 3DMDVultus software was used to calculate the volume change from the normal to swollen photos and was then compared to the actual swelling volume, which was calculated with a scale and knowledge of the products density (in g/cm^3). Their study found the 3DMD scanner to be accurate to $1.2cm^3$. Using the difference between their two measurements, the interclass coefficient was found to be 0.89, demonstrating good to excellent reliability. Other studies have validated the 3DMD scanner's use in measuring the

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face[141–143]. The ability of the 3DMD scanner to accurately measure volume has been validated in breast and hand applications[144-145] . These studies showed excellent reliability, with interclass coefficients above 0.95. The sum of this work shows that the 3DMD system can be used clinically to measure facial swelling reliably and to a high degree of accuracy.

2.10.4 The 3DMD FACIAL SCANNING SYSTEM

The 3DMD face system (3DMD LLC., Atlanta, GA, USA) uses a synchronized multicamera configuration to obtain six images (two color and four black and white), which are then merged into a single three-dimensional image or model (Figure 9). Three pairs of stereo cameras are aligned in a triangular fashion and connected to a desktop computer. Once the device is calibrated to obtain field depth and orientation, the patient may be positioned in the field for image capture. Image capture time is 1.5 milliseconds and no ionizing radiation is used. All images are stamped with the time and date of acquisition and the three-dimensional image is stored as a 3D object (.obj) file.

The 3D files can then be analyzed using the 3DMDVultus software (3DMDVultus 64-bit 2.5.0.1, 3DMD LLC, Atlanta, GA, USA) on a personal computer. The 3DMDVultus software allows for cropping of 3D photographs, facial landmark placement, distance and angle calculations, as well as surface area and volume calculations. The manufacturer claims an accuracy of 1.5% of the total observed variance and a geometrical accuracy of less than 0.2mm.

Figure 9. The 3DMDface system (3DMD LLC., Atlanta, GA, USA).

CHAPTER 3. THE USE OF PERIOPERATIVE STEROIDS IN ORTHOGNATHIC SURGERY IN CANADA

3.1 PURPOSE

In September 2017 a survey of the Canadian Oral and Maxillofacial Surgeons (CAOMS) was conducted. The purpose of this survey was to investigate current practices related to the use of glucocorticoids in orthognathic surgery performed in Canada. The primary outcome of the survey was to examine which steroid regimens are commonly used by surgeons in Canada. The secondary outcome of the survey was to understand why surgeons might have a preference for certain steroid types or doses.

3.2 METHODS

A short questionnaire consisting of 4 questions was created using an online survey software (Opinio by Objectplanet). An email with a link to the survey was sent to the CAOMS membership, along with a short description of the survey. Only one entry per member was allowed. The survey was opened from September 17, 2017 to December 31, 2017. Descriptive statistics were used to determine a central tendency and variation in steroid dosing regimens.

3.3 RESULTS

A total of 132 out of a possible 399 CAOMS members responded to the survey for a 33% response rate. 124 respondents answered yes to <u>Question 1</u>: Do you perform orthognathic surgery. All of the 124 respondents who answered yes to question 1 also answered yes to <u>Question 2</u>: Do you use perioperative steroids for orthognathic surgery?

<u>Question 3</u> asked: What regimen of steroids do you use? Of the 124 respondents, 60 (48.4%) use methylprednisolone perioperatively and 64 (51.6%) use dexamethasone at the time of surgery. After surgery, 64 (51.6%) surgeons reported using methylprednisolone and 54 (43.5%) use dexamethasone. A total of 6 (4.8%) surgeons did not report the use of post-operative steroids. Additionally, 26 of the 124 surgeons reported the use of an additional intramuscular injection of methylprednisolone of 40-80mg prior to discharge from hospital.

A breakdown of the different perioperative and postoperative steroid regimens is seen in table 4 and table 5 below. Steroid doses were grouped into similar dose ranges for ease of interpretation of our data. For example, methylprednisolone is available in 120mg and 125mg vials and these doses are therefore grouped together. Dosing frequency and total number of doses was not accounted for when grouping postoperative steroid regimens. For example, MP 125mg administered every 4 hours for 6 doses was grouped with MP 125mg given every 6 hours for 4 total doses.

Table 4. Breakdown of Perioperative doses of methylprednisolone (MP) and dexamethasone (Dex).

MP Dose	< 120mg	120 / 125mg	250mg	500mg	1000mg	2000mg
N= 60	4	19	5	3	28	1

Dex Dose	≤ 5mg	6-10mg	11-20mg	> 20mg		
N= 64	1	49	13	1		

Table 5. Breakdown of Postoperative doses of methylprednisolone (MP), dexamethasone (Dex) and no steroid.

MP Dose	< 120mg	120 / 125mg	250mg	No Steroid
N= 64	9	54	1	N= 6

Dex Dose	≤ 5mg	6-10mg	> 10mg	
N= 54	7	45	2	

The 4th Question on the survey asked: Why do you use this steroid regimen? Respondents were provided with four options: 1) Familiarity with the regimen, 2) Regimen that was used during the surgeon's training, 3) Literature supporting the steroid regimen, and 4) Other. Respondents were able to select all, one or none of these options. Finally, a space was left at the end of this question for respondents to insert text justifying their use of a certain steroid regimen. Overall, we received 52 responses (42%) for familiarity, 82 (66%) for training, 22 (18%) for literature and 8 (6%) for other. Four text responses refer anecdotal experience and two respondents stated hospital protocols for justification of their steroid regimen.

3.4 DISCUSSION

The results of this cross-sectional, observational study show that among Canadian Oral and Maxillofacial (OMF) Surgeons there is no consensus on the most appropriate dose of perioperative or postoperative steroids for orthognathic surgery. This is in line with the study by Kormi et al. who found no consensus among OMF surgeons in Finland regarding steroid regimens for craniomaxillofacial surgery[6].

Our survey showed that all surgeons performing orthognathic surgery use perioperative steroids. Overall, a total of 18 different steroid regimens were reported. Respondents were split in half between using methylprednisolone and dexamethasone. Within the methylprednisolone group, the two most popular perioperative doses were 1000mg and 120/125mg. When grouping similar doses of steroids, a total of ten different perioperative steroid regimens was seen.

Surgeons favored methylprednisolone over dexamethasone postoperatively, but this was not found to be significant (P >0.05). The most popular postoperative regimen of steroids was methylprednisolone 120/125mg. Six surgeons (4.8%) did not use postoperative steroids and 26 surgeons (20.1%) administered additional intramuscular methylprednisolone during the patient's hospital stay. When grouping similar postoperative steroid doses, a total of seven different regimens was noted.

Overall, no consensus was seen among Canadian OMF Surgeons regarding perioperative or postoperative steroid dosing. Multiple different steroid regimens are used nationwide and surgeon's rationale for using different steroid regimens varied widely. No relevant literature or clinical studies were cited by respondents when asked to justify the use of a particular steroid regimen. Our findings are in keeping with previously published studies[6,146]. Additional high-

quality evidence is needed to support the use of high-dose intraoperative steroids in orthognathic surgery.

CHAPTER 4. PROSPECTIVE RANDOMIZED CONTROL TRIAL

4.1 PURPOSE OF THE STUDY

The aim of this prospective, double-blinded randomized control trial is to evaluate the effects of perioperative steroid dosing on postoperative outcomes.

The primary outcome measure is:

- To determine if a 125 milligram dose of perioperative methylprednisolone is as effective as a 1000 milligram dose for the prevention of facial swelling after orthognathic surgery.

The secondary outcome measures include:

1) To evaluate the effect of two perioperative steroid doses on patient-reported postoperative outcomes including:

- Pain

- Perceived swelling

- Nausea

- Vomiting

- Sleep

- Mood

2) To evaluate the effect of two perioperative steroid doses on postoperative outcomes including:

- Length of stay in hospital

- Postoperative infection

3) To measure postoperative swelling and describe its resolution after orthognathic surgery

4.2 ETHICS APPROVAL

Ethics approval was submitted to the Nova Scotia Health Authorities Research Ethics Board (NSHA REB) for clinical trial approval. Full NSHA REB approval was granted to the study on August 2, 2017 (NSHA REB ROMEO File# 1022601). The study THE PROSPECTIVE EVALUATION OF PERIOPERATIVE STEROID DOSING ON POSTSURGICAL EDEMA was registered on clinicaltrials.gov.

4.3 PATIENTS

A prospective evaluation of patients undergoing orthognathic surgery was conducted at the Department of Oral and Maxillofacial Surgery at the Queen Elizabeth II Health Sciences Centre, in Halifax, Nova Scotia, Canada. Patients were enrolled in the study from January 1, 2018 to February 21, 2019. Any patient undergoing Lefort 1 osteotomy, bilateral sagittal split osteotomies, functional genioplasty or any combination thereof, with or without the extraction of third molars was included and asked to enrol in our study.

Patients were excluded from our study based on the following criteria:

1) Patients with pertinent medical history that precludes the use of high-dose steroids including:

- Known hypersensitivity to steroids

- Type 1 diabetic patients

- Systemic fungal infections

- Latent tuberculosis

- Herpes simplex keratitis

- Acute psychoses

- Cushing's syndrome

- Peptic ulcer disease

- Pregnant patients

- Breast feeding mother

- Markedly elevated creatinine

2) Patients undergoing maxillomandibular advancement surgery for the treatment of obstructive sleep apnea

3) Patients who suffered an undesired buccal plate fracture during BSSO procedure

4.4 CONSENT

The study protocol and risks of the study were explained in detail to all patients eligible for enrollment. This was carried out by one of the OMFS residents in clinic performing the patient's preoperative history and physical examination. If the patient agreed to participate, a signed consent form was obtained.

4.5 RANDOMIZATION

Patients were randomized into two groups using a 2:2 randomized block design. A computer-generated algorithm developed the randomization sequence which allowed for allotment of each patient into either 1000mg (group 1) or 125mg of methylprednisolone perioperatively. Patients were also assigned a numeric code by the resident performing their preoperative assessment. The dose of steroid to be used perioperatively was attached to the patient's preoperative assessment form and relayed to the anesthesiologist prior to surgery. The patient as well as the resident and research assistants conducting the data analysis were blinded to which steroid dose was used perioperatively.

4.6 STEROID PROTOCOL

Patients were assigned to either Group 1 or Group 2 based on the protocol described above. Patients assigned to Group 1 received 1000mg of methylprednisolone IV perioperatively. Patients assigned to Group 2 received 125mg of methylprednisolone IV perioperatively. All patients were ordered a total of 6 postoperative doses of methylprednisolone 125mg IV which was to be given every 4 hours.

4.7 PREOPERATIVE PROTOCOL

The day of surgery patients were assessed in the preoperative clinic by the anesthesiologist and surgical resident. Ibuprofen 600mg and Acetaminophen 650mg was given orally approximately thirty minutes prior to surgery.

4.8 SURGICAL PROTOCOL

Orthognathic surgery was performed under general anesthetic in the Victoria General Hospital in Halifax, Nova Scotia. The surgery was performed by one of six staff Oral and Maxillofacial Surgeons and his resident or fellow. Perioperative intravenous methylprednisolone, either 1000mg or 125mg, was administered by the anesthesiologist prior to surgical incision. A nasogastric tube was inserted by the anesthesiologist or surgeon prior to surgery.

4.9 POSTOPERATIVE PROTOCOL

All patients were taken to the post-anesthetic recovery unit after surgery. Their nasogastric tubes were put to suction and removed either 30 minutes after surgery or once drainage from the tube stopped. Ice was applied to the face bilaterally and instructions were given to all patients and their nurses to keep ice to the face on and off for the first 48 hours after surgery. All patients were prescribed liquid Ibuprofen 600mg orally to be given every 6 hours after surgery. All patients were prescribed liquid Acetaminophen 650mg orally to be given every 4 hours after surgery. A narcotic pain medication, usually hydromorphone 2-4mg orally or morphine 5-15mg subcutaneously, was given on an "as needed" basis after surgery. A postoperative appointment was held in the Oral and Maxillofacial Surgery clinic at the Victoria General Hospital immediately prior to discharge from hospital. Patients had to meet the following criteria prior to hospital discharge:

- The patient was ambulatory

- The patient had an adequate oral intake

- The patient's pain was adequately controlled with oral medications only

4.10 DATA COLLECTED AT THE TIME OF SURGERY

Data related to patient age, gender, BMI and duration of surgery were recorded on the patient's perioperative chart at the time of surgery. The procedure as well as the magnitude of movement of the Lefort 1 (LF), Bilateral Sagittal Split Osteotomy (BSSO) or Functional Genioplasty (FG) was recorded in millimeters by the attending surgeon. A positive number denoted an advancement whereas a negative value denoted a setback. The number of wisdom teeth removed at the time of surgery was also noted by the attending surgeon.

4.11 DATA COLLECTED AFTER SURGERY

Three-dimensional facial photographs were obtained after surgery to assess swelling. These were taken at each of the patient's scheduled follow-up appointments after surgery. Time points were labelled T1 (prior to hospital discharge), T2 (two weeks postoperative), T3 (four weeks postoperative), T4 (six weeks postoperative) and T5, T6, T7, etc... as needed for further timepoints.

Photographs labeled T1 (prior to hospital discharge) and T3 (four weeks postoperative) were compared for analysis of volume change. To further analyze facial swelling change over time, patients with at least four postoperative 3D facial photographs were included in this analysis (Section 5.10).

Patients were asked to complete a survey during their postoperative appointment immediately prior to hospital discharge. This survey can be found in Appendix A. Using a visual analog scale (VAS), patients were asked to report their:

- Perceived facial swelling

- Worst pain in hospital

- Pain at discharge

- Worst nausea

- Nausea at discharge

- Number of times vomited

- Restfulness of sleep in hospital

- Mood in hospital

For VAS scores involving swelling, pain and nausea a score of 0 indicated "none" or "least severe" and 10 indicated "worst" or "most severe". Restfulness of sleep was scored out of 10 on VAS, with 0 indicating "best sleep ever" and 10 indicating "worst sleep ever". Mood was also scored out of 10 on VAS, with 0 indicating "low mood" and 10 indicating "high mood".

Patient charts were accessed electronically and the number of days the patient was admitted to hospital after surgery was taken as their length of stay in hospital. If a patient was readmitted to hospital after discharge, these days were not counted in LOS.

Patient charts were followed until the patient was discharged from the surgeon's postoperative care at their "braces off" appointment. Surgical site infections that were documented during this period were noted.

4.12 POSTOPERATIVE FACIAL SCANNING PROTOCOL

4.12.1 IMAGE CAPTURE

Postoperative three-dimensional facial photographs were taken of all patients using the 3DMD facial scanner. Scans were taken immediately prior to hospital discharge (T1) and then at all postoperative visits with the surgeon. Each photograph taken after T1 was labelled in order (T2, T3, T4, etc.). A final photograph was taken when the patient presented for their "braces off" appointment (T0), at the completion of their orthodontic treatment.

Facial scans were obtained by dental assistants or OMFS residents. Patients were seated and positioned in the scanning field with a natural head position. Hair was tucked behind the ears and pulled off the forehead using hair elastics, pins or surgical caps if necessary. Patients were instructed to bite into their splint or into their back teeth if no splint was in place. They were asked to maintain a neutral facial expression for image capture. All captured images had patient identifiers as well as date and time stamps recorded.

4.12.2 IMAGE SELECTION AND QUALITY CONTROL

All images were assessed by two blinded observers (MF, JS) for quality control. Images of poor quality that precluded the ability to view and analyze the entire face were eliminated from the study (Figure 10). Excessive hair over the face and in front of the ears, growth of facial hair, facial expressions and lip or chin tape that obscured the view of the entire face and important facial landmarks were removed from the analysis of facial swelling.
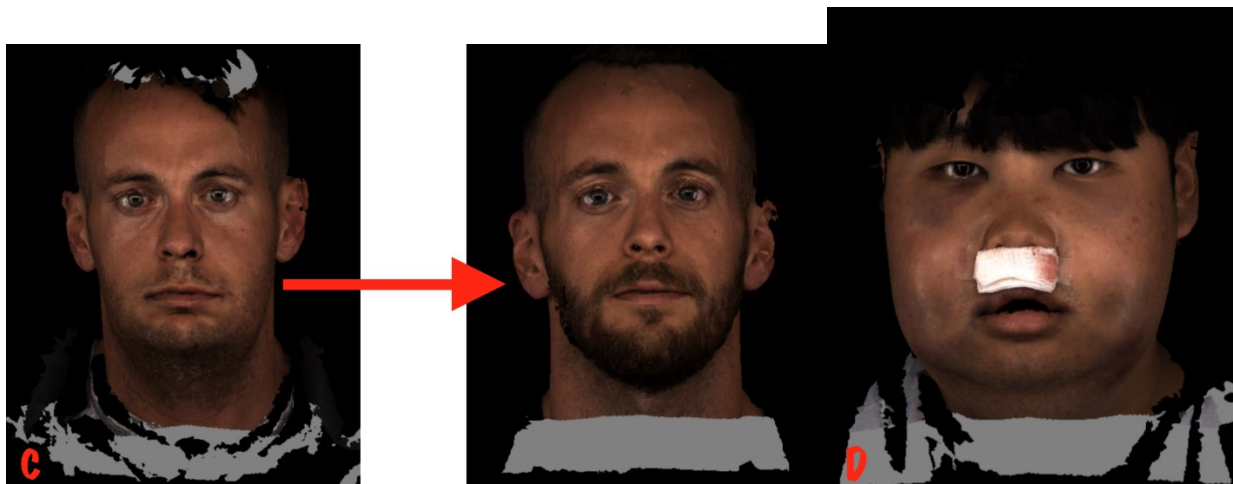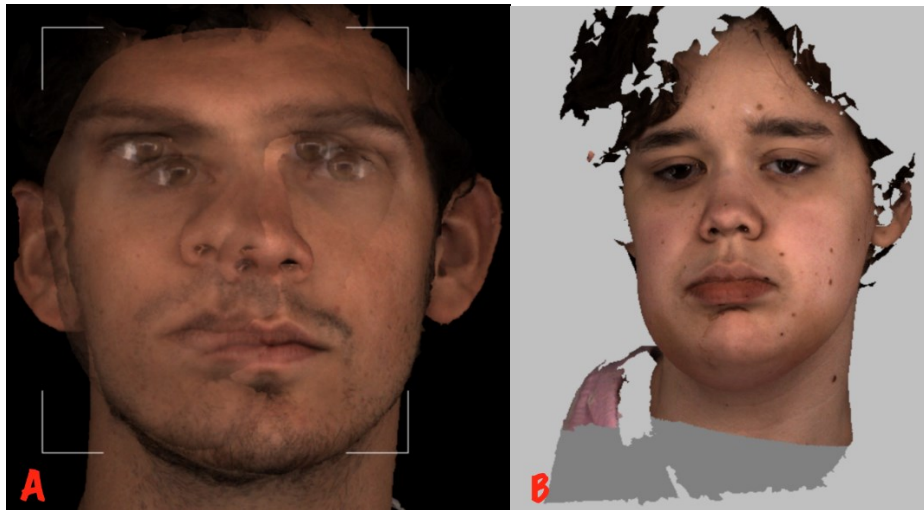
Figure 10. Examples of 3D photos removed from analysis. A) Improperly calibrated sensors leading to double image. B) Hair over forehead and hiding the ears. C) Growth of facial hair from T1 to T3 making volume calculation imprecise. D) Moustache dressing over face obscuring nasal landmarks and making volume calculation imprecise.

4.12.3 IMAGE ALIGNMENT AND CROPPING PROTOCOL

All images were viewed and processed using the 3DMDVultus software program. Images were first aligned in 3 planes using specific anatomic points and a grid system, similar to the protocol described by Kau and Van der Vlis[134]. In the frontal plane, the pupils were aligned on a horizontal grid line. In the right lateral view, a line passing from the middle of the tragus of the ear to the top of the ala of the nose was aligned with a horizontal grid line. In the bird's-eye and worm's-eye views the face was aligned with a grid lines using the malar prominences of the cheeks and bridge of the nose.

With the photos aligned, they were then cropped using a specific protocol (Figure 11). Using the right lateral image, a vertical line was placed 2cm anterior to the pretragal fold. This distance was measured using a grid system. This line is placed with its center perpendicular to the ala-tragus line. The vertical line was rotated 45 degrees forwards and the forehead and hair above this line was cropped out. This line was the reset to its vertical position and rotated backwards 22.5 degrees and the neck and shoulders below this line was cropped out.
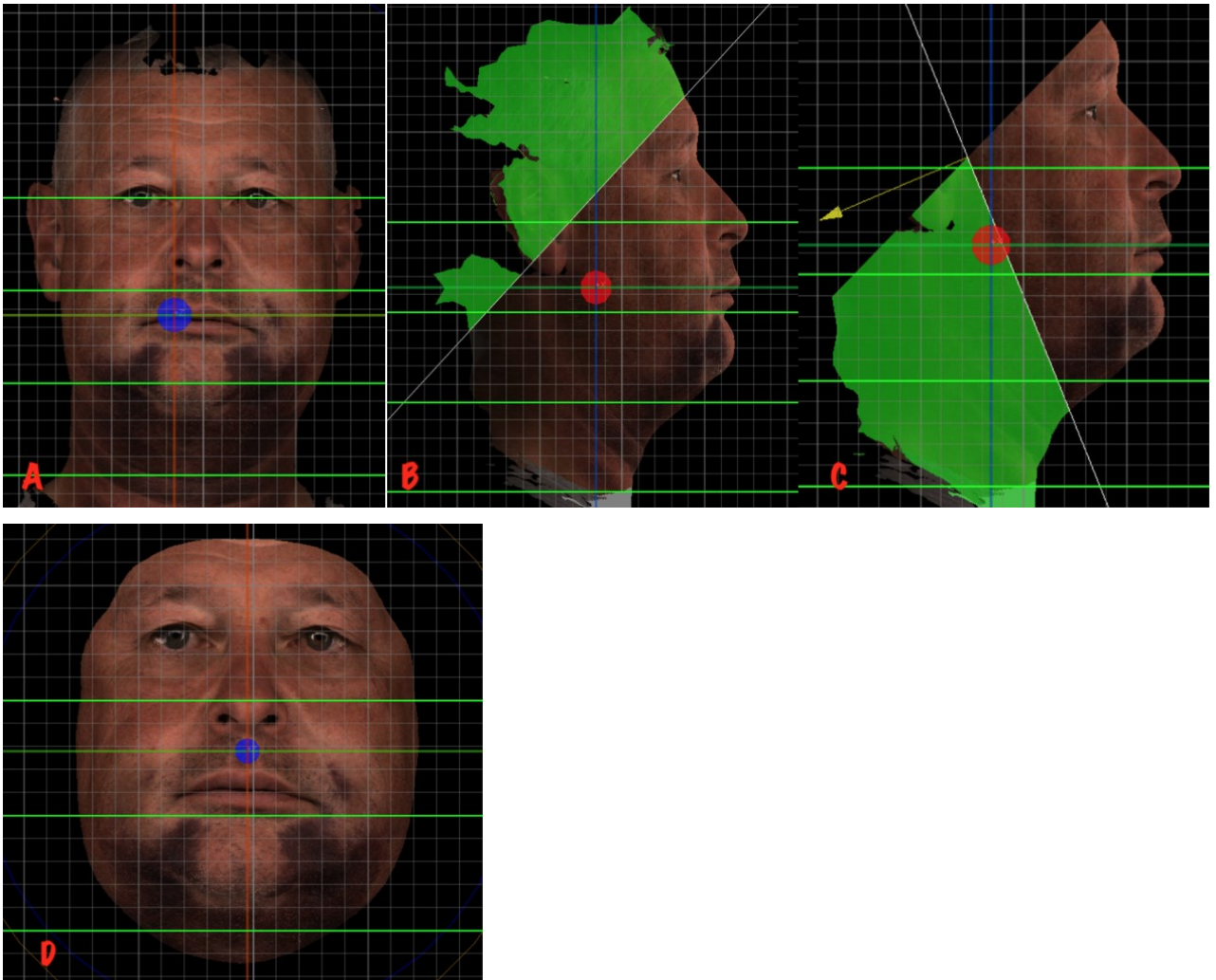
Figure 11. Image alignment and cropping protocol. A) The image is first aligned in 3 planes using the 3DMDVultus software and grid system. B) In the right lateral view, the forehead is cropped by placing a vertical line 2cm anterior to the pretragal fold and rotating it forward 45 degrees.   C) The neck is cropped by taking the same vertical line and rotating it backwards 22.5 degrees. D) A facial shell is created.

4.12.4 IMAGE OVERLAY AND VOLUME CALCULATION

When comparing two cropped images, they are first aligned one over the next using the grid system in 3 planes (frontal, right lateral and worm's or bird's-eye views) (Figure 12). Care is taken to align the forehead, bridge of the nose and the lateral and medial canthi. Next the superimposition tool is used to align one photo to the next using an area painted on the forehead and bridge of the nose with the paintbrush tool. A root mean squared (RMS) is generated, which indicated the level of agreement between the two superimposed images. The manufacturer recommends an RMS < 0.5mm. The RMS for all photos in our study was < 0.2mm.
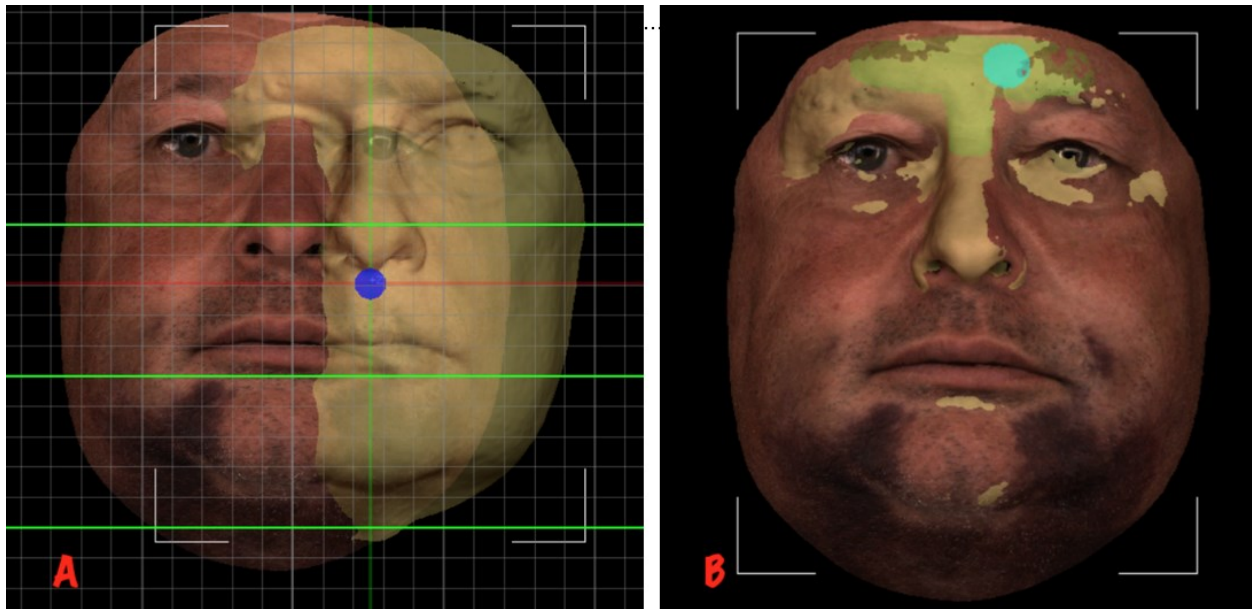
Figure 12. Image overlay and superimposition. A) The two facial shells are overlaid on each other using stable anatomic points, including the forehead, bridge of nose and medial and lateral canthi. This is performed in all 3 planes. B) The superimposition tool is used in the 3DMDVultus program. The paintbrush tool is used to outline an area over the forehead and bridge of nose for improved superimposition.

This method was described by Van der Meer[11] and Kau[12]. With the images

superimposed, the volume calculation tool was used to calculate the volume difference between

the two cropped and superimposed facial shells (Figure 13). All volumes were expressed in cubic

centimeters (cm^3). A histogram is generated which illustrates areas of the face where volume

changes were the greatest.
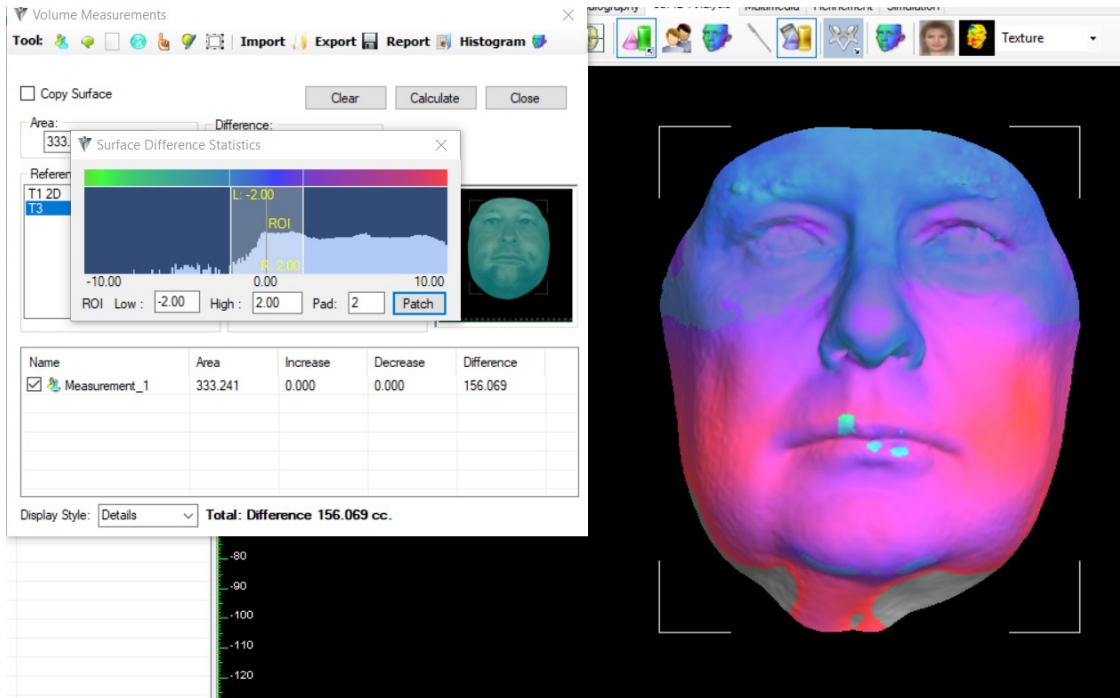
Figure 13. Volume calculation readout. Using the volume calculation tool in the 3dMDVultus software, a measurement is made of the volume difference between the two facial shells. This difference is expressed in cm^3. A histogram is generated showing the areas of the face where change in volume/swelling was greatest.

4.13 ASSESSMENT OF RELIABILITY OF IMAGE CROPPING AND ALIGNMENT PROTOCOL

A strict method for cropping was developed for overlaying and analyzing volume differences between two three-dimensional photographs of a patient taken at two different time points. The reproducibility of the method was assessed with intra- and interrater reliability testing.

Pairs of patient photographs were selected for assessment. Inclusion criteria for reliability testing was the presence of two photographs taken of the patient at two separate time points. Patients were excluded if at least one photo was not of adequate quality for assessment of facial swelling (i.e. hair over the face). For inter-rater reliability, two raters (MF, JS) calculated the volume difference between the two photos, independently. For intra-rater reliability, a single rater (JS) calculated the volume difference between the two photos on two different occasions, at least one week apart. Assessment of inter- and intrarater reliability was made using the Intraclass correlation coefficient (ICC). The ICC has an upper limit of 1.0, which indicates a perfect level of agreement. A number of different scales have been used to interpret Intraclass correlation coefficients. A guideline for interpretation of ICC is shown in Table 6. An ICC of 0.7 or higher is considered acceptable for research[147,148].

Table 6. Common guidelines for the interpretation of the intraclass correlation coefficient. Adapted from Koo TK, Li MY: A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. J Chiropr Med 15: 155, 2016.

ICC Interpretation	Intervals	
	Koo and Li (2017)	Cicchetti and Sparrow (1981)
Poor	<0.50	<0.40
Fair	0.50 - 0.75	0.40 - 0.60
Good	0.75 – 0.90	0.60 – 0.75
Excellent	0.90 - 1	0.75 – 1

4.14 STATISTICAL ANALYSIS

Statistical analysis of the data was performed by a statistician at the Research Methods Unit at the Centre for Clinical Research in the NSHA. Analyses were performed using SAS STAT software, version 12.1 (SAS Institute, Cary, NC) was used. All variables were divided into continuous and categorical variables. For all statistical tests, a 95% confidence interval was used and a P value less than 0.05 was considered statistically significant.

An initial sample size of 120 patients (60 in each group) was calculated using G*Power Software Version 3.1.9.4 (Franz Faul, Edgar Erdfelder, Albert-Georg Lang, and Axel Buchner, 2006, 2009), based on the following parameters:

- Power of 90%

- Significance level of 0.05

- An average facial swelling volume of $59.01cm^3$ and standard deviation of $8.11cm^3$ found in a similarly conduced study by Kau et al. (2007)[132]

- An in vivo repeatability coefficient of $5.9cm^3$ calculated by van der Meer et al. (2014) using the 3dMD facial scanner[11]

After a roughly 50% dropout rate was realized due to missed or insufficient quality photos, the sample size was increased to 250 patients to ensure an adequately powered study.

Group 1 and Group 2 were compared for each of the continuous and categorical variables. Continuous variables included: age (in years), BMI (in kg/m^2), surgery duration (in minutes), length of stay in hospital (in days), volume change (in cm^3), and number of times vomited. Pain, perceived swelling, nausea, sleep quality and mood were scored out of 10 on VAS.

Categorical variables were divided into dichotomous and polychromatous variables. Dichotomous variables included: group (1000mg vs 125mg methylprednisolone), sex (male/ female) and presence of infection (yes/ no). Procedure type (any combination of Lefort, BSSO, FG) was the only polychromatous categorical variable tested.

For normally distributed data sets, a Pearson's correlation was used to compare two continuous variables, a student's t-test was used to compare continuous variables and dichotomous categorical variables and an analysis of variance test (ANOVA) was used to compare polychromatous categorical variables.

For non-parametric data, a Wilcoxon rank-sum test was used to compare continuous variables and dichotomous variables. Chi-squared test was used to compare dichotomous categorical variables. A Spearman correlation was used to compare the strength of association between two continuous variables. An analysis of variance test (ANOVA) was used to compare polychromatous categorical variables. A multivariate analysis was used, when appropriate, to further investigate the association between patient and surgical factors and facial swelling.

CHAPTER 5. RESULTS

5.1 RELIABILITY OF THE 3DMD FACIAL SCANNER FOR ASSESSMENT OF FACIAL VOLUME

In total, thirty patients were randomly selected for inter- and intrarater reliability testing. All time points between the two photographs were at least 26 days apart. For interrater calculations, the mean difference between measurements was 2.05 ± 6.00 cm3. The ICC for interrater reliability was excellent being 0.93 (95% confidence interval (CI) = 0.86 to 0.97). For intrarater calculations, the mean difference between measurements was 0.81 ± 6.68 cm3 and the ICC was excellent at 0.95 (95% CI= 0.90 to 0.98).

5.2 PATIENT DEMOGRAPHICS

The demographics for all patients are shown in Table 7. A total of 250 participants with an average age of 26.2 ± 12.0 years were enrolled in the study. This included 80 males and 170 females with an average BMI of 25.3 ± 5.8 kg/m^2. The average duration of surgery for all patients was 131.4 ± 45.7 minutes with a mean length of stay in hospital of 1.91 ± 0.66 days. 28 patients (11%) underwent LF only, 62 (25%) underwent BSSO only, 111 (44%) had LF/ BSSO, 32 (13%) had LF/ BSSO/ FG, 9 (4%) had LF/ FG and 8 patients (3%) had BSSO/ FG procedures.

Table 7. Demographics and surgical factors for all patients.

Variables	n (%)	Mean ± SD
Age (years)		26.2 ± 12.0
Gender		
male	80 (32%)	
female	170 (68%)	
BMI (kg/m^2)		25.3 ± 5.8
Duration of surgery (minutes)		131.4 ± 45.7
Length of stay (days)		1.91 ± 0.66
Procedure		
LF	28 (11%)	
BSSO	62 (25%)	
LF/ BSSO	111 (44%)	
LF/ BSSO/ FG	32 (13%)	
LF/ FG	9 (4%)	
BSSO/ FG	8 (3%)	

5.3 GROUP DISTRIBUTION

The group comparison for patient and surgical factors is shown in Table 8. Group 1 consisted of 129 patients, 46 males and 83 females, with a mean age of 26.8 ± 12.7 years and BMI of 24.9 ± 5.6 kg/m^2. Group 2 consisted of 121 patients, 34 males and 87 females, with a mean age of 25.6 ± 11.3 years and BMI of 25.7 ± 6.0 kg/m^2. None of the patient factors were different between groups (all $P > 0.05$).

Patients in Group 1 had a mean duration of surgery of 136.9 ± 48.0 minutes and averaged 1.96 ± 0.69 days in hospital. The time from surgery to taking the T1 photo was 1.8 ± 0.6 days and 38.5 ± 16.0 for the T3 photo for this group. In Group 1, 13 patients underwent LF, 30 had BSSO, 58 had LF/ BSSO, 18 had LF/ BSSO/ FG, 4 had LF/ FG and 6 had BSSO/ FG. Patients in Group 2 had a mean duration of surgery of 125.6 ± 42.6 minutes and averaged 1.85 ± 0.61 days

in hospital. The time from surgery to taking the T1 photo was 1.7 ± 0.5 days and 38.4 ± 12.7 for the T3 photo for this group. In Group 2, 15 patients underwent LF, 32 had BSSO, 53 had LF/ BSSO, 14 had LF/ BSSO/ FG, 5 had LF/ FG and 2 had BSSO/ FG. None of the surgical factors were different between groups (all $P > 0.05$).

Table 8. Demographics and surgical factors for all patients between groups.

Variables	Group 1		Group 2		P- value
	n (%)	Mean ± SD	n (%)	Mean ± SD	
Age (years)		26.8 ± 12.7		25.6 ± 11.3	0.52
Gender					0.20
male	46 (36%)		34 (28%)		
female	83 (64%)		87 (72%)		
BMI (kg/m^2)		24.9 ± 5.6		25.7 ± 6.0	0.41
Duration of surgery (minutes)		136.9 ± 48.0		125.6 ± 42.6	0.08
Length of stay (days)		1.96 ± 0.69		1.85 ± 0.61	0.19
Infection					0.62
No	116 (90%)		111 (92%)		
Yes	13 (10%)		10 (8%)		
Procedure					N/A*
LF	13 (10%)		15 (12%)		
BSSO	30 (23%)		32 (26%)		
LF/ BSSO	58 (45%)		53 (44%)		
LF/ BSSO/ FG	18 (14%)		14 (12%)		
LF/ FG	4 (3%)		5 (4%)		
BSSO/ FG	6 (5%)		2 (2%)		

* No P-value calculated for procedure due to small n for LF/ FG and BSSO/ FG subgroups.

5.4 EFFECT OF STEROID DOSE ON SWELLING

Of the 250 patients enrolled, 102 had either had missing photos at T1 or T3, or their photos were of insufficient quality to be analyzed and were excluded. This left 148 (59.2%) patients that had photos taken at T1 and T3 that were of adequate quality for analysis of facial swelling.

Average facial swelling for Group 1 was $42.5 \pm 23.8cm^3$ and for Group 2 was $45.3 \pm 30.0cm^3$ (P= 0.90). There was no significant difference between these two groups with respect to patient age, gender or BMI (all P > 0.05). No difference between Group 1 and Group 2 was found with respect to duration of surgery and length of stay in hospital (both P > 0.05).

When comparing swelling, five patients were identified whose postoperative facial swelling was greater than two standard deviations (SD) from the group mean facial swelling. All patients were in the 125mg group. This is shown in Figure 14. The patient and surgical variables for these outliers are shown in Table 9. Two of these patients underwent LF/ BSSO/ FG, two had BSSO and one had LF/ BSSO. These five patients were operated on by 3 of the 6 total surgeons.

When reviewing the medical histories, medication and anesthesia records for the 5 outliers, two patients had attention deficit hyperactivity disorder and took stimulant medications. One patient had celiac disease and had an allergy to gluten. The remaining two patients were healthy. None of the 5 outliers had medication allergies. All outliers received all intraoperative and postoperative doses of methylprednisolone and took ibuprofen, as prescribed. None of the outliers received sugammadex postoperatively, which could potentially bind steroid rendering it ineffective. These five patients were removed from the analysis of facial swelling between groups to allow for comparison of two normally distributed populations and the use of parametric testing.
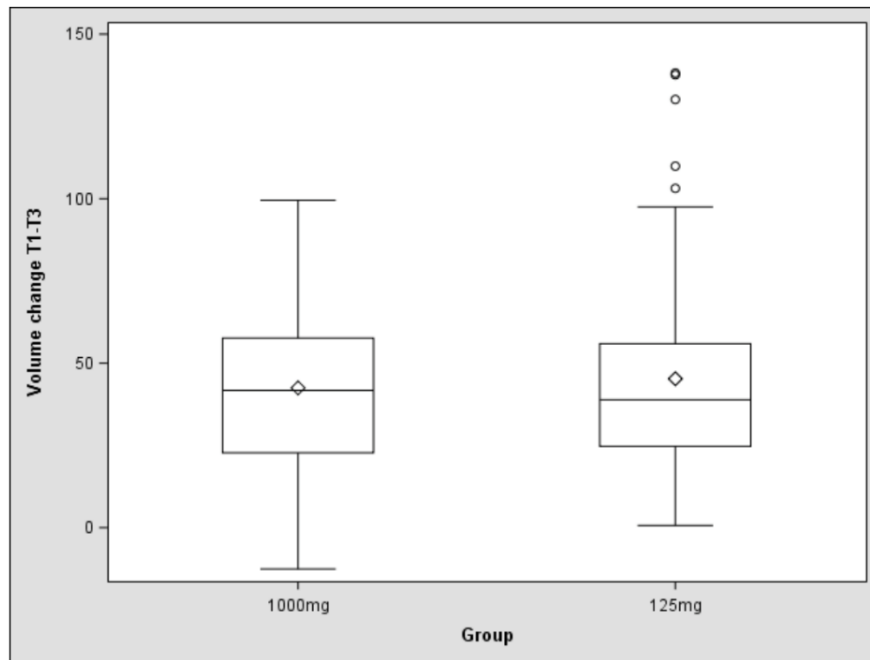
Figure 14. Box plot of swelling vs group. Five outliers are seen in the 125mg group, having facial swelling greater than 2SD from the mean facial swelling in that group.

Table 9. Patient and surgical variables for outliers in facial swelling.

Variables	No Outlier for Volume (n= 143)		Volume > 100cm^3 (n=5)		P Value
	n (%)	Mean ± SD	n (%)	Mean ± SD	
Age (years)		26.6 ± 12.2		16.8 ± (1.1)	0.08
Gender					0.66
male	44 (31%)		2 (40%)		
female	99 (69%)		3 (60%)		
BMI (kg/m^2)		25.0 ± 5.4		23.1 ± 4.4	0.41
Group					0.019*
1000mg	76 (53%)			0 (0%)	
125mg	67 (47%)			5 (100%)	
Swelling (cm^3)		41.0 ± 22.6		123.8 ± 16.3	<0.001*
Duration of surgery (minutes)		131.3 ± 43.6		126.2 ± 37.6	0.78
Length of stay (days)		1.9 ± 0.6		1.8 ± 0.4	0.62

* denotes statistical significance

5.4.1 EFFECT OF STEROID DOSE ON SWELLING AFTER OUTLIERS REMOVED

With these 5 outliers removed, there was 143 patients remaining for analysis of facial swelling. Group 1 included 76 patients, 26 males and 50 females, with an average age of 27.0 ± 12.8 years and BMI of $24.7 \pm 6.0 kg/mg^2$. Group 2 included 67 patients, 18 males and 49 females, with an average age of 26.2 ± 11.6 and BMI of $25.3 \pm 4.7 kg/m^2$. No patient factors differed between groups (all $P > 0.05$).

Duration of surgery for Group 1 patients was 135.4 ± 44.2 minutes, with a LOS of 1.96 ± 0.64 days. Group 1 included 11 LF, 13 BSSO, 36 LF/ BSSO, 10 LF/ BSSO/ FG, 2 LF/ FG and 4 BSSO/ FG. In Group 2, duration of surgery was 126.7 ± 42.8 minutes, with a LOS of 1.85 ± 0.58 days. Group 2 included 7 LF, 17 BSSO, 35 LF/ BSSO, 5 LF/ BSSO/ FG, 2 LF/ FG and 1 BSSO/ FG. There was no difference in surgical factors between groups (all $P > 0.05$). Patient and surgical variables for the cohort undergoing analysis of facial swelling is found in Table 10.

Table 10. Patient and surgical factors for patients undergoing facial swelling analysis (n= 143).

Variables	Group 1		Group 2		P- value
	n (%)	Mean ± SD	n (%)	Mean ± SD	
Age (years)		27.0 ± 12.8		26.2 ± 11.6	0.95
Gender					0.34
male	26 (34%)		18 (27%)		
female	50 (66%)		49 (73%)		
BMI (kg/m^2)		24.7 ± 6.0		25.3 ± 4.7	0.17
Duration of surgery (minutes)		135.4 ± 44.2		126.7 ± 42.8	0.27
Length of stay (days)		1.96 ± 0.64		1.85 ± 0.58	0.25
Swelling (cm^3)		42.5 ± 23.8		39.4 ± 21.2	0.42
Time to T1 (days)		1.78 ± 0.58		1.69 ± 0.47	0.42
Time to T3 (days)		38.5 ± 16.0		38.9 ± 13.0	0.62
Infection					0.99
no	68 (89%)		60 (90%)		
yes	8 (11%)		7 (10%)		
Procedure					N/A*
LF	11 (14%)		7 (10%)		
BSSO	13 (17%)		17 (25%)		
LF/ BSSO	36 (47%)		35 (52%)		
LF/ BSSO/ FG	10 (13%)		5 (7%)		
LF/ FG	2 (3%)		2 (3%)		
BSSO/ FG	4 (5%)		1 (1%)		

* No P-value calculated for procedure due to small n for LF/ FG and BSSO/ FG subgroups

Facial swelling in patients who received 1000mg of methylprednisolone perioperatively was measured to be 42.5 ± 23.8 cm^3, compared to 39.4 ± 21.2 cm^3 in patients who received 125mg of methylprednisolone perioperatively. This difference was not statistically significant (t= 0.82, P= 0.42). A multivariate regression analysis was performed to independently evaluate the effect of steroid dose on swelling while controlling for patients variables of age, BMI and gender, as well as other surgical variables of surgery type and duration. After adjusting for these patient and surgical variables, we found no statistically significant association between steroid

group and facial swelling (F= 0.01, P= 0.91).). Again, when keeping the 5 outliers and using non-parametric testing, the difference in facial swelling between groups was still not statistically significant (P= 0.90).

5.5 EFFECT OF STEROID DOSE ON SECONDARY OUTCOMES

A total of 172 patients completed surveys prior to hospital discharge. The demographics of these patients is shown in Table 11. There was no significant difference between patients in Group 1 and 2 with respect to patient and surgical factors (all P > 0.05).

Table 11. Patient and surgical factors for patients who completed surveys (n= 172).

Variables	Group 1		Group 2		P- value
	n (%)	Mean ± SD	n (%)	Mean ± SD	
Age (years)		26.4 ± 12.1		24.4 ± 10.3	0.25
Gender					0.62
male	26 (32%)		26 (29%)		
female	55 (68%)		65 (71%)		
BMI (kg/m^2)		24.5 ± 4.4		25.1 ± 5.7	0.44
Duration of surgery (minutes)		135.5 ± 43.5		123.7 ± 39.8	0.07
Length of stay (days)		1.93 ± 0.57		1.89 ± 0.61	0.69
Procedure					N/A*
LF	8 (10%)		13 (14%)		
BSSO	19 (23%)		24 (26%)		
LF/ BSSO	36 (44%)		39 (43%)		
LF/ BSSO/ FG	12 (15%)		10 (11%)		
LF/ FG	4 (5%)		4 (5%)		
BSSO/ FG	2 (3%)		1 (1%)		

* No P-value calculated for procedure due to small n for LF/ FG and BSSO/ FG subgroups

Results of patient reported secondary outcomes, separated into Group 1 and Group 2, is shown in Table 12. The steroid dose given perioperatively did not have an effect on patient reported swelling, worst pain, pain at POD2, worst nausea, nausea at POD2, vomiting or sleep quality (all $P > 0.05$). Steroid dose did have a significant effect on mood, with Group 2 having a better mood score than Group 1 ($P= 0.05$).

Table 12. Patient reported outcomes between groups.

Variables	Group 1		Group 2		P- value
	Mean ± SD	n	Mean ± SD	n	
Perceived Swelling	5.65 ± 2.09	81	5.67 ± 2.21	91	0.91
Worst Pain	5.82 ± 2.08	81	6.02 ± 2.28	91	0.54
Pain POD2	3.45 ± 1.88	81	3.37 ± 2.01	91	0.68
Worst Nausea	3.75 ± 3.12	81	3.58 ± 4.00	91	0.31
Nausea POD2	1.05 ± 1.91	81	1.12 ± 2.19	91	0.49
Vomiting (# of episodes)	0.91 ± 1.68	81	0.53 ± 1.23	91	0.23
Sleep Restfulness	4.72 ± 2.43	81	4.93 ± 2.43	91	0.64
Mood	5.19 ± 2.27	56	6.03 ± 2.00	57	0.05*

* denotes statistical significance

The length of stay in hospital for patients in Group 1 was $1.96 ± 0.69$ days and in Group 2 was $1.85 ± 0.61$ days. This was not significant ($P= 0.19$). Infection rates were not significantly different between groups ($P= 0.62$). Thirteen patients (10%) in Group 1 developed post-operative infections, compared to ten patients (8%) in Group 2.

5.6 EFFECT OF PATIENT FACTORS ON SWELLING

In our study, younger patients were found to swell more after surgery, with Spearman correlation coefficient showing a weak negative correlation between patient age and postoperative facial swelling (r_s= -0.194). A Spearman correlation coefficient over 0.7 illustrates a strong correlation between variables. When removing the effect of other patient and surgical variables, however, younger age was found to have a significant positive effect on postoperative swelling (F= 5.93, P= 0.02). No correlation was found between BMI and swelling (r_s= -0.024). Gender was not shown to influence swelling (X^2= 1.41, P= 0.16).

5.7 EFFECT OF SURGICAL FACTORS ON SWELLING

Mean facial swelling of patients grouped by procedure is shown in Table 13. Patients who underwent LF/ BSSO/ FG had the most swelling (61.5 ± 28.1 cm^3) and the LF group had the least measured swelling (34.5 ± 27.32cm^3). The difference in facial swelling between procedures was found to be statistically significant (X^2= 11.49, P= 0.043). When performing multivariate analysis controlling for patient and other surgical variables, procedure was shown to significantly affect measured swelling (F=2.65, P= 0.03).

There was a statistically significant difference in the duration of surgery between procedure groups (X^2= 140.98, P < 0.001), with BSSO requiring the least time to complete (87 ± 23.8 minutes) and LF/ BSSO/ FG taking the longest (180.3 ± 29.2). The relation between procedure and surgical duration is shown in Figure 15.

Duration of surgery had a weak positive correlation with facial swelling. This correlation was not found to be statistically significant (r_s= 0.136).

Table 13. Facial swelling grouped by procedure (n= 148).

Procedure	n (%)	Mean Swelling (cm3) ± SD	P- value
			0.043*
LF	18 (13%)	34.5 ± 27.3	
BSSO	30 (21%)	43. 7 ± 31.9	
LF/ BSSO	71 (50%)	42. 1 ± 22.7	
LF/ BSSO/ FG	15 (10%)	61.5 ± 28.1	
LF/ FG	4 (3%)	42.0 ± 14.9	
BSSO/ FG	5 (3%)	44.0 ± 35.8	

* Denotes statistical significance
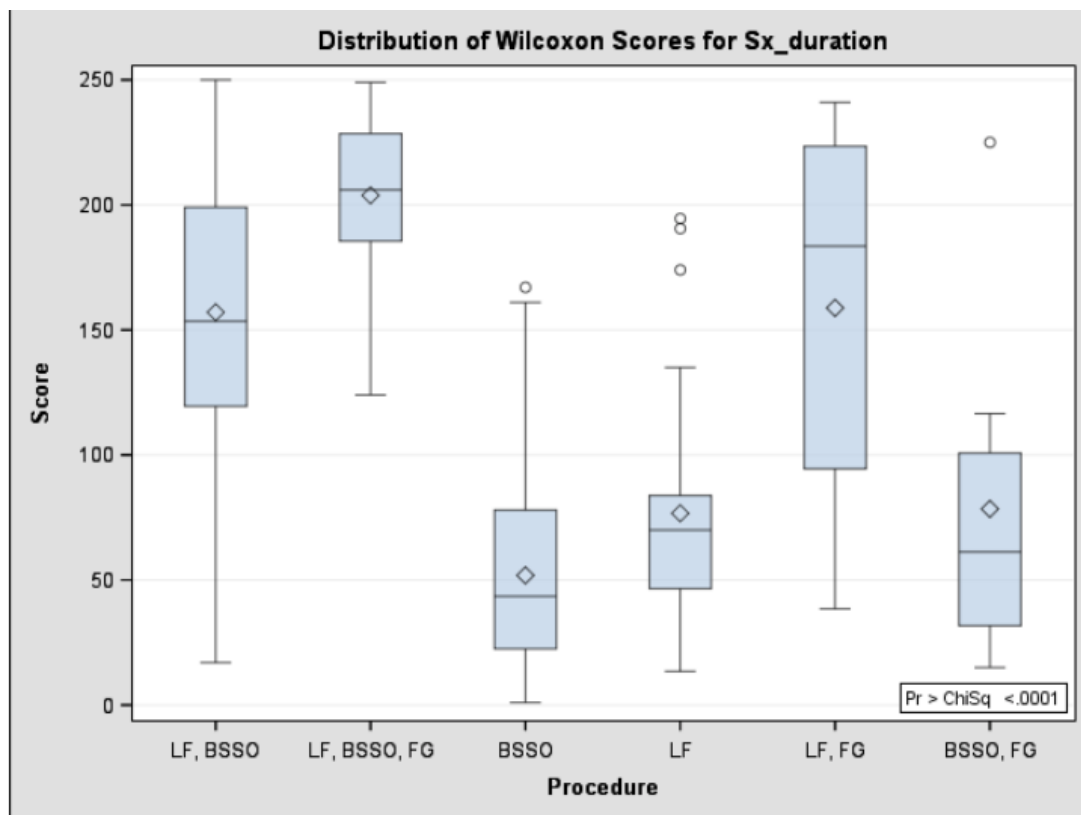
Figure 15. Duration of surgery for each procedure group.

5.8 EFFECT OF PATIENT FACTORS ON SECONDARY OUTCOMES

Patient-reported secondary outcomes and length of stay in hospital were not found to be associated with patient factors of age, gender or BMI (all P >0.05). The association between patient factors and patient-reported secondary outcomes, as well as LOS is shown in Table 14.

Rates of postoperative infection were found to be correlated to patient age (Z= 0.0063, P= 0.013). The average age of patients experiencing post-operative infection (32.4 ± 15.0 years) was significantly higher than the age of patients who did not have infection (25.6 ± 11.6 years). Gender (X^2= 0.40, P= 0.52) and BMI (Z= 0.1139, P= 0.22) were not correlated to infection rates after surgery. Rates of infection were roughly equal between males (8%) and females (10%) and the average BMI of patients with infection (26.2 ± 5.2kg/m^2) was not significantly different than the BMI of patients without infection (25.2 ± 5.9kg/m^2).

Table 14. Effect of patient factors on patient-reported secondary outcomes and LOS.

| Variables | Gender | | | Age | BMI |
	Male Mean ± SD	Female Mean ± SD	*P-value*	r_s	r_s
Perceived Swelling	5.79 ± 2.07	5.60 ± 2.18	0.78	0.093	0.070
Worst Pain	5.63 ± 2.19	6.05 ± 2.17	0.34	0.012	-0.042
Pain POD2	3.18 ± 2.02	3.50 ± 1.91	0.30	-0.096	-0.095
Worst Nausea	3.00 ± 2.96	3.94 ± 3.82	0.17	0.043	-0.066
Nausea POD2	0.68 ± 1.31	1.25 ± 2.28	0.22	0.108	0.027
Vomiting (# of episodes)	0.80 ± 1.72	0.68 ± 1.35	0.38	-0.018	-0.141
Sleep Restfulness	5.17 ± 2.21	4.68 ± 2.51	0.22	0.150	0.068
Mood	5.50 ± 2.16	5.66 ± 2.18	0.68	0.139	0.153
LOS (days)	2.0 ± 0.7	1.9 ± 0.6	0.16	0.047	0.061

r_s= Spearman Correlation Coefficient; a coefficient >0.7 represents a strong correlation.

5.9 EFFECT OF SURGICAL FACTORS ON SECONDARY OUTCOMES

Patient-reported outcomes of worst pain, pain on POD2, worst nausea, nausea on POD2, sleep restfulness and mood were not significantly correlated with the surgical factors of procedure type or duration of procedure (all P > 0.05). Patient perceived swelling was shown to be significantly correlated to procedure type (X^2= 18.21 P= 0.0027). Patients who did not undergo a BSSO procedure as part of their treatment reported less swelling than patients who had a mandibular surgery. This is shown in Figure 16. The number of vomiting episodes after surgery was found to correlate with surgery type (X^2= 19.55, P= 0.0015), with patients who did not undergo LF procedure having significantly less vomiting. Table 15 shows the effect of surgical factors on patient-reported secondary outcomes and length of stay in hospital.

Length of stay in hospital showed a significant correlation to procedure as well. Patients who did not undergo a LF procedure had significantly shorter stays after surgery than patients who did undergo a LF as part of their treatment (X^2= 99.59, P <0.001). In our study, infection was found to be associated with BSSO surgery as 0 of 23 infections that occurred in our study were in the LF or LF/ FG groups. A fisher's exact test found a significant association of infection with BSSO (X^2= 4.40, P= 0.03). Infection was not correlated to duration of surgery (X^2= 0.44, P= 0.51).
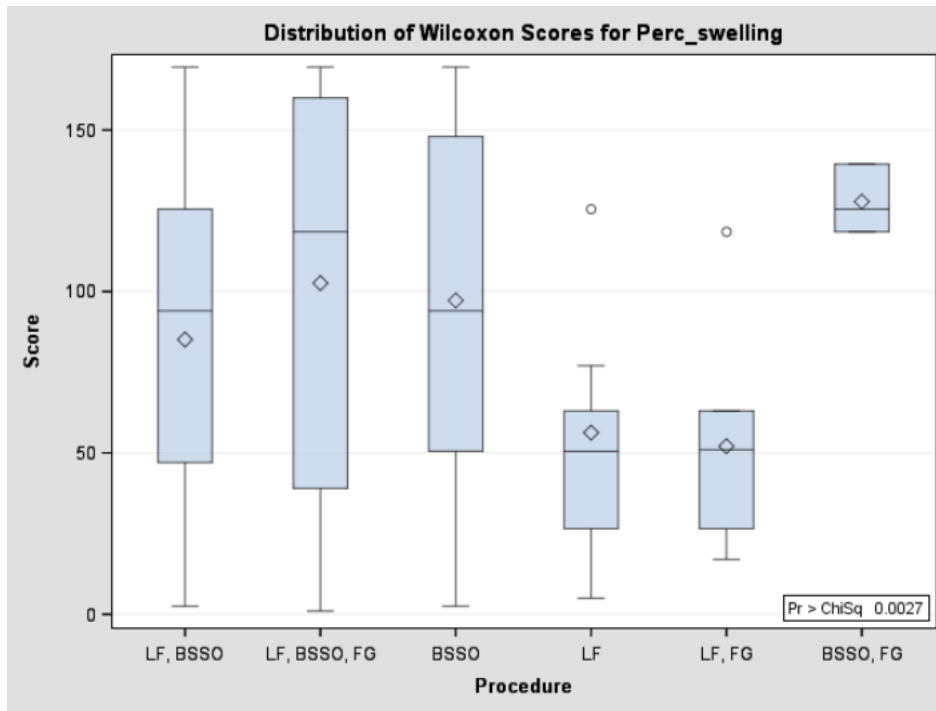
Figure 16. Patient-perceived swelling by procedure.

Table 15. Effect of procedure and duration of surgery on patient-reported outcomes and LOS.

Variables	Procedure		Duration of Surgery
	X^2	P-value	r_s
Perceived Swelling	18.21	0.027*	-0.018
Worst Pain	1.18	0.947	-0.082
Pain POD2	5.38	0.370	-0.178
Worst Nausea	6.49	0.261	0.124
Nausea POD2	4.70	0.453	0.071
Vomiting (# of episodes)	19.55	0.0015*	0.343
Sleep Restfulness	4.25	0.514	-0.069
Mood	4.09	0.537	-0.122
Length of Stay (days)	98.59	<0.001*	0.582

r_s= Spearman Correlation Coefficient; a coefficient >0.7 represents a strong correlation.
*denotes statistical significance

5.10 SWELLING CHANGE OVER TIME

An analysis of swelling change over time was performed. For this analysis, patients were selected based on the following criteria:

1) 3D photos taken at T1 and T5 and at least 2 other time points (T2, T3, T4 and/or T6).

2) All photos must be of sufficient quality for analysis of volume.

A total of 37 patients were included in this analysis, with an average age of 28.2 ± 12.2, including 9 males (24%) and 28 females (86%) with an average BMI of $25.4 \pm 5.3 \text{kg/m}^2$. The average duration of surgery was 135.0 ± 46.0 minutes. This cohort included 4 LF, 9 BSSO, 15 LF/ BSSO, 6 LF/ BSSO/ FG, 2 LF/FG and 1 BSSO/FG. Seventeen of these patients received 1000mg of methylprednisolone perioperatively, twenty received 125mg.

Volume change for the analysis of swelling resolution (or change) over time was taken as a difference from time point T5. The median number of days after surgery for T5 point was 71 days (10.1 weeks). The facial shell volume of each individual time point minus the facial shell volume at T5 represents the amount of swelling (in cm3) present at that time point. The average swelling and number of days after surgery at each time point is shown in Table 16.

Table 16. Analysis of swelling resolution over time.

Time Point	Time after surgery (days)	Δ Time (days)	Swelling (cm^3) Mean ± SD	Δ Swelling (cm^3)	Rate of swelling change (cm^3/day)	Swelling Reduction (%)	P-value*
T1	2	-	52.7 ± 31.7	-	-	-	-
T2	15	13	16.9 ± 11.4	35.73	2.75	67.9	< 0.001
T3	28	13	9.3 ± 8.7	7.60	0.58	82.3	< 0.001
T4	42	14	6.8 ± 8.4	2.52	0.18	87.1	< 0.001
T5	71	29	0	6.81	0.23	100	< 0.001
T6	87	16	-0.3 ± 1.7	0.31	0.002	100.6	0.23

Abbreviations: Δ= change in (value)
*Significance of swelling change from previous measured value.

All patients experienced a statistically significant reduction in swelling over time to T5 (P < 0.001). On average, roughly two-thirds of swelling was resolved by the end of the second postoperative week (T2), and after six weeks only 15% of the initial swelling remained. The rate of swelling resolution was greatest between the first two time points, T1 and T2 (Figure 17). When divided into Group 1 (n=17) and Group 2 (n=20), there was no statistically significant difference in the resolution of swelling over time (F= 54.71, P= 0.7688). Resolution of swelling over time plotted for Group 1 and Group 2 is shown in Figure 18.
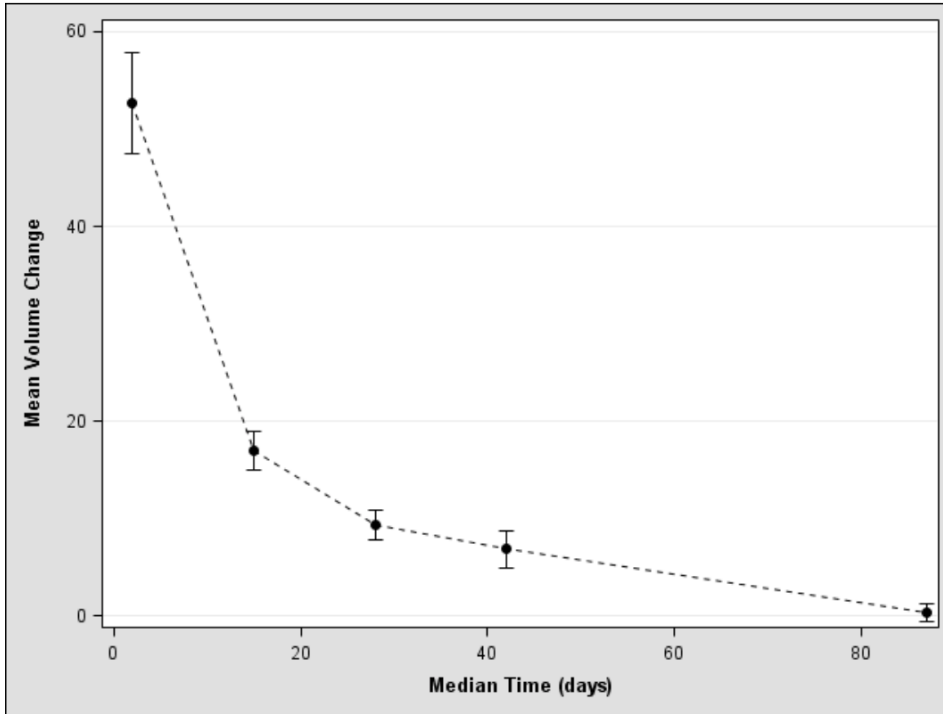
Figure 17. Rate of swelling resolution over time for all patients (n= 37).
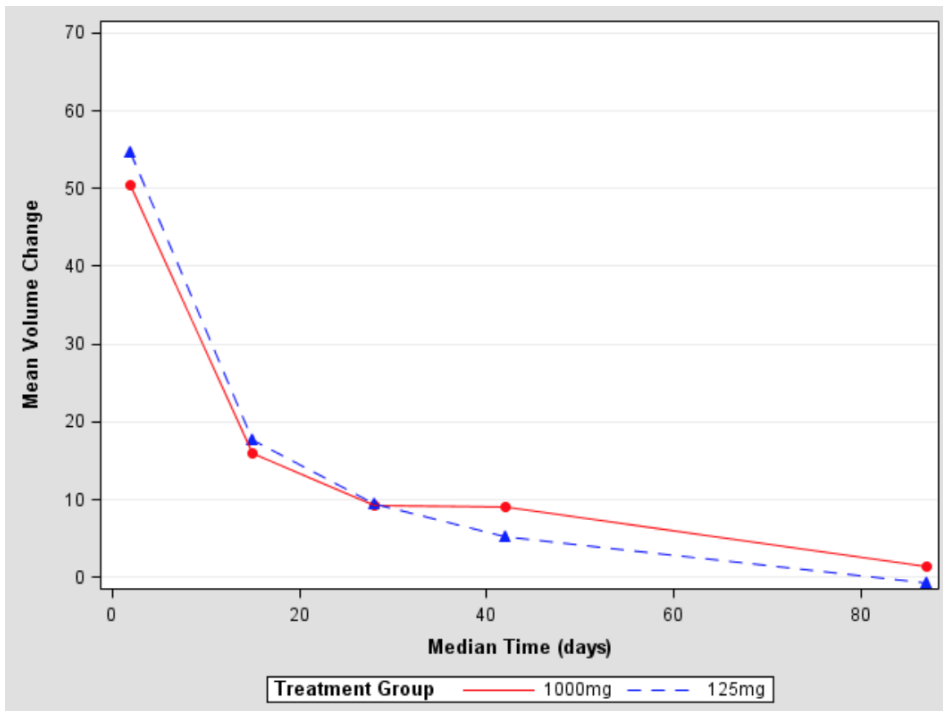
Figure 18. Rate of swelling resolution over time between groups.

CHAPTER 6. DISCUSSION

Orthognathic surgery includes a number of versatile procedures employed in the correction of dentofacial deformities. Despite being safe and reliable, many post-surgical sequalae arise which can be concerning for the patient and their care team, and can lead to delays in hospital discharge and return to function[2,149]. Due to the rich vasculature of the face, intense facial swelling is encountered after most orthognathic surgical procedures. Facial swelling is problematic as it contributes to postoperative pain, limits and delays enteral nutrition, impairs speech, and causes emotional distress for patients[3,31,32]. In rare cases, it can lead to airway compromise and prolonged periods of intubation[44,45].

Several methods are used by surgeons to limit facial swelling after surgery including careful surgical technique and the use of ice, non-steroidal anti-inflammatories, facial cooling devices, drains, taping and pressure dressings. The use of glucocorticoid therapy to limit and promote the resolution of facial swelling has been a mainstay in orthognathic surgery since the 1970's[1].

Despite a lengthy history of use in orthognathic surgery, most of the literature evaluating the efficacy of glucocorticoids as an anti-edema agent is weak. Many studies have employed crude or arbitrary methods for evaluation of swelling[112,116,123,136]. More recently, methods using three-dimensional technologies have been developed to more accurately quantify facial swelling[12,133,134]. Unfortunately most studies using these measurement tools are limited by small sample sizes[132,150]

Currently there is no consensus on the ideal type and dose of perioperative glucocorticoids for orthognathic surgery[4,5]. Systemic steroid therapy can have untoward consequences and a minimally effective dose should be used to avoid adverse steroid-related

events after orthognathic surgery. The primary purpose of our double-blinded, randomized control trial was to evaluate the effect of a smaller, 125mg perioperative dose of methylprednisolone on postoperative facial swelling, compared to our standard dose of 1000mg. Secondary outcomes measures included evaluating the effect of the higher steroid dose for prevention of pain, nausea and vomiting and assessing for adverse effects related to sleep, mood and postoperative infection. We also aimed to examine the correlation between these secondary outcome measures and patient factors (age, BMI, gender) as well as surgical factors (surgery type and duration). Finally, we wanted to describe the resolution of facial swelling after orthognathic surgery.

6.1 METHODOLOGICAL ASPECTS

Steroid doses of 1000mg and 125mg of methylprednisolone were chosen for comparison based on a number of factors. First, a dose of 1000mg of methylprednisolone given perioperatively for orthognathic surgery has been used at our center for over thirty years. A survey was sent out to the Canadian OMFS community to evaluate the use of perioperative steroids in orthognathic surgery and to help guide our choice of regimens for comparison. A 125mg dose of methylprednisolone was next most commonly used steroid regimen reported and this dose was selected for comparison with our standard dose of 1000mg. Due to the difference in biological half-life and differences in post-operative redosing schedules, dexamethasone was not used in this study for comparison with 1000mg of methylprednisolone. A comparison between methylprednisolone and dexamethasone would be an interesting basis for future studies. Finally, a control group (no steroid) was not used in our study as this would not be ethically responsible given the strong evidence supporting steroid use in orthognathic surgery.

The greatest challenge of this study was realizing a standardized follow-up for capturing 3D photographs to assess post-operative swelling. There was little difference between groups in the time after surgery that the T1 (Group 1= 1.8 ± 0.6 days, Group 2= 1.7 ± 0.5 days, P= 0.32) and T3 (Group 1= 38.5 ± 16.0 days, Group 2= 38.4 ± 12.7, P= 0.73) photographs were taken. This variance, especially further out from surgery, could potentially influence the magnitude of swelling calculated. Similar studies (Kau, Van der Vlis and Yamamoto et al.) did not disclose if postoperative images were taken at the exact time points (to the day) stated in their study protocol[132–134]. Missed photographs and poor photo quality were also limiting factors in data analysis. Due to these factors, only 59.2% of study participants were included in the analysis.

Factors involved in determining when photographs were taken after surgery included the individual surgeon's postoperative follow-up protocol and patient convenience. Furthermore, many patients in the study travelled from great distances for the surgery potentially affecting their ability to return for follow-up.

Several studies evaluated facial swelling and looked to quantify it at specific timepoints after orthognathic surgery. Kau et al. found that 60% of the initial facial swelling was resolved at 1 month and 83% resolved by 3 months after surgery[132]. Findings by Van der Vlis et al. were similar, showing roughly 50% resolution of swelling by 3 weeks after surgery and 80% resolved at 3 months[134]. Yamamoto et al. showed 66% of facial edema subsided by 1 month and 95% of swelling was resolved at 3 months[133]. All three of these studies found facial swelling to be greatest at the first timepoint measured, which was 1 day[132], 1 week[134] and 3 days[133] after surgery respectively. The fastest rate of swelling resolution was found in all studies to be in the first month of the patient's recovery. Our study found that 82% of swelling was resolved by T3 (28 days after surgery) and 87% was resolved by T4 (42 days). Given our study findings and those in

other similar studies, and that the T3-T4 timepoint in our study offered the greatest grouping of similarly timed photographs, this was the best choice for comparison to the T1 (immediate postoperative) photographs for facial swelling analysis in our study.

6.2 EFFECT OF PERIOPERATIVE STEROID DOSE ON POSTOPERATIVE FACIAL SWELLING AND SECONDARY OUTCOME MEASURES

Our study confirms that a perioperative dose of 125mg of methylprednisolone is as effective as a 1000mg dose for the prevention of facial swelling after orthognathic surgery (P=0.42). The measured facial swelling in Group 1 (1000mg) was $42.5 \pm 23.8 \text{cm}^3$ and was 39.4 $\pm 21.2 \text{cm}^3$ in Group 2 (125mg). In both groups, T1 and T3 photos were taken at almost identical time points between groups, as shown in Table 17 below. When using a multivariate analysis model to control for patient factors (age, BMI, gender) and surgical factors (procedure type and duration of surgery), no significant association between facial swelling and steroid dose was seen (F= 0.01, P= 0.91). Again, when keeping the 5 outliers and using non-parametric testing, the difference in facial swelling between groups was still not statistically significant (P= 0.90).

Table 17. Swelling and time after surgery to T1 and T3 photos between groups.

Variables	Group 1	Group 2		P- value
	Mean ± SD	Mean ± SD	n (%)	
Swelling (cm³)	42.5 ± 23.8	39.4 ± 21.2		0.42
Time to T1 (days)	1.78 ± 0.58	1.69 ± 0.47		0.42
Time to T3 (days)	38.5 ± 16.0	38.9 ± 13.0		0.62

Our findings are similar to those of Lin, Widar, and Weber, who showed that increasing steroid doses did not result in decreased swelling after orthognathic surgery. Lin et al. performed a randomized control trial between patients receiving either 5mg or 15mg of dexamethasone during surgery and found no difference in postoperative facial swelling between groups (P > 0.05 for all time points evaluated)[150]. Widar et al. showed no difference in swelling between two treatment groups of betamethasone (8mg and 16mg, P > 0.30)[113]. When increasing the cumulative dose of postoperative dexamethasone, Weber et al. did not significantly reduced swelling between treatment groups (P-value not reported)[115].

A 1000mg dose of methylprednisolone did not provide extra anti-inflammatory (or anti-edema) benefit over the 125mg dose. This may be explained by the non-genomic effects of glucocorticoids. Research into the non-genomic effects of glucocorticoids has shown that at a "very high dose" (defined as > 100mg prednisone equivalent), all cytosolic glucocorticoid receptors are saturated and non-genomic glucocorticoid actions can occur. These fast-acting, non-genomic actions of glucocorticoids have been shown to shift cell membrane pathways away from arachidonic acid, prevent leukocyte degranulation and promote synthesis of anti-inflammatory endocannabinoids[151,152]. A dose dependency curve has been generated by Buttgerit et al. showing the current view on the dose dependency of genomic and non-genomic effects of glucocorticoids[71]. At a dose of 125mg of methylprednisolone (equivalent to 156mg prednisone), the therapeutic effects of the steroid dose are maximized (Figure 19).

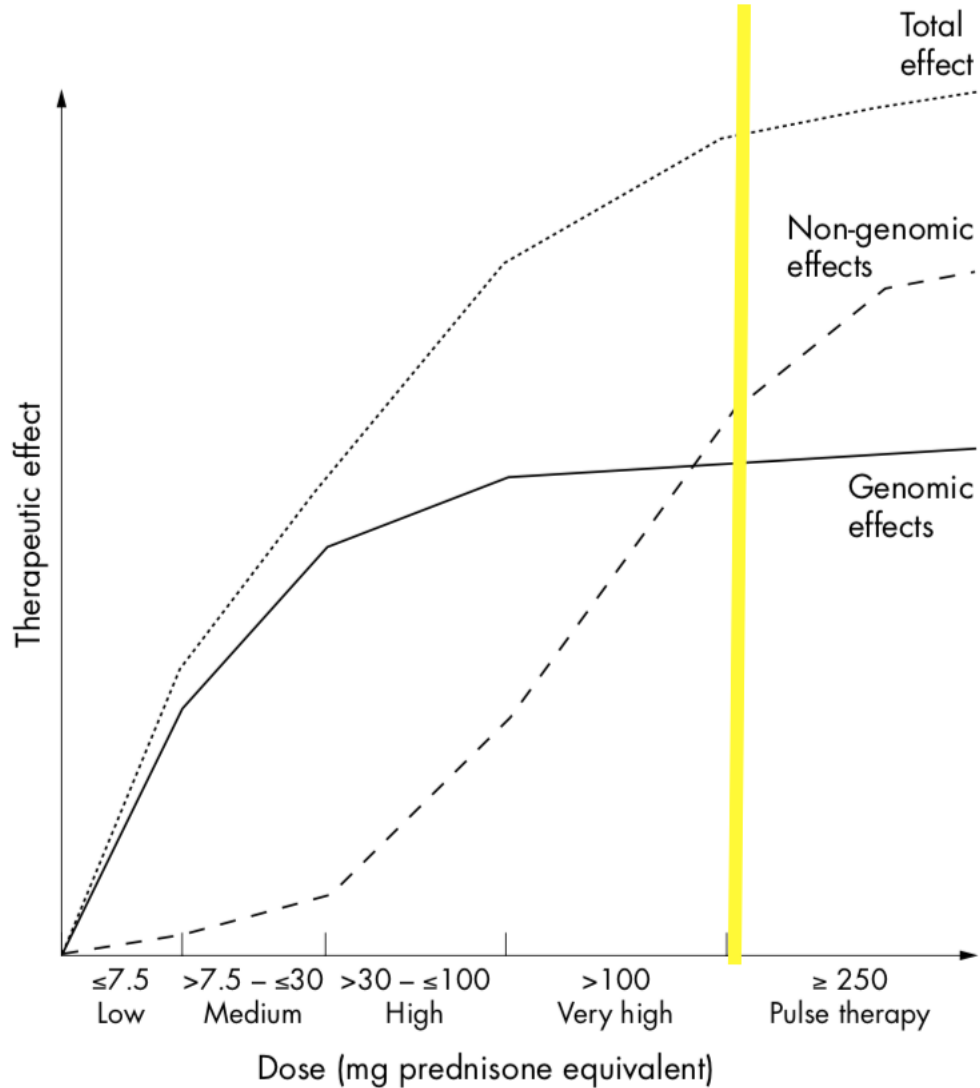Figure 19. Current view on the dose dependency of genomic and non-genomic effects of glucocorticoids. The yellow line represents a dose of 125mg of methylprednisolone showing an optimized total therapeutic effect. Adapted from Buttgereit F: Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. Annals of the Rheumatic Diseases 61: 718, 2002.

In our study we identified 5 outliers, with facial swelling volumes greater than 2SD from the mean swelling for all patients (Figure 20). All five patients were in the 125mg methylprednisolone group (Figure 14, Table 9). A possible mechanism explaining this finding could be individual variability in cytosolic glucocorticoid receptors. It has been shown that cGCR numbers can vary between patients and can be affected by disease states and certain treatment[153]. Again, at steroid doses >100mg prednisone equivalent it is assumed that all cytosolic glucocorticoid receptors are saturated and non-genomic mechanisms predominate. It is possible that at a dose of 125mg of methylprednisolone, not all cGCR were saturated in these patients due to individual variability of receptor numbers and optimal genomic and non-genomic effects were not realized. Again, for the purpose of comparing facial swelling between Group 1 and Group 2, these outliers were removed to allow a comparison between two normally distributed populations with parametric testing. When kept for analysis and non-parametric testing was employed, the difference between groups when evaluating facial swelling was still insignificant (P= 0.90).

With the outliers removed, there was a slightly larger volume of swelling experienced by patients in the 1000mg group postoperatively. While this difference was not significant, this could be accounted for by the mineralocorticoid effect of methylprednisolone. Methylprednisolone has a relative mineralocorticoid activity of 0.5, compared to other commonly used synthetic glucocorticoids, such as dexamethasone which have none. The mineralocorticoid effect of glucocorticoids works mainly via mineralocorticoid receptors in the distal nephron and colon, upregulating the expression of epithelial sodium channels. The result is increased sodium and water retention and swelling. By administering increasing doses of

methylprednisolone, it is possible that the anti-edema benefit of the steroid is increasingly offset by its water-retaining properties.

High-dose systemic glucocorticoid use in orthognathic surgery has been shown to be safe[4,5,96]. The results of our study indicate that there is no increased risk of adverse steroid-related effects when using a larger dose of 1000mg of methylprednisolone versus a 125mg dose. This is evident as the secondary outcome measures of pain, nausea, vomiting, sleep, length of stay and postoperative infection in our study were not found to be significantly different between steroid treatment groups (all P > 0.05). Currently, no studies exist comparing steroid doses and these outcomes after orthognathic surgery[4,5]. The only significant secondary outcome measure was related to mood, with patient in Group 1 having a lower mood (5.19 ± 2.27) than patients in Group 2 (6.03 ± 2.00) (P= 0.05). The finding of a higher, or better mood, in the group receiving a lower dose of glucocorticoid cannot be well explained. With short-term use, a dose-dependent relationship between steroid dose and an elevated mood usually exist. Only with chronic steroid use is depression or a lower, more irritable mood seen[154].

6.3 EFFECT OF PATIENT FACTORS ON POSTOPERATIVE FACIAL SWELLING AND SECONDARY OUTCOME MEASURES

The effects of patient age, BMI and gender, and their correlation with facial swelling is not well studied in the orthognathic surgery literature[4,5]. Most studies evaluating facial swelling, either in orthognathic surgery or 3rd molar removal, only evaluated for homogeneity between treatment groups. In their study, Yamamoto et al. looked at the correlation of age, BMI and gender with measured facial swelling after orthognathic surgery as a secondary outcome measure. They found only weak correlations of these variables with facial swelling (correlation

coefficients from 0.01-0.34) and no regression statistics were performed in their study[133]. Van der Vlis et al. examined the rate of resolution of facial swelling after orthognathic surgery and found that despite having the same amount of initial swelling, the resolution of facial swelling was faster in patients with an elevated BMI[134].

The association between patient factors of age, gender and BMI was initially found not to be strongly correlated with postoperative facial swelling, with all Spearman correlation coefficients < 0.7. A coefficient > 0.7 indicates a good correlation[147,148]. When performing a multivariate analysis of swelling and controlling for other patient and surgical factors (procedure and duration of surgery), age and gender were found to have a statistically significant correlation with facial swelling. Younger age (F= 5.93, P= 0.02) and male gender (F= 4.29, P= 0.04) were associated with increased facial swelling. Proinflammatory cytokines interleukin-6 and TNF-α, which play a major role in post-traumatic inflammation, have been shown to more inducible in men than in women. Estrogen also appears to have a suppressive effect on these cytokines[155]. These physiologic differences can potentially explain the gender difference seen in our study. It is unclear why younger age was associated with increased swelling in our study.

Female sex is often found to be associated with increased pain scores after surgery[47]. When looking specifically at pain after orthognathic surgery, the literature is inconclusive. Mobini et al. evaluated pain after orthognathic surgery in thirty patients using a numeric rating scale. They found that women reported more pain than men (6.3 versus 5.3) and consumed more opioids (131 versus 78 morphine mg equivalents) after surgery[49]. These authors did not comment on the statistical significance of their findings. Widar et al. did not find age or gender to correlate with postoperative pain (all P >0.30) when evaluated at 1 day and 6 months after orthognathic surgery[113]. Female sex is also a well-recognized risk factor for nausea and vomiting after

orthognathic surgery[56,57,156]. In our study, patient age, BMI and gender were not found to

correlate well with patient-reported secondary outcomes, including pain, nausea and vomiting,

sleep and mood (all Spearman coefficients <0.7).

The correlation of patient age to the development of SSI after orthognathic surgery is

unclear. Two large retrospective studies found that age had no correlation to the development of

SSI after orthognathic surgery (P= 0.85[65] and P=0.53[157]). In a retrospective analysis of 336

BSSO patients, Bouchard et al. found that SSI occurred more commonly older patients (P=

0.02)[158]. In our study, rates of postoperative infection were found to be correlated to patient age

(P= 0.013). The average age of patients with SSI in our study was significantly higher than the

age of patients who did not have infection (32.4 versus 25.6 years). No correlation was seen

between BMI or gender and infection rates (P= 0.52 and P=0.22 respectively). These findings

support the current literature[65,157,158]. No correlation was seen between any patient factors and

length of stay in hospital after orthognathic surgery in our study (all P > 0.05).

6.4 EFFECT OF SURGICAL FACTORS ON POSTOPERATIVE FACIAL SWELLING AND SECONDARY OUTCOME MEASURES

With more tissue cutting, dissection and stretching, one would expect more local

inflammation and swelling. With respect to orthognathic surgery, this principal has largely been

proven in the literature. Four studies quantifying the facial swelling of 136 patients drew the

same conclusion: patients who underwent a Lefort 1 osteotomy, had less swelling than patients

who underwent a BSSO or bimaxillary surgery[112,116,132,134]. Our study came to the same

conclusion. When performing a multivariate analysis of facial swelling, controlling for patient

variables and surgical time, we found that the procedure type was correlated to the amount of

postoperative swelling (F= 2.65, P= 0.03). Facial swelling experienced by the LF only group was found to be lower than the swelling in patients who underwent mandibular procedures (BSSO and/or FG). This is shown in Figure 20.
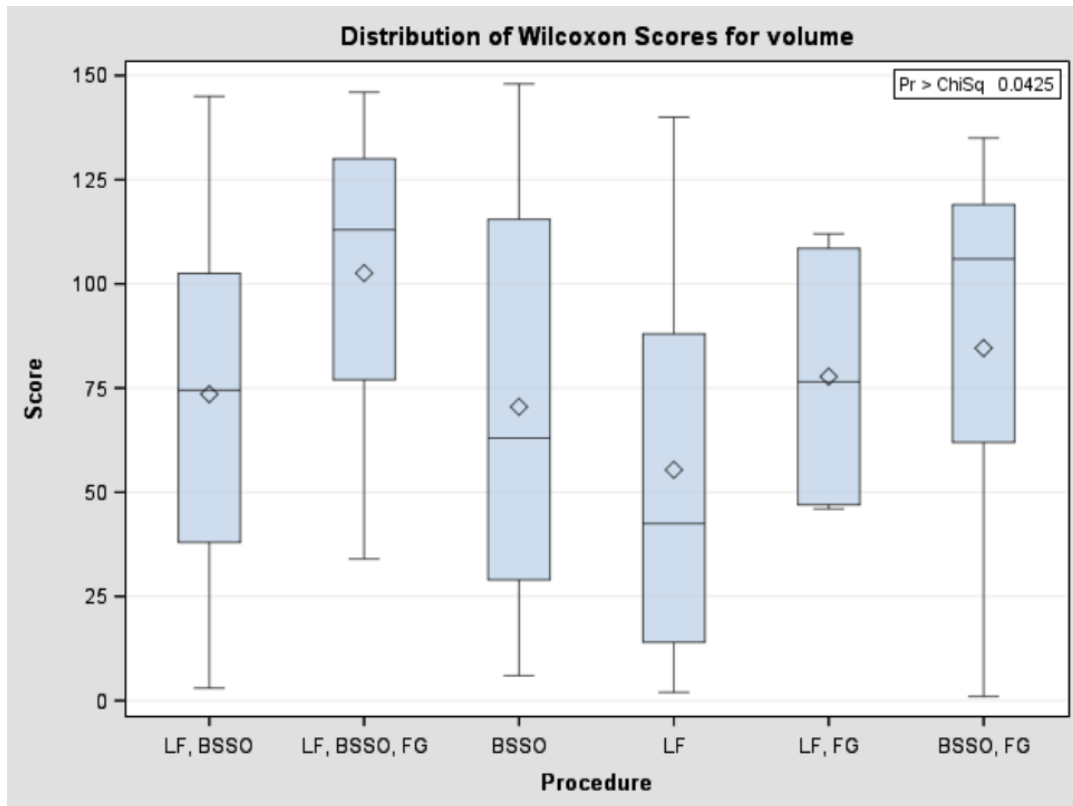
Figure 20. Facial swelling stratified by surgical procedure.

The difference in facial swelling between procedure types was also reflected when patients reported their own perceived facial swelling. Patients who underwent LF with or without concomitant genioplasty reported significantly less swelling compared to patients who underwent BSSO procedures (4.3 ± 1.7 versus 5.9 ± 2.1, Z= 0.001, P= 0.002). This is shown in Figure 21.
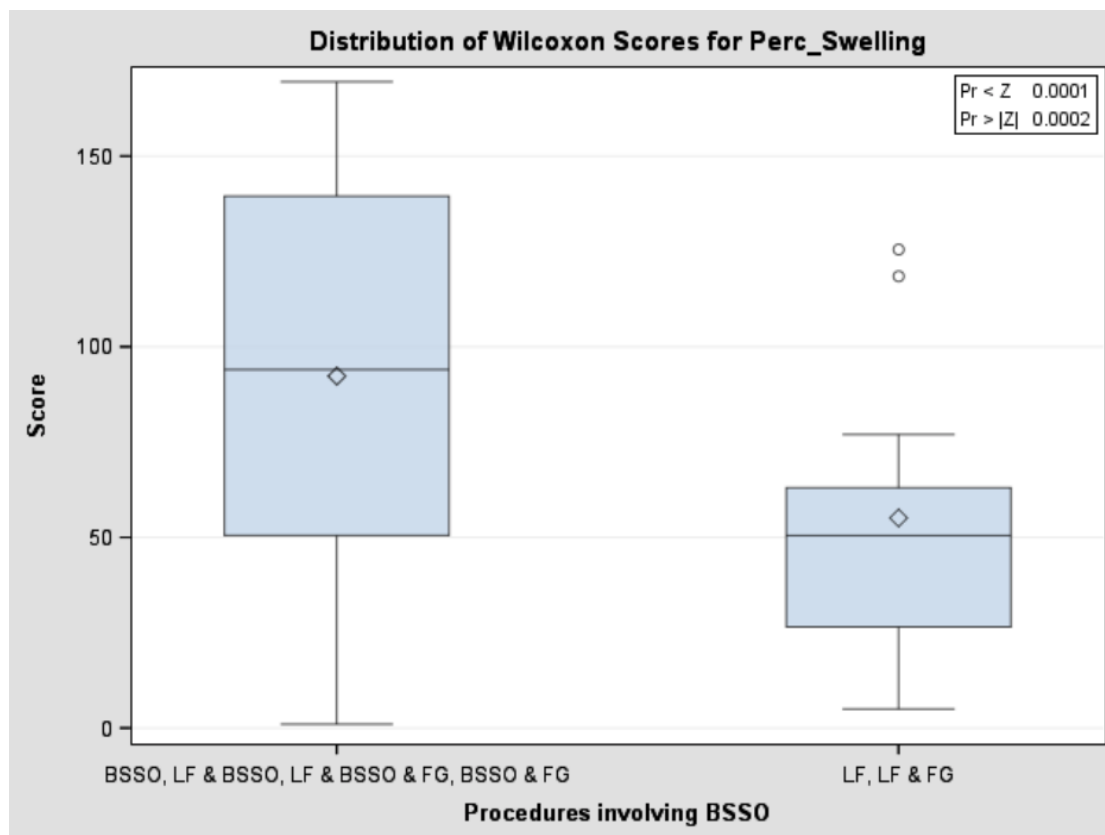
Figure 21. Differences in patient perceived facial swelling between patients who underwent BSSO and those who did not.

Our study did not demonstrate a correlation between duration of surgery and facial swelling, either by Spearman correlation coefficient (r_s= 0.14) or by multivariate regression analysis (F= 0.23, P= 0.63). Yamamoto et al. came to the same conclusion in their study when measuring facial swelling after orthognathic surgery using a combination of CT and laser scanning (P >0.05)[133].

Vomiting after surgery was also found to be strongly associated with surgery type in our study (P = 0.0015). Patients who underwent Lefort procedures were significantly more likely than patients who did not have a Lefort to experience vomiting episodes postoperatively (0.9 ± 1.6 times and 0.2 ± 0.7 times respectively, Z= 0.0001, P< 0.0001). Initially, postoperative nausea

was not found to be correlated to surgery type either when at its worst (P= 0.26) or at the time of discharge from hospital (P= 0.45). When dividing our patients into Lefort and non-Lefort groups, differences were found for worst nausea (4.1 ± 3.8 and 2.6 ± 2.8 respectively, Z= 0.011, P= 0.02) but not for nausea experienced at the time of discharge (P= 0.64). Our findings fit with those of Silva et al. and others who found that Lefort surgery is a significant risk factor for PONV[56,57,156]. The remaining patient-reported outcomes of pain, sleep and mood were not found to be correlated to surgery type or duration (all P > 0.05).

In a retrospective review of 2268 orthognathic surgery patients, Davis et al. found that patients who did not undergo mandibular surgery (i.e. Lefort 1 only) had significantly lower infection rates compared to patients who underwent BSSO procedures (P= 0.02)[65]. In our study, the overall infection rate was 9.2% and all 23 infections occurred in patients who had a BSSO as part of their treatment. This association was statistically significant (P= 0.03) with a relative risk for infection for patients who underwent BSSO as part of their treatment of 1.19 (95% CI 1.13, 1.27). The mean duration of surgery for patients who developed postoperative infections was also slightly higher than that of patients who did not have infection (137.8 ± 53.8 and 130.8 ± 44.9 minutes, respectively), but this was not significant (P= 0.51).

In our study, length of stay in hospital was correlated to both surgery type and duration (both P < 0.001), which was an expected finding. At our center, patients who have only mandibular surgery tend to be discharged from hospital sooner than patients who have a maxillary surgery. This is largely due to protocol at our center, where patients undergoing Lefort 1 generally stay two days in hospital, compared to BSSO patients who usually stay only one. A slower return to full oral intake in Lefort 1 patients may play a role as well, but this was not measured in our study. Again, our study has shown that patients undergoing Lefort 1 procedures

experience more postoperative nausea and vomiting than patients who did not have a Lefort surgery.

6.5 RESOLUTION OF FACIAL SWELLING AFTER ORTHOGNATHIC SURGERY

When evaluating the resolution of facial swelling, we found a swelling reduction of approximately 65% at two weeks post-surgery. Over 85% of the swelling was resolved by four weeks after orthognathic surgery. The findings of our study are summarized in Table 16, and Figures 17 and 18. We also found that the rate of resolution of facial swelling was greatest between the first and second time points measured. Our findings are in line with other similarly conducted studies as shown in Table 18. All studies, including our own, found a peak rate of swelling resolution in the early stages of recovery, between the first two time points measured.

Table 18. Comparison of the resolution of facial swelling after orthognathic surgery between similarly conducted studies.

Study	% Swelling Resolved				$T_{100\%}$	Peak Rate of Resolution
	1 Week	2 Weeks	4 Weeks	3 Months		
Present study	•	65	85	100	10 weeks	2 weeks
Kau 2007	15	•	60	83	6 months	1 month
Van der Vlis 2014	•	43	63	80	12 months	3 weeks
Yamamoto	33	•	67	95	6 months	1 week
Lin 2017	66	•	86	•	6 months	1 week

Abbreviations: $T_{100\%}$= endpoint time for swelling comparison, where swelling is assumed to be 100% resolved.

One difference between these studies and the present one was the selection of an endpoint for calculation of swelling volumes. In our study, we chose T5 which was a median time of 71 days, or just over ten weeks after surgery to compare against. At this timepoint, we are assuming that all measurable swelling is resolved. Three of the other studies used 6 months for a comparison endpoint, and another used 12 months. Van der Vlis et al. evaluated facial swelling to an endpoint of 12 months and found that facial swelling continued to decrease between 6 and 12 months, with roughly 2cm^3 (or 6% of the total swelling) resolving over this time[134]. As our endpoint is sooner, we may not be capturing the last portion of facial swelling and be slightly overestimating its resolution at each time points.

The resolution of facial swelling after orthognathic surgery is of great interest to both surgeons and patients. For patients, swelling is one of the most distressing parts of the postoperative period[3,159]. For surgeons, it is important to provide patients with reasonable expectations for the postoperative period. Three-dimensional facial scanning technologies have provided clinicians with an accurate and reproducible tool with which to measure facial swelling after orthognathic surgery. By providing accurate predictions of the resolution of facial swelling, surgeons may be able to reduce the patient's anxiety about the postoperative period and improve the delivery of informed consent. When examining the existing literature and the results of this study, it is apparent that swelling resolves fastest in the early period after orthognathic surgery, with over two-thirds of swelling dissipating in the first month.

6.6 CLINICAL IMPLICATIONS AND RECOMMENDATIONS

Since 2012, the Choosing Wisely movement has gained momentum in North America and across the world[160]. One of the primary mandates of this movement has been to encourage medical professionals to critically appraise practice habits, including the use and prescribing of medications, in order to identify treatments that are not evidence-based and that could expose patients to harm. The goal of the Choosing Wisely campaign is to improve patient care and reduce healthcare costs.

In Oral and Maxillofacial Surgery, orthognathic surgery has been practiced safely and effectively for almost a century. Facial swelling has long been identified as a common, but troublesome after-effect of surgery and has been managed with potent systemic glucocorticoids since the 1970's. Despite their long history of use, evidence is lacking to support a particular type or dose of steroid[6,146]. While case reports have identified adverse psychiatric effects after short-term, high-dose glucocorticoid administration[8–10,107], the majority of the literature has demonstrated that these medications can be used safely in orthognathic surgery[4,5,99,112,113,115].

We should use the minimally effective steroid dose to manage facial swelling in orthognathic surgery, since we know that the incidence of drug-related side effects are dose dependent[7]. Our study has demonstrated that the efficacy of methylprednisolone in mitigating facial swelling does not necessarily improve with increasing doses of medication. We have shown that a 125mg dose of methylprednisolone is as efficacious as a 1000mg dose in managing facial swelling after orthognathic surgery.

A 125mg dose of methylprednisolone is commercially available and is used in a multitude of other clinical situations to manage acute inflammatory conditions. Multiple systematic reviews have found doses of methylprednisolone over 85mg to be sufficient to

produce a significant decrease in facial edema after orthognathic surgery[4,5]. Given that an equivalent dose of steroids greater than 100mg of prednisone is capable producing rapid, non-genomic effects, a dose of 125mg of methylprednisolone may be ideal for clinical situations where rapid and potent control of inflammation is desired.

The findings of our interrater and intrarater reliability testing show our method of cropping, overlaying and calculating facial swelling using the 3DMDface scanning system to be highly reproducible and suitable for future clinical studies. Future research should include a comparison between different steroid types (i.e. methylprednisolone versus dexamethasone), now that relative equivalence between to commonly used doses of methylprednisolone has been established. Evaluating the value of added postoperative steroid doses is also recommended.

CHAPTER 7. CONCLUSIONS

The following main conclusions can be drawn from the results of the present double-blinded, randomized control trial:

1) A perioperative methylprednisolone dose of 125mg can be used as effectively as a 1000mg dose for the management of postoperative facial edema in orthognathic surgery.

2) A 1000mg dose of methylprednisolone can be used safely to manage facial swelling after orthognathic surgery but offers no benefits over a lower dose of 125mg for limiting swelling, pain or PONV after orthognathic surgery.

3) Increased facial swelling after orthognathic surgery is associated with BSSO surgery, male gender and younger age.

4) Facial swelling resolves fastest in the early period after orthognathic surgery, with over two-thirds of swelling dissipating in the first month postoperatively.

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APPENDIX A. POSTOPERATIVE PATIENT QUESTIONNAIRE

Prospective Evaluation of Perioperative Steroid
Dosing on Postsurgical Edema in Orthognathic
Surgery
Department of Oral and Maxillofacial Surgery
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Pt #: _____ Protocol: _____

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Participant Information Form

# PARTICIPANT NAME :

Operative Assessment and Procedure:

  I.   Age: _____

 II.   Sex: Male / Female

III.   Home Medications:

        _____

 IV.   Allergies: _____

  V.   Treating Surgeon: _____

Participant Questionnaire

You may choose not to answer any of the following questions.

1. Please indicate the **WORST LEVEL OF PAIN** you have experienced throughout your recovery (circle number):
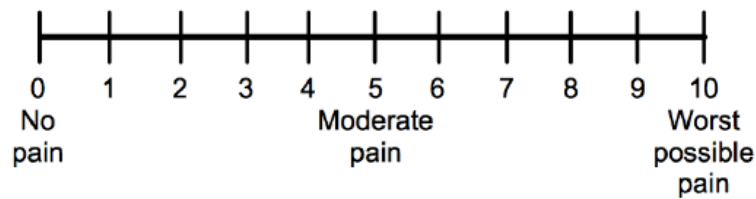
```
 0   1   2   3   4   5   6   7   8   9   10
 No              Moderate            Worst
pain              pain              possible
                                      pain
```

1

nova scotia
health authority

Research Ethics Board

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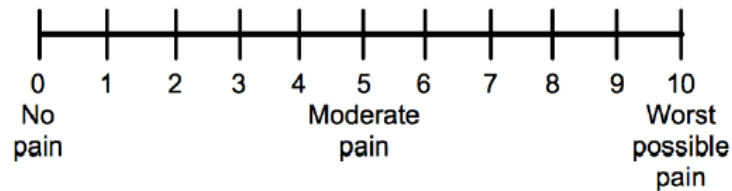
Pt #: _____ Protocol: _____

2. Please indicate the level of **PAIN** you are experiencing **TODAY** (circle number):

```
|——|——|——|——|——|——|——|——|——|——|
0    1   2   3   4   5   6   7   8   9   10
No                  Moderate              Worst
pain                  pain                possible
                                           pain
```
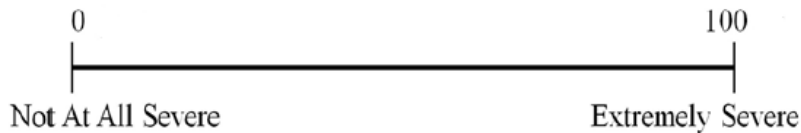
3. Please indicate the severity of your **SWELLING** that you are experiencing **TODAY** (mark an X on the line/out of 100%):

```
0                                    100
|————————————————————————————————————|
Not At All Severe          Extremely Severe
```
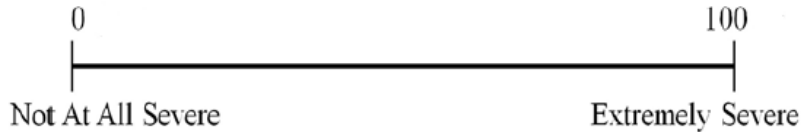
4. Please indicate the **WORST LEVEL OF NAUSEA** that you have experienced throughout your recovery (mark an X on the line/out of 100%):

```
0                                    100
|————————————————————————————————————|
Not At All Severe          Extremely Severe
```
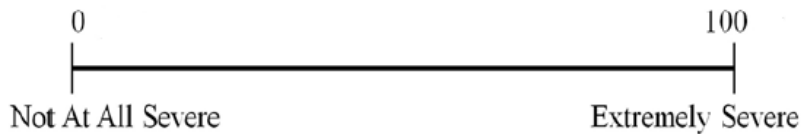
5. Please indicate your level **NAUSEA** **TODAY**(mark an X on the line/out of 100%):

```
0                                    100
|————————————————————————————————————|
Not At All Severe          Extremely Severe
```

2

Prospective Evaluation of Perioperative Steroid
Dosing on Postsurgical Edema in Orthognathic
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Pt #: _____ Protocol: _____

6. Have you **VOMITED** during your recovery? y/n

7. If yes, how many times? ____
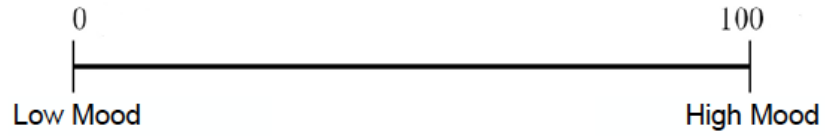
8. Please indicate how your sleep was **LAST NIGHT.**

0   100
|——————————————————————————————|

Best Sleep Ever   Worst Night Ever
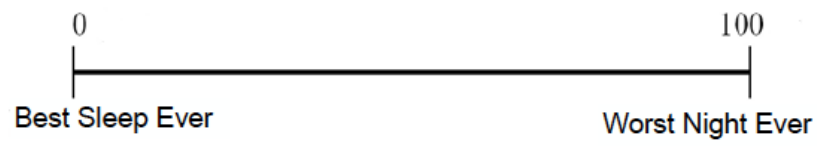
9. Please indicate how your **MOOD** was while in hospital

0   100
|——————————————————————————————|

Low Mood   High Mood

10a. Do you AGREE with the statement: "While in hospital, I had a lot of sudden mood changes."

        -Yes   -No

10b. Do you AGREE with the statement: "It is normal for me to have a lot of sudden mood changes."

        -Yes   -No

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