A PROSPECTIVE EVALUATION OF PERI-OPERATIVE GLUCOCORTICOID USE IN THE MANAGEMENT OF CERVICOFACIAL INFECTIONS OF ODONTOGENIC ORIGIN

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Abstract

Odontogenic cervicofacial infections requiring inpatient management are treated in a routine manner by oral and maxillofacial surgeons in Manitoba. After a standardized pre-operative workup, patients undergo surgical intervention including extraction of necessary teeth and incision and drainage of associated abscess(es). Patients are treated post-operatively with antibiotics, steroids, and medications for supportive care until appropriate for discharge.

Benefits of intravenous corticosteroids in patients undergoing dentoalveolar and maxillofacial surgery include improved comfort, reduced post-operative edema, and shortened time to recovery.[1] Corticosteroids also aid in reducing the risk of morbidity by limiting mass effect from edema and associated airway obstruction.[1] In addition, their anti-inflammatory effect limits further swelling from manipulation of soft tissues during surgical procedures.[1] Current literature supports the use of corticosteroids in the management of primary and deep space neck infections.[1,2] However, corticosteroid dosing regimens are currently determined by the clinical judgment of the attending surgeon and are not standardized.

The purpose of this study was to provide guidance for optimal dosing of methylprednisolone in the management of odontogenic cervicofacial infections. This prospective study followed the inpatient course of 28 patients with various cervicofacial infections of odontogenic origin. All patients were treated with a standardized surgical protocol, antibiotics, and steroids. Patients were randomized to receive one of two methylprednisolone dosing regimens. 14 patients were assigned to receive one dose of methylprednisolone 125mg IV at the time of surgery. The remaining 14 patients received one dose of methylprednisolone 125mg IV at the time of surgery and three consecutive doses of methylprednisolone 125mg IV every six hours post-operatively. Patients

were evaluated at the time of hospital presentation and daily throughout admission. Outcomes evaluated included C-reactive protein (CRP) levels, white blood cell (WBC) count, length of hospital admission, and trismus. By examining differences in outcome success variables, the goal of this study was to support future evidence-based dosing decisions in the peri-operative treatment of inpatients in Manitoba. Data analysis showed a greater reduction in CRP throughout admission in the four-dose methylprednisolone group that was statistically significant. No significant difference in daily WBC count or trismus was found.

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Introduction and Literature Review

Corticosteroids and Mechanism of Action

The term "corticosteroids" is used to describe an essential class of endogenous hormones produced in the adrenal cortex. Corticosteroids regulate a vast number of physiologic processes and metabolic functions essential for life including glycemic control, endovascular repair, inflammatory and immune responses, and the physiologic stress response.[3] Beginning with cholesterol, their synthesis ends in the production of mineralocorticoids (mainly aldosterone), glucocorticoids (mainly cortisol), and gonadocorticoids (androgen hormones).

Corticosteroids are released into the bloodstream via the hypothalamic-pituitary-adrenal axis (HPA Axis) (Figure 1). The hypothalamus secretes corticotropin releasing hormone (CRH), which in turn stimulates adrenocorticotropic hormone (ACTH) release from the anterior pituitary gland. ACTH then stimulates several receptors in the adrenal cortex, made up of the zona glomerulosa, zona fasciculata, and the zona reticularis. In the zona glomerulosa, mineralocorticoids (mainly aldosterone) are released to regulate renal salt retention, water balance, and blood pressure. Gonadocorticoids are released by the zona reticularis and play a role in regulating male and female reproductive functions. Lastly, glucocorticoids (mainly cortisol) are released by the zona fasciculata to regulate glucose metabolism and perform several anti-inflammatory and immunosuppressive functions.

In general terms, the HPA axis is responsible for regulation of the neural and endocrine response to stress. Cortisol is secreted in a diurnal pattern with serum cortisol levels peaking in the morning shortly after waking. Serum cortisol concentrations then fall throughout the day as they exert a negative feedback effect on both the anterior pituitary gland and hypothalamus. In response

to physiologic stress, neural inputs to the hypothalamus stimulate production of CRH and subsequently ACTH from the anterior pituitary gland. This leads to increased circulating cortisol production by the zona fasciculata of the adrenal cortex. Although physiologic stress is the most important driver of cortisol production, it is also released in response to hypoglycemia. For this reason, the end effects of increased cortisol production include increased serum glucose levels, protein and fat catabolism (to increase energy supply in response to starvation or inadequate intake), increased blood pressure (to enhance nutrient delivery to cells in need), immune system depression, and inhibition of inflammatory mediators.

Due to their major role in maintaining homeostasis and metabolism, glucocorticoids have multiple targets in the musculoskeletal, renal, cardiovascular, endocrine, and nervous systems. They also have powerful anti-inflammatory and regulatory effects on the immune system. Both endogenous and exogenous glucocorticoids have a profound effect on the concentration, distribution, and function of peripheral leukocytes and inflammatory mediators. Glucocorticoids act to inhibit the inflammatory response through depression of mast cell and basophil secretion, suppression of tissue macrophages and phospholipase A2, and reduced expression of COX-2.[3] Through these mechanisms, glucocorticoids are well-known to be beneficial in the peri-operative period for their limitation of inflammatory effects. In addition, glucocorticoids inhibit the formation of prostaglandins and leukotrienes through the COX pathway, thereby limiting the vasodilatory and capillary permeability effects of these enzymes. Peri-operative steroid administration leads to reduced fluid leakage into the surrounding tissues, thus promoting decreased soft tissue swelling and mass effect.

The core molecular structure of all corticosteroids is comprised of four lipophilic rings.[4] Through addition or subtraction at certain positions around these central carbon rings, specific

steroid properties can be enhanced or reduced.[4] Since the 1950s, researchers have been devising methods to minimize the mineralocorticoid side effects of synthetic glucocorticoids on salt and water balance while maximizing the desired anti-inflammatory and immunomodulatory effects.[3] The advent of synthetic glucocorticoids through chemical modification has yielded steroid compounds with varying pharmacodynamic and pharmacokinetic properties. Duration of action and elimination half-life are the two pharmacokinetic parameters that are primarily affected. The potency or intensity of glucocorticoid effects is the main differentiating pharmacodynamic property. Table 1 highlights the relative potency and duration of action for several common synthetic glucocorticoids.

The significant anti-inflammatory and immunosuppressive effects of glucocorticoids are mediated by two distinct means: genomic and non-genomic effects.[5] Glucocorticoids have largely been recognized to exhibit their pharmacological effects via classical genomic mechanisms.[6] The lipophilic glucocorticoid crosses through the cell membrane, attaches to the cytosolic glucocorticoid receptor and heat shock protein, binds to glucocorticoid-responsive elements on genomic DNA, and interacts with nuclear transcription factors.[6] To exert their genomic action through this process, glucocorticoids take at least 30 minutes to several hours to demonstrate their effects.[6]

Buttgreit et al. developed a model to evaluate the non-genomic effects of five commonly used synthetic glucocorticoids.[6] As shown in Table 2, a significant difference was found between the genomic (classical) and non-genomic potencies of the glucocorticoids studied. For example, while dexamethasone is commonly quoted as being five times more potent than methylprednisolone, Buttgreit et al. showed that the potencies of their non-genomic effects are essentially equivalent (2.5 vs. 2.9).[6] These differences in genomic and non-genomic potencies may be especially relevant

depending on the setting of steroid use. While dexamethasone is five times more potent than methylprenisolone in its genomic effects relevant to treating chronic conditions, both steroids have similar non-genomic effects for the short-term reduction of inflammation and tissue swelling in the peri-operative period. An increasing knowledge of glucocorticoid potencies and mechanisms of action allows clinicians to tailor treatment regimens to optimize onset, duration of action, and targeted benefits while limiting unwanted side effects.

Pharmacologic Use of Synthetic Corticosteroids

Methylprednisolone is an intermediate-acting synthetic glucocorticoid first described in the literature in the 1950s and granted FDA approval in the United States in 1957.[4] By adding a 6-α methyl group to the basic lipophilic double-ring steroid structure, researchers developed a novel synthetic glucocorticoid with a greater glucocorticoid effect and decreased mineralocorticoid effect than prednisolone.[4] In North America, methylprednisolone sodium succinate is sold as Solumedrol. Solumedrol is administered via intravenous route and has rapid absorption, onset of action, and distribution. The half-life of Solumedrol is 12-36 hours.[7]

Methylprednisolone is metabolized by the liver into inactive metabolites, primarily 20-alpha hydroxymethylprednisolone and 20-beta hydroxymethylprednisolone.[8] Metabolism in the liver occurs primarily via the CYP3A4 member of the CYP450 oxidizing enzyme family.[8] Excretion of an intravenously administered dose is completed in approximately twelve hours, therefore ideal dosing of methylprednisolone is every 4-6 hours.

Methylprednisolone is recommended for clinical scenarios in which rapid and profound anti-inflammatory action is required. Indications for use include anaphylaxis, status asthmaticus, drug reactions, contact dermatitis, urticaria, and dermatologic conditions such as pemphigus

foliaceous or vulgaris and exfoliative dermatitis.[8] Methylprednisolone can also be used as an adjunctive therapy for many autoimmune conditions such as systemic lupus erythematosus, acute rheumatic fever, ulcerative colitis, or acute gout.[8]

Methylprednisolone, like other synthetic glucocorticoids, is an FDA pregnancy category C drug and is excreted into breastmilk.[8] The use of this medication in pregnant or breastfeeding women is not advised. Except for short-term emergency therapy, methylprednisolone is also contraindicated in patients with arrested tuberculosis, acute psychoses, Cushing's syndrome, peptic ulcer disease, herpes simplex keratitis, and varicella.[8]

Corticosteroids in the Management of Odontogenic Cervicofacial Infections

Primary and deep space cervicofacial infections are a common presentation to emergency departments and an in-depth knowledge of their management is essential to the daily practice of otolaryngology, emergency medicine, and oral and maxillofacial surgery.[9] The most common portals of bacterial entry into the primary and deep fascial spaces of the head and neck region are the pharyngeal tonsils, teeth, salivary glands (sialadenitis), and lymph nodes (lymphadenitis).[10,11] Other potential causes include trauma to the esophagus or oropharynx, laceration of the floor of the mouth, mandibular fracture, tumor necrosis and hematogenous spread from distant sources. One of the major sources of morbidity in primary and deep space cervicofacial infections is mass effect and subsequent airway obstruction or collapse produced by profound edema.[1] Additionally, surgical manipulation of the soft tissues during intraoral or transcervical incision and drainage or debridement can contribute to increased swelling around the airway.[1] Inflammation and spasm of the masticatory musculature can also occur in the context of infection, which can result in severe trismus.[1]

When evaluating a patient in whom an odontogenic cervicofacial infection is suspected, a routine diagnostic workup is followed. A history and physical examination are performed including a complete intraoral evaluation with focus on the floor of mouth, dentition, pharynx, and oropharynx.[12] Any signs raising concern for impending airway obstruction should prompt immediate intervention. Understanding the common presentation of cervicofacial infections is crucial to the early recognition and efficient management of these patients. Localizing symptoms such as odynophagia, dysphagia, trismus, odontalgia, and dysphonia are commonly described by patients with odontogenic cervicofacial infections.[12] Mayor and colleagues found that the most common symptoms associated with deep space neck infections were odynophagia (84% of patients), dysphagia (71%), fever (68%), neck pain (55%), neck swelling (45%), trismus (39%), and respiratory distress (10%).[13] Signs of cervicofacial infection on examination include neck swelling, elevation of the floor of the mouth, drooling or poor management of secretions, limited mouth opening, diaphoresis, elevated temperature, uvular deviation, and bulging of the pharyngeal wall or lingual aspect of the mandible (Figure 2, Figure 3).[12]

Once a thorough history and physical examination have been performed, several imaging modalities can be used for diagnosis and treatment planning. Traditionally, inspiratory lateral cervical radiography has been used as it is simple and easily accessible. In cases of prevertebral and retropharyngeal space abscesses, lateral cephalometric imaging may still hold merit. Increased diameter from the anterior aspect of the vertebral body to the air column in the posterior pharyngeal wall (>7 mm at C-2), loss of cervical lordosis, and presence of air in the soft tissues suggest space involvement.[14] In most institutions, this method is now rarely used due to the 33% false-negative rate as well as the wide availability of computed tomography (CT) scans.[12] CT is currently the predominant imaging modality for diagnosis of cervicofacial deep space infections due to its

ability to localize abscesses in the head and neck region, relative availability, and low cost (Figure 4). Although CT is less effective than ultrasound at delineating abscess formation from cellulitis, CT scans are easily interpreted by surgeons and allow for precise surgical planning. Miller and colleagues confirmed that when combining clinical examination with CT findings, surgeons were able to accurately identify drainable purulent collections with 89% accuracy.[15] It should also be noted that panoramic radiographs remain a useful imaging modality in localization and diagnosis of the infected dentition (Figure 5).

The management of odontogenic cervicofacial infections requires both prompt medical management and decisive surgical intervention. Cervicofacial infections of odontogenic origin almost always require surgical management, typically in the form of dental extraction for source control and incision and drainage of associated collection(s). When incision and drainage is performed, Topazian and Goldberg recommend following important principles: incision through healthy skin and mucosa when possible, avoidance of the site of maximum fluctuance due to unsightly scar formation, placement of the incision in a natural skin fold and dependent position, blunt dissection, drain placement, and removal of drains when drainage becomes minimal.[16] Medical management aims to reduce septic load and restore compromised head and neck functions such as breathing, eating, swallowing, and management of secretions.[16] This typically includes prompt IV access, fluid resuscitation, and administration of broad-spectrum IV antibiotics.[16] Although broad spectrum IV antibiotic therapy is started empirically, it should be tailored to culture and sensitivity results when available.

Benefits of intravenous corticosteroids in patients undergoing dentoalveolar and maxillofacial surgery include improved comfort, reduced post-operative edema, and shortened time to recovery.[1] Corticosteroids are used in a wide range of both maxillofacial and otolaryngologic conditions due

to their ability to inhibit the inflammatory response through inherent anti-inflammatory and anti-edematous properties.[2] Along with these properties, corticosteroids are also strong antipyretics and antiemetics. Historically, significant deep space neck infections have been responsible for severe morbidity and death. However, with advances in both surgical and medical management protocols, antibiotic therapy, and medical imaging, mortality in these infections has been reduced to 2.4%.[11]

In the past, some researchers and clinicians have expressed concern that the use of exogenous corticosteroids during treatment of an active infection may have an adverse impact on recovery due to their immunosuppressive nature. Chronic exogenous steroid use may also induce mood changes, hyperglycemia, hypertension, immunosuppression, avascular necrosis, and osteoporosis. In some patients, particularly diabetic or immunocompromised individuals, long-term use may lead to unacceptable complications. However, the literature suggests that short-term, high-dose corticosteroid use in the setting of cervicofacial infections is both safe and effective.[2] A recent meta-analysis examining the use of combined corticosteroid and antibiotic regimens for treatment of peri-tonsillar abscesses and other otolaryngologic alimentary tract illnesses showed statistically significant improvement in outcomes such as pain, trismus, temperature, and length of hospital stay in treatment groups relative to controls.[2]

Overarchingly, the current body of evidence supports the use of intravenous corticosteroids as an adjunctive treatment in the management of primary and deep space neck infections.[1,2,12] Corticosteroid use is therefore part of the current standard of care in clinical situations where rapid anti-inflammatory action is required. However, there is no consensus on the optimal administration regimen and dosing is currently determined by the clinical judgement and experience of the attending surgeon.[1] One commonly used regimen is to administer a single dose of methylprednisolone 125mg intravenously (IV) at the time of surgery. Another commonly used

regimen is to administer one dose of methylprednisolone 125mg IV at the time of surgery, followed by three consecutive doses of methylprednisolone 125mg IV every six hours post-operatively. Evidence-based guidance for determining ideal corticosteroid dosing in this context is currently limited.

The purpose of this study was to provide guidance for optimal dosing of methylprednisolone in the management of odontogenic cervicofacial infections. This prospective study followed the inpatient course of 28 patients with various cervicofacial infections of odontogenic origin. All patients were treated with a standardized surgical protocol (incision/drainage and extraction of necessary teeth), intravenous antibiotics, and one of two corticosteroid dosing regimens. 14 patients were randomized to receive a single dose of methylprednisolone 125mg IV at the time of surgery, while the remaining 14 patients received one dose of methylprednisolone 125mg IV at the time of surgery and three additional doses every six hours post-operatively. The only impact of study involvement was the steroid dosing schedule, as all patients continued to receive the current standard of care (surgical management, IV antibiotics, and corticosteroids). By examining differences in outcome success variables and complications between two commonly used methylprednisolone dosing regimens, the goal of this study was to support future evidence-based dosing decisions in the peri-operative treatment of inpatients in Manitoba.

Materials and Methods

Ethics approval was obtained according to the standard protocols of the University of Manitoba Biomedical Research Ethics Board (BREB) prior to the outset of this study. The participant population consisted of adult patients over the age of eighteen presenting with active acute or chronic cervicofacial infections of odontogenic origin between July 2022 and March 2023.

These patients were referred to the Oral and Maxillofacial Surgery Department at the Health Sciences Centre in Winnipeg, Manitoba by primary care physicians, dentists, and emergency room physicians throughout the province. At the time of presentation, patients were deemed to require surgical management under general anesthesia in the operating room and subsequent admission for supportive medical management by the Oral and Maxillofacial Surgery service on-call attending surgeons and residents.

All patients were assessed with a standardized history and physical examination prior to medical and surgical management. Pre-treatment imaging was also undertaken, which typically included a panoramic radiograph and an infused CT scan of the neck. All proposed treatment interventions were discussed with each patient. The material risks, benefits, and expected outcomes of both the medical and surgical interventions were reviewed in detail. A Consent to Procedure, Treatment, and Investigations Form was signed by all participants, as is routine for all patients admitted to Health Sciences Centre under the Oral and Maxillofacial Surgery service. A study-specific Patient Information and Informed Consent Form was also signed at this time and patients were provided a copy for their records.

Once written consent was obtained, each patient was formally admitted to hospital under the Oral and Maxillofacial Surgery service on-call attending surgeon. Patients were placed on the Health Sciences Centre emergency surgery list at the appropriate level of urgency. Each study participant underwent surgical management within 0-12 hours from the time of consent depending on operating room availability.

Treatment of all patients occurred at the Health Sciences Centre adult operating room and inpatient wards, which is the primary operating location for the University of Manitoba's attending

oral and maxillofacial surgeons in the Winnipeg Regional Health Authority (WRHA). Surgical management for each patient included extraction of necessary dentition for source control as well as transcervical and/or intraoral incision and drainage of affected fascial spaces of the head and neck region. Incision and drainage and subsequent tissue debridement was performed by one of four on-call attending oral and maxillofacial surgeons with the assistance of residents or interns. All patients remained admitted to the inpatient wards at Health Sciences Centre for supportive medical care throughout their post-operative course until deemed appropriate for discharge from hospital.

To participate in this study, patients were required to meet the following inclusion criteria: adult patient over the age of 18 years old, presenting with a cervicofacial infection of odontogenic origin, and requiring hospital admission and surgical intervention under the care of the Oral and Maxillofacial Surgery Department at Health Sciences Centre.

The following groups were excluded from study participation: patients who were unable to provide consent to study participation prior to surgery, either directly or via an alternative decision maker; patients with pre-existing medical conditions precluding the use of high-dose corticosteroids including known steroid hypersensitivity, severe immunocompromise, Type 1 diabetes or poorly controlled Type 2 diabetes (defined as HbA1C > 8.0%), systemic fungal infections, latent tuberculosis, herpes simplex keratitis, acute psychosis, Cushing's syndrome, peptic ulcer disease, significant renal insufficiency or markedly elevated serum creatinine, pregnancy, or breastfeeding; patients with concomitant facial fractures; patients with pathologic soft tissue or bony entities; and patients with cervicofacial infections of non-odontogenic origin (where adequate source control may be unachievable).

All patients were treated via a routine surgical protocol (including transcervical and/or intraoral incision and drainage and extraction of necessary teeth), antibiotics, and intravenous corticosteroids. 14 patients were randomly assigned to receive one dose of methylprednisolone 125mg IV at the time of surgery and no post-operative doses. The remaining 14 patients received one dose of methylprednisolone 125mg IV at the time of surgery and three consecutive doses of methylprednisolone 125mg IV every 6 hours post-operatively for a total of four doses. Both groups received treatment within the current standard of care for cervicofacial infections of odontogenic origin and represented dosing regimens that are commonly being used in practice. Solu-Medrol Act-O-Vials (125mg) containing methylprednisolone sodium succinate for injection USP, sterile powder, and diluent were administered according to the above dosing protocols.

Each patient's course in hospital was closely followed throughout their admission. Patients were attended to by oral and maxillofacial surgeons, residents, and ward nursing staff as per protocol for all patients admitted under the Oral and Maxillofacial Surgery service at Health Sciences Centre. Specific outcome measures including bloodwork and physical exam findings were evaluated at the time of hospital presentation, daily throughout admission during morning inpatient rounds, and at the time of hospital discharge.

Outcomes evaluated included C-reactive protein (CRP) levels, white blood cell (WBC) count, length of hospital admission (in days), trismus (in mm), and daily clinical examination findings. CRP levels (an acute phase reactant) were used as a hematologic biomarker of inflammation while WBC counts were used as a marker of infection severity and immune response. Length of hospital admission, trismus (or maximum interincisal mouth opening), and clinical examination findings were used as indicators of clinical recovery, functional improvement, and infection resolution. Bloodwork (including CRP and WBC levels) was drawn by emergency

room, inpatient ward, or operating room staff in a standard sterile fashion in keeping with hospital procedure. Maximum interincisal mouth opening was measured as a marker of trismus between the incisal edges of each patient's anterior maxillary and mandibular dentition during passive mouth opening. These measurements were taken daily using laminated, single-use intraoral rulers called Therabite Range of Motion scales (Henry Schein product # 255-009).

Study participation did not require any additional procedures or treatment outside of typical protocol and therefore did not change patients' pre-operative, intraoperative, or post-operative management. No additional follow-up visits, hospitalization time, or imaging studies were required beyond the standard of care for the Oral and Maxillofacial Surgery Department. Aside from assignment to one of two intravenous steroid dosing regimens currently in use, this study posed no departure from standard management of patients with odontogenic cervicofacial infections at our centre. As a result, no additional risks were undertaken by patients involved in the study as perioperative glucocorticoids would be administered to all patients in this context regardless of study enrolment.

Statistical Analysis

Data was collected and tabulated for a total of 28 patients. 14 patients were randomly assigned to receive one dose of methylprednisolone 125mg IV at the time of surgery and no post-operative doses. The remaining 14 patients received one dose of methylprednisolone 125mg IV at the time of surgery and three consecutive doses of methylprednisolone 125mg IV every 6 hours post-operatively, for a total of four doses. Data collected included patient demographics (age and sex), length of hospital admission (in days), as well as daily measurements of CRP, WBC, and trismus

(maximal interincisal mouth opening in mm). Statistical analyses were carried out using an integrated development environment program (RStudio 3.3.0+).

Multiple linear regressions (MLR) are used to investigate the joint effect of several explanatory variables on a response variable.[17] MLR is an example of a multivariate analysis where a single outcome variable can be related to two or more explanatory variables simultaneously.[17] The ordinary least squares method is used to assign multiple lines of best fit among variables in the data set. Multiple regression analyses are performed to identify explanatory variables associated with the response variable, determine the extent to which one or more of the explanatory variables are linearly related to the response variable, and possibly predict the value of the response variable from the explanatory variables.[17] Three MLRs were performed in our study analysis. The response variables for these three regressions were: change in CRP (ΔCRP) divided by length of stay (LOS), change in WBC count (ΔWBC) divided by LOS, and change in trismus (Δtrismus) divided by LOS. The explanatory variables that were included in each MLR were patient age, sex, and treatment arm (1 methylprednisolone dose vs. 4 methylprednisolone doses).

For each MLR, we subsequently evaluated the "goodness of fit" represented by the adjusted R^2 value. The adjusted R^2 value represents the proportion (often expressed as a percentage) of variance in the response variable that can be explained by its relationship to the explanatory variables.[17] Assessing goodness of fit is particularly important when using MLR equations for predictability. In our regressions, the adjusted R^2 values for ΔCRP/LOS, ΔWBC/LOS, and Δtrismus/LOS in relation to sex, age, and treatment arm were 0.06, -0.06, and 0.09 respectively. These low values show that the MLR analyses were a poor fit for the data and did not allow for an accurate prediction of the relationship between the explanatory and response variables.

After running the multiple linear regression analyses as outlined above, alternative statistical analyses were undertaken. An F-test (variance-ratio test) was completed to determine whether variance was equal or unequal between the two treatment groups. This calculation allowed us to accept the null hypothesis (that the population variances are equal) or the alternative hypothesis (that the population variances are unequal).[17] Variance was found to be unequal for ΔCRP/LOS and ΔWBC/LOS, and equal for Δtrismus/LOS. After completing the F-test, an unpaired, one-tailed t-test was performed with the appropriate variance assumption to examine differences in the means for each of the variables between the two treatment arms. An unpaired t-test was used because the patients in each of the two treatment groups were unrelated.[17] A one-tailed t-test was chosen over a two-tailed t-test because we assume that there will be a directional impact of the methylprednisolone treatment on CRP, WBC count, and trismus. A p-value was then calculated from this result to determine statistical significance for any difference in means between the two treatment groups.

Upon evaluation of the data, length of stay was not analyzed as an independent outcome marker because of significant confounding factors. Due to the demographics of the study patient population, length of stay in hospital was highly variable and complicated by issues such as patients' comorbid medical conditions, social situation, or need for return transportation to a rural area. Therefore, it was not felt to provide an accurate reflection of recovery speed between the two treatment arms. A decision was made not to analyze length of stay as an independent marker of treatment success due to these confounding variables.

Results

This prospective study followed the inpatient course of 28 patients with various cervicofacial infections of odontogenic origin. 14 patients were randomized to receive a single-dose regimen of methylprednisolone while the remaining 14 patients received a four-dose regimen. Study participants included 17 male and 11 female patients. Patient ages ranged from 21 to 75 years with an average age of 40.7 years. Length of hospital admission ranged from 2 to 9 days with an average length of stay of 4.6 days.

Our initial statistical analysis showed that multiple linear regressions for response variables ΔCRP/LOS, ΔWBC/LOS, and Δtrismus/LOS were poorly predicted by the explanatory variables (age, sex, and corticosteroid regimen). This was evidenced by low adjusted R^2 values. In each of the three regressions, the adjusted R^2 values for ΔCRP/LOS, ΔWBC/LOS, and Δtrismus/LOS in relation to sex, age, and corticosteroid regimen were 0.06, -0.06, and 0.09 respectively. This means that the relationship between the explanatory and response variables accounted for less than 10% of the variance in the response variable in each of the three regressions. These MLRs therefore could not be used to accurately predict the effect of the explanatory variables on the response variable.

Our subsequent statistical analysis involved an F-test to determine equal or unequal variance assumptions between the two treatment arms in each of the three response variables outlined above. This allowed for the calculation of an unpaired, one-tailed t-test for comparison of the means of the two treatment arms for each of the response variables.

In the variance assumption F-test for ΔCRP/LOS between the two treatment arms, we explored the null hypothesis (variances being equal) vs. the alternative hypothesis (variances are not equal).

The resultant p-value was less than 0.05 (0.0462), therefore we rejected the null hypothesis and accepted the alternative hypothesis that the variances of the two distributions were not equal. From there, an unpaired one-tailed T-test was completed which showed a p-value less than 0.05 (0.0256). This demonstrates that there was in fact a statistically significant difference in the mean ΔCRP/LOS between each of the two treatment arms. The average daily decrease in CRP across hospital admission was greater in the 4-dose methylprednisolone treatment group than the 1-dose group (Figure 6).

In the variance assumption F-test for ΔWBC/LOS between the two treatment arms, we explored the null hypothesis (variances being equal) vs. the alternative hypothesis (variances are not equal). The resultant p-value was less than 0.05 (0.0187), therefore we rejected the null hypothesis and accepted the alternative hypothesis that the variances were not equal. From there, an unpaired one-tailed T-test was completed which showed a p-value greater than 0.05 (0.478). This shows that there was no statistically significant difference in ΔWBC/LOS between the two methylprednisolone treatment arms (Figure 7).

Lastly, in the variance assumption F-test for Δtrismus/LOS between the two treatment arms, we explored the null hypothesis (variances being equal) vs. the alternative hypothesis (variances are not equal). The resultant p-value was greater than 0.05 (0.895), therefore we accepted the null hypothesis that the variances of the two distributions were equal. From there, an unpaired one-tailed T-test was completed which showed a p-value greater than 0.05 (0.277). This shows that there was no statistically significant difference in Δtrismus/LOS between the two treatment arms (Figure 8).

Discussion

The purpose of this study was to provide guidance for optimal dosing of methylprednisolone in the management of odontogenic cervicofacial infections. Current literature supports the use of intravenous corticosteroids as an adjunctive treatment in the management of primary and deep space neck infections, however, glucocorticoid dosing regimens are currently determined by the clinical judgment of the attending surgeon. This prospective study followed the inpatient course of 28 patients with various cervicofacial infections of odontogenic origin. 14 patients were randomly assigned to receive one dose of methylprednisolone 125mg IV at the time of surgery and no post-operative doses. The remaining 14 patients received one dose of methylprednisolone 125mg IV at the time of surgery plus three doses of methylprednisolone 125mg IV every six hours post-operatively. Patients were evaluated at the time of hospital presentation, daily throughout admission, and at the time of discharge. Outcomes evaluated included C-reactive protein (CRP) levels as a biomarker of inflammation, white blood cell (WBC) count as a biomarker of infection, length of hospital admission (days), and trismus (in mm).

Data analysis showed a greater average daily reduction in CRP throughout admission in the four-dose methylprednisolone group compared to the single-dose group that was statistically significant (p-value 0.0462). Recall that CRP is a pentameric protein synthesized by the liver whose levels increase in response to inflammation.[18] CRP is thus an acute phase reactant primarily induced by the action of IL-6 during the acute phase of an inflammatory or infective process.[18] Our study findings are in keeping with the known profound suppressive effect of methylprednisolone on inflammatory cytokines, chemokines, and other mediators of inflammation. It follows that patients who received four doses of methylprednisolone would have

a greater daily reduction in inflammatory mediators throughout their hospital stay than those who received a single dose.

We also know from the literature that exogenous corticosteroids can affect the circulating white blood cell count.[19] WBC count is a complex endpoint to follow as it is impacted by multiple factors in patient recovery. While a resolving infection would be expected to cause a fall in WBC levels, the process of surgical intervention and the administration of corticosteroids can both independently cause WBC levels to rise. Glucocorticoids typically result in increased polymorphonuclear leukocytes (PMNs) in the blood due to increased production in the marrow space and decreased removal from vascular circulation.[19] In contrast, mature leukocytes, eosinophils, monocytes, and basophils decrease after the administration of glucocorticoids. This is generally considered to be secondary to redistribution, however some lymphocytes will also undergo glucocorticoid-induced apoptosis.[19] The timing and degree to which steroid-induced changes in WBC levels occur is highly variable between patients and can happen 24 hours to several days into treatment. Our study involved administration of exogenous steroids for 24 hours or less in both treatment arms, which may cause variable effects on WBC levels. In addition, the stage at which patients present with a cervicofacial infection (inoculation, cellulitis, or abscess) would impact the degree of WBC elevation and thus the resulting change seen with treatment. A patient presenting with an infection in the cellulitis phase would be expected to have a higher WBC elevation than those presenting in the inoculation or abscess phase. No statistically significant difference in the mean daily change in WBC level was found between the two treatment groups, which is likely explained by these confounding factors.

Our study also found no statistically significant difference in the mean daily reduction of trismus throughout hospital stay between the two treatment arms (p-value 0.138). Return to normal

interincisal mouth opening was used as a marker of improved swelling in the masticator muscles and floor of the mouth, however this variable is also highly dependent on patient cooperation. All patients in the post-operative phase were counselled frequently throughout admission to engage in both active and passive stretches to return interincisal opening to the pre-infection range of motion as quickly as possible. Return of normal function decreases the likelihood of scar tissue formation and concomitant temporomandibular joint dysfunction, which may chronically limit mouth opening. In some instances, both inpatient and/or outpatient physiotherapy referrals may be necessary to return the patient to pre-morbid functioning. Because this variable is impacted by patient effort and participation in the post-operative period, this could have affected the results of the study independent of glucocorticoid dosing regimen.

While valuable information was obtained regarding differences in patient-centered outcomes (changes in CRP levels, WBC count, resolution of trismus, across length of hospital stay) between the two treatment groups, the results were insufficiently powered due small sample size (28 patients) and thus definitive conclusions could not be drawn. However, the data collected add to the existing body of research supporting the use of corticosteroids as a beneficial adjunct in the management of odontogenic cervicofacial infections. The data from this study could also be pooled with similar studies from other sites in the future. A multicentre study would benefit from larger patient samples and geographically diverse patient populations, thus improving the statistical power and external validity of its findings.

Methylprednisolone was used in this study as it is the corticosteroid of choice among surgeons at our centre. Alternative corticosteroids, however, may be preferred in other settings due to cost, availability, or surgeon preference. The advent of synthetic glucocorticoids through chemical modification has yielded compounds with varying pharmacodynamic and pharmacokinetic

properties. Duration of action, elimination half-life, and potency are the parameters that are principally affected. As highlighted in Table 1, there are numerous synthetic glucocorticoids with differing anti-inflammatory potencies, duration of action, and equivalent dosing. For example, dexamethasone is another common corticosteroid used at many centres throughout Canada, however its long half-life can make post-operative dosing more difficult in patients with a short course in hospital. Comparison between methylprednisolone and other corticosteroids was outside of the scope of this study. Further research examining differences in outcome variables between multiple synthetic glucocorticoids may prove valuable in the future.

The methylprednisolone dosing regimens chosen for this study are the two most commonly used at our centre. Participants were randomized to receive either one dose of methylprednisolone 125mg IV at the time of surgery or one dose of methylprednisolone 125mg IV at the time of surgery plus three additional doses every six hours post-operatively. Although both dosing regimens are currently used by oral and maxillofacial surgeons in Manitoba, it is important to note that common corticosteroid dosing practices vary across jurisdictions and individual practitioners. For example, other centres may employ weight-based corticosteroid dosing regimens in the management of head and neck infections (typically 1-3mg/kg IV).[1] Weight-based dosing may prove to be superior to fixed-dose regimens, as patient body weight or composition could have significant effects on the absorption, distribution, metabolism, or elimination of the drug. Further studies to directly compare weight-based and fixed-dose corticosteroid regimens may be useful, particularly in patients with obesity.

A common concern presented by clinicians and researchers when discussing corticosteroid dosing is the unwanted side effects associated with high-dose regimens. These include adrenal suppression, avascular osteonecrosis, and increased infection rate with decreased healing.[20]

Although there is a small risk of temporary adrenal suppression with high doses of corticosteroids, this suppressive effect is typically only seen when administered at higher than physiologic levels for longer than 5-14 days.[20] In this study, corticosteroids doses were given for no longer than 24 hours. In response to the possible risk of avascular necrosis associated with corticosteroids, Precious et al. completed a large retrospective review of 2773 patients which showed no increased risk of femoral head necrosis or subsequent need for hip replacement in patients receiving high-dose short-duration corticosteroids for orthognathic surgery.[21] Although some animal studies have shown decreased wound healing associated with corticosteroid administration, ten human trials showed no statistically significant decrease in healing. There is currently no meta-analysis data to support that corticosteroids meaningfully reduce healing rate.[19] Due to the short duration of high-dose steroids used in our study (less than 24hrs), impaired healing and increased infection rate were not of significant concern.

A placebo control group was not included in our study as a strong body of evidence supports corticosteroid use in the treatment of cervicofacial infections.[1,2] Withholding this treatment would be unethical as it is already within the current standard of care. Blinding of patients or researchers was also not included in the study design due to logistical challenges. Although our endpoints were objective (CRP level, WBC count, length of admission, degree of trismus), inherent bias could be introduced through trismus measurement error or tendency to discharge patients sooner or later.

The outcomes examined in this study focused only on short-term data measured during hospital admission. These endpoints were chosen because corticosteroids are used as adjunctive treatment during the acute phase of infection and management, therefore the perioperative period is when they exert most of their beneficial effects. Long-term follow-up was expected to be difficult in this context as patients do not routinely see oral and maxillofacial surgeons once their

infection has resolved, so patient attrition would likely be high. However, the lack of long-term data collection precluded us from determining if there were any clinically or statistically significant differences in long-term outcomes (recurrence rates, readmission, etc.) between the two groups.

It is also important to consider is that not all odontogenic cervicofacial infections are alike. Cervicofacial infections may include infections in any of the fascial spaces of the head and neck region. Fascial spaces of the head and neck can be categorized into primary and secondary spaces. Although patients with primary space infections (such as submandibular, submental, and sublingual space infections) may warrant hospital admission, medical management, and surgical incision and drainage, these infections tend to be inherently less aggressive. Patients with secondary space infections (such as lateral pharyngeal, retropharyngeal, pretracheal, or danger space infections) often present with higher acuity. Secondary or "deeper" space infections have a more profound effect on airway edema, which may lead to infiltration of the carotid vasculature or mediastinum and higher morbidity.[22] Subcategorizing patients with primary or secondary space infections would highlight those who are more likely to have a prolonged hospital admission, greater degree of trismus, and more septic picture on presenting bloodwork (higher CRP and WBC elevations).

In addition to location, cervicofacial infections vary by their stage at presentation. The clinical course of odontogenic cervicofacial infections can be divided into three key stages: inoculation, cellulitis, and abscess formation.[22] The inoculation stage is characterized by soft, diffuse, and mildly tender swelling for 0-3 days. The cellulitis phase is characterized by board-like, red, and severely painful swelling for 1-5 days. Lastly, abscess formation occurs after approximately 5-7 days and is characterized by the cessation of redness and severe pain of the cellulitis phase to produce a localized purulent collection. Depending on the stage of infection at which patients

present, they may naturally require more or less time admitted to hospital. Furthermore, patients in the cellulitis phase of infection may not develop a drainable collection for some time, which may impact medical and surgical management decisions. Subcategorizing patients based on the stage of their infection may be helpful to account for these differences in future studies.

Lastly, cervicofacial infections may also vary by their microbial profile. When patients are initially admitted with an odontogenic cervicofacial infection, they are started on empiric broad-spectrum intravenous antibiotics for presumed polymicrobial infection. Odontogenic infections are typically polymicrobial with a combination of facultative and anaerobic bacterial species.[22] At the time of surgical incision, drainage, and debridement, appropriate wound swabs or aspirates are collected for culture and sensitivity testing. Each patient's antibiotic regimen is subsequently tailored to target principal strains based on these results. The virulence of the predominant bacterial species in the infection can have a significant effect on patients' clinical course in hospital. Although most polymicrobial odontogenic infections are susceptible to penicillin-based antibiotics, it may take several days to obtain sensitivity data to confirm the appropriate choice of agent. This delay can affect patient recovery, leading to increased length of hospital stay or necessitating repeat surgical debridement regardless of corticosteroid treatment.

Overall patient health and co-morbidities also play a significant role in the treatment course of odontogenic cervicofacial infections. Diabetic or immunocompromised patients make up a significant portion of those admitted with odontogenic cervicofacial infections in Manitoba due to their elevated infection risk. The prevalence of non-insulin dependent diabetes in many First Nations communities, especially in Manitoba and Northern Ontario, is also several-fold higher than in the general population.[23] Although severely immunocompromised and poorly controlled diabetic patients were excluded from this study, these populations represent an important group in

whom the treatment of odontogenic cervicofacial infections poses unique challenges. Blunting of the immune response, hyperglycemia, and insulin resistance can occur with even short-term use of corticosteroids, which may lead to unacceptable side effects in these patients. Poorly controlled diabetes also causes diminished host defences and poor vascularity in small vessel beds, increasing the risk of surgical complications. Associated malnutrition, alcohol abuse, renal disease, or other chronic disease states may compound the immunocompromise in these patients and further complicate their management. Immunocompromised and diabetic patients are the most likely groups to have severe infections resulting in higher morbidity or ICU level care, therefore further research on the optimization of corticosteroid dosing in the management of these patients would be of interest in the future.

It is important to note that social determinants of health contribute considerably to the risk for and management of cervicofacial infections. Although not always the case, patients presenting to hospital with odontogenic cervicofacial infections are more likely to come from a lower socioeconomic background. Poor dentition and barriers to primary dental care put these patients at increased risk for infection and may lead to presentation at a more severe stage. Patients with associated substance use or malnutrition often require longer hospital admission than those with isolated odontogenic cervicofacial infections, as these patients require monitoring for withdrawal or refeeding syndrome. Furthermore, patients who meet discharge criteria from a medical standpoint may face social issues such as lack of safe housing, transportation, or primary care and require more time in hospital to address these challenges prior to disposition. Although assignment of patients to the treatment arms of this study was randomized, data on social factors was not collected to ensure both groups were similar. Social determinants of health may have had an impact

on study findings by contributing to longer hospital admission in some participants regardless of the corticosteroid treatment regimen they received.

Future Directions

The results of this study highlighted the importance of corticosteroids as an adjunctive treatment in the management of odontogenic cervicofacial infections. Cervicofacial infections are a common presentation to hospital and thus carry the potential for substantial patient morbidity and health care system burden. Corticosteroids represent a relatively safe, effective, non-invasive, and cost-efficient treatment adjunct to improve patient outcomes. Further research to delineate the ideal dosing regimen is needed to support evidence-based decision-making, optimize corticosteroid benefits, and minimize unwanted side effects. Although the results of this study showed that treatment with the four-dose corticosteroid regimen led to a larger average reduction in CRP level throughout hospital admission compared to the single-dose regimen, it is difficult to determine the clinical significance of this difference. Large multicentre studies are necessary to determine the best corticosteroid agent and dosing schedule, particularly in more challenging cases such as severe deep space infections, immunocompromised patients, or resistant antimicrobial strains. Longer-term data would also be beneficial to explore corticosteroid effects on outcomes such as recurrence and readmission rates. Perioperative corticosteroids and their effects in odontogenic cervicofacial infections will remain an important field of study in oral and maxillofacial surgery to continue to improve patient outcomes.

References

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Appendices

Figure Legends

Figure 1. Hypothalamopituitary axis. In: Mehta, S., Milder, E.A., Mirachi, A.J., & Milder, E. [2006]. Step-Up: A High-Yield, Systems-Based Review for the USMLE Step 1 [3rd ed., p. 165] Philadelphia, PA: Lippincott Williams & Wilkins.

Figure 2. Clinical photograph of a patient with classic signs of an odontogenic cervicofacial infection (pre-operative). ***A,*** Significant neck swelling in the submandibular and submental regions, elevation of the floor of the mouth, with a non-palpable inferior border of the mandible. ***B***, Worm's eye view of the same patient. The erythematous, cellulitic region has been marked with a marking pen to track cellulitic spread or reversal.

Figure 3. Clinical photograph of a patient showing limited mouth opening (trismus) and deflection of the mandible to the right on maximum interincisal opening (pre-operative). with classic signs of an odontogenic cervicofacial infection. Significant neck swelling in the submandibular and submental regions, elevation of the floor of the mouth, non-palpable inferior border of the mandible. The patient has limited mouth opening to approximately 20mm with a deflection of her mandibular dental midline to the right on maximum opening.

Figure 4. Examples of soft tissue coronal and axial slices of an infused CT neck, an imaging modality commonly used in the diagnosis of odontogenic cervicofacial infections. ***A,*** Coronal slice through a CT Neck Infused showing a large left submandibular abscess of odontogenic origin with mass effect and deviation of the airway to the right. ***B***, Axial slice through a CT Neck Infused showing a large left submandibular abscess and mild concomitant airway narrowing secondary to edema and inflammation.

Figure 5. Example of a panoramic radiograph showing a grossly carious tooth 38 with periapical radiolucency and evidence of hard tissue destruction. Standard panoramic radiography is a useful imaging modality for the localization and diagnosis of infected dentition.

Figure 6. Comparison of mean daily change in CRP throughout hospital admission for the 4-dose and 1-dose methylprednisolone groups. CRP levels were measured for all participants at the time of hospital presentation, daily throughout admission, at upon discharge. Each patient's overall change in CRP was divided by length of stay to provide an average daily change in CRP. The mean daily change in CRP for the 4-dose methylprednisolone group (mean = 29.09) was compared to the 1-dose methylprednisolone group (mean = 20.62) using an unpaired, one-tailed t-test. A larger mean daily CRP reduction in the 4-dose group was shown to be statistically significant ($p = 0.026$).

Figure 7. Comparison of mean daily change in WBC throughout hospital admission for the 4-dose and 1-dose methylprednisolone groups. WBC levels were measured for all participants at the time of hospital presentation, daily throughout admission, at upon discharge. Each patient's overall change in WBC was divided by length of stay to provide an average daily change in WBC. The mean daily change in WBC for the 4-dose methylprednisolone group (mean = 1.37) was compared to the 1-dose methylprednisolone group (mean = 1.40) using an unpaired, one-tailed t-test. No statistically significant difference between the mean daily change in WBC was found between the two treatment groups ($p = 0.478$).

Figure 8. Comparison of mean daily reduction in trismus throughout hospital admission for the 4-dose and 1-dose methylprednisolone groups. Maximal interincisal opening measurements were taken for all participants at the time of hospital presentation, daily throughout admission, at upon discharge as a marker of trismus. Each patient's overall change in maximal interincisal opening (in mm) was divided by length of stay to provide an average daily change in trismus. The mean daily reduction in trismus for the 4-dose methylprednisolone group (mean = 2.99) was compared to the 1-dose methylprednisolone group (mean = 2.44) using an unpaired, one-tailed t-test. No statistically significant difference between the mean daily reduction in trismus was found between the two treatment groups ($p = 0.277$).

Figures

Figure 1

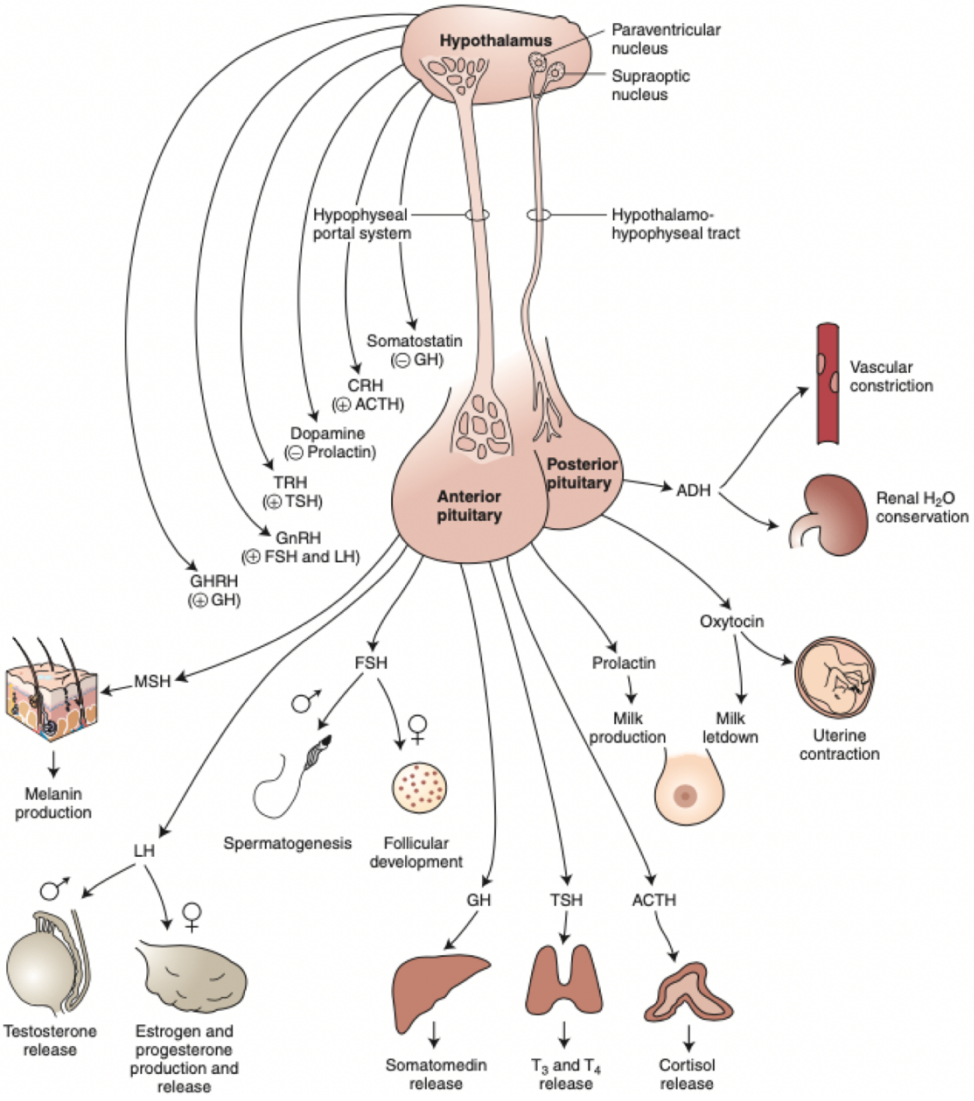
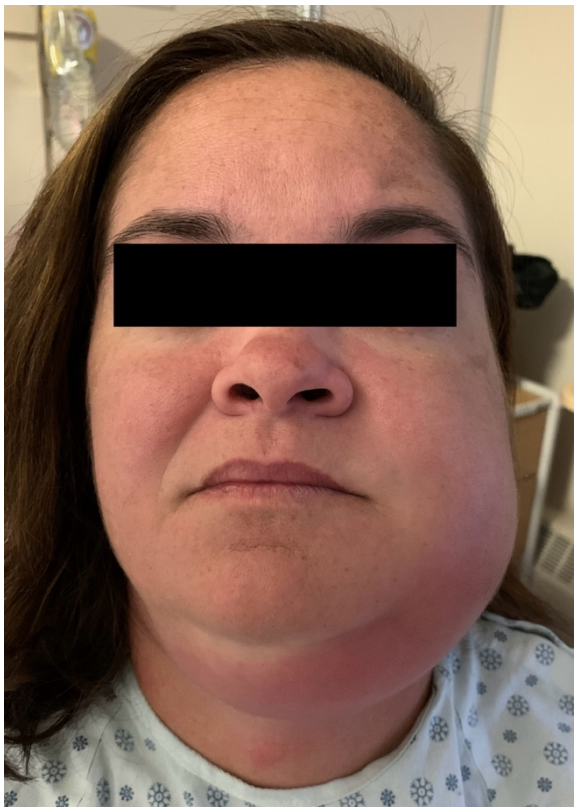


Figure 2

A.



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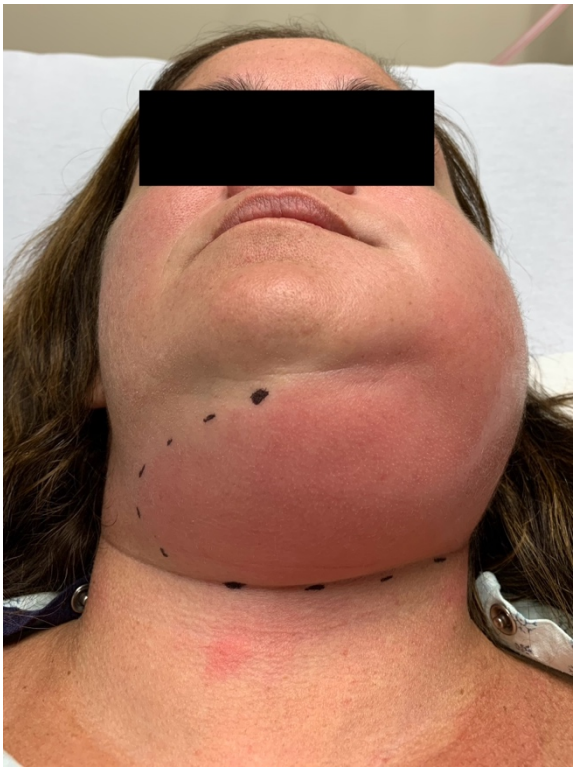


Figure 3

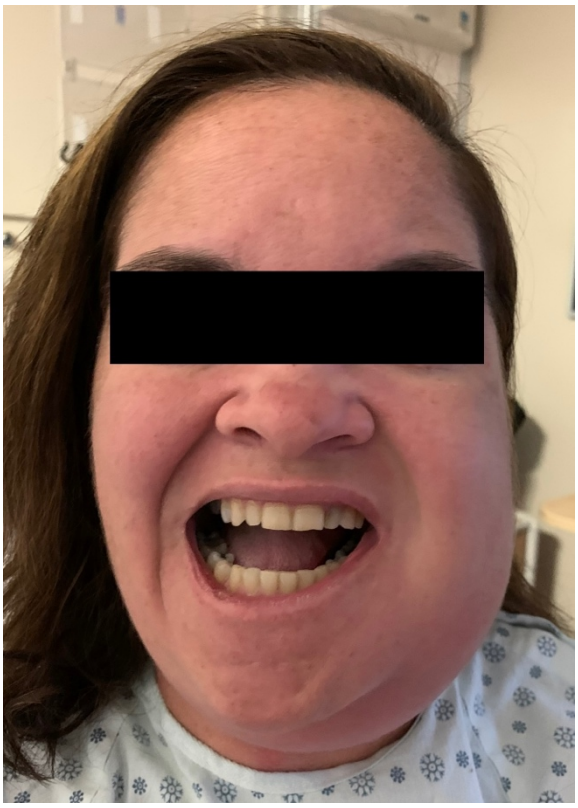
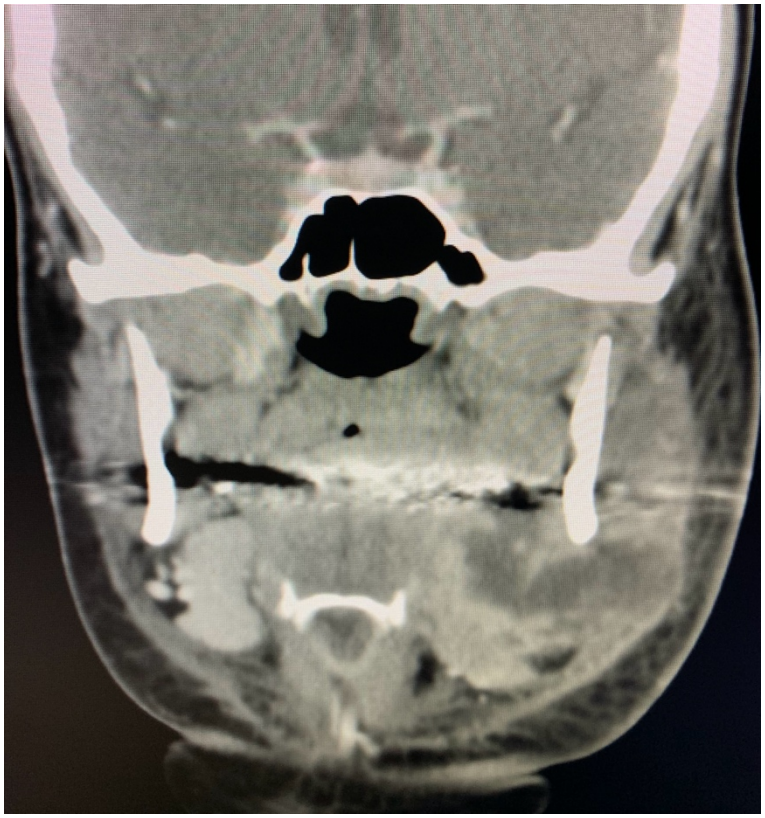


Figure 4

A.



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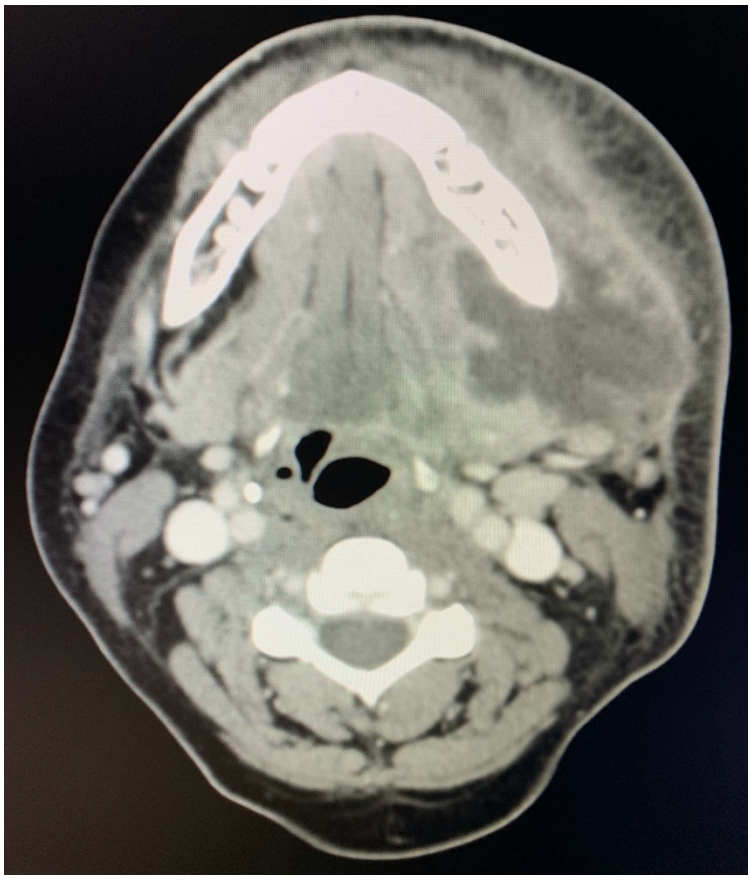

Figure 5

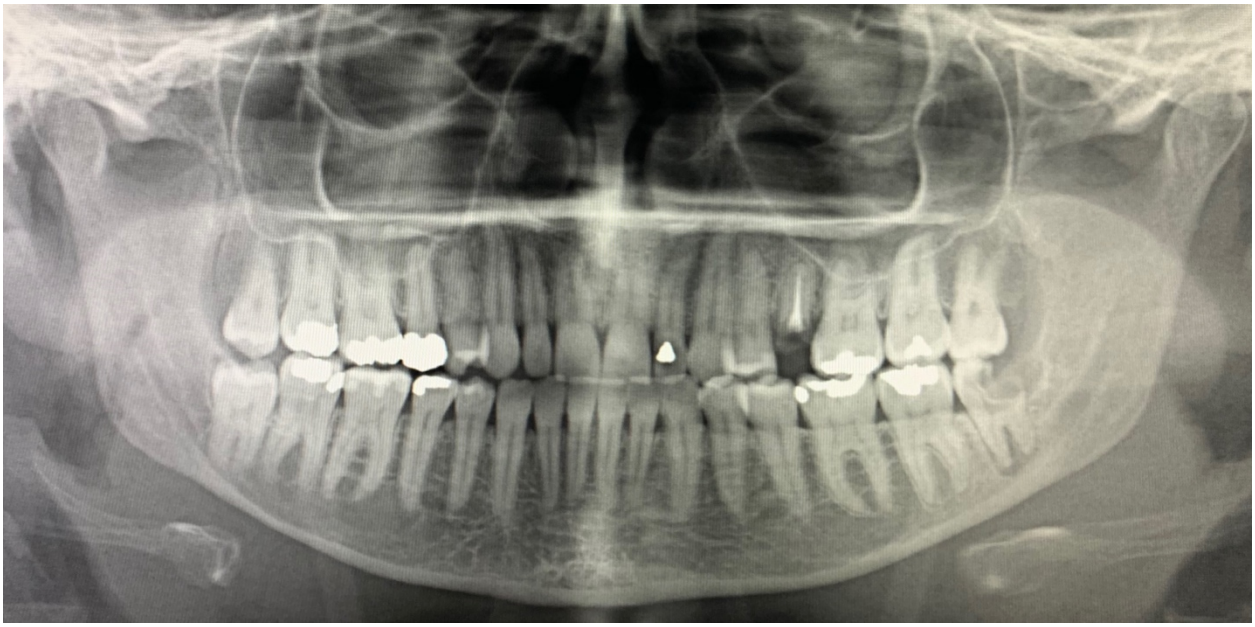

Figure 6

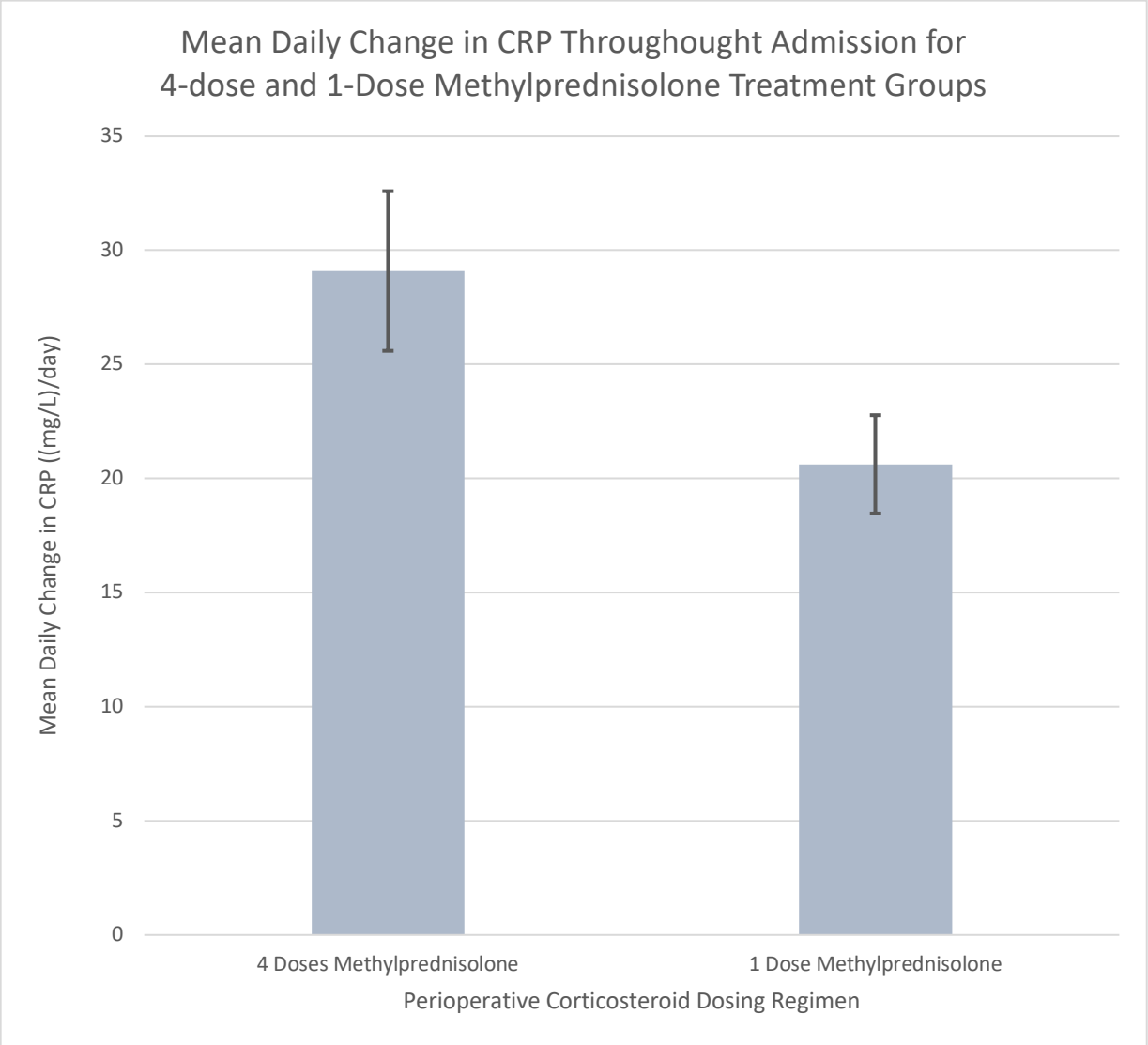
Mean Daily Change in CRP Throughought Admission for
4-dose and 1-Dose Methylprednisolone Treatment Groups
Mean Daily Change in CRP ((mg/L)/day)
35
30
25
20
15
10
5
0
4 Doses Methylprednisolone
1 Dose Methylprednisolone
Perioperative Corticosteroid Dosing Regimen

Figure 7

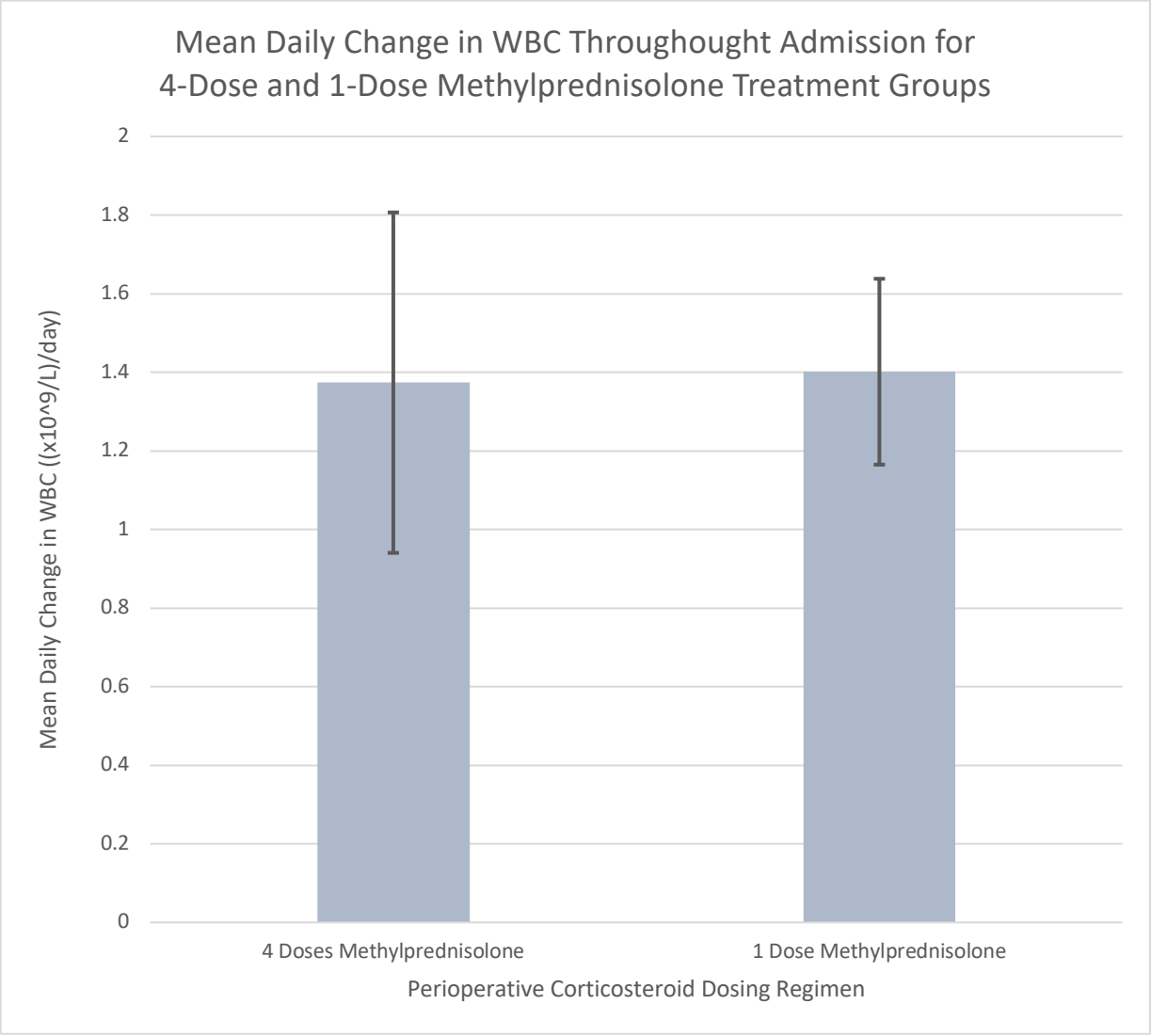
Mean Daily Change in WBC Throughought Admission for
4-Dose and 1-Dose Methylprednisolone Treatment Groups
Mean Daily Change in WBC ((x10^9/L)/day)
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
4 Doses Methylprednisolone
1 Dose Methylprednisolone
Perioperative Corticosteroid Dosing Regimen

Figure 8

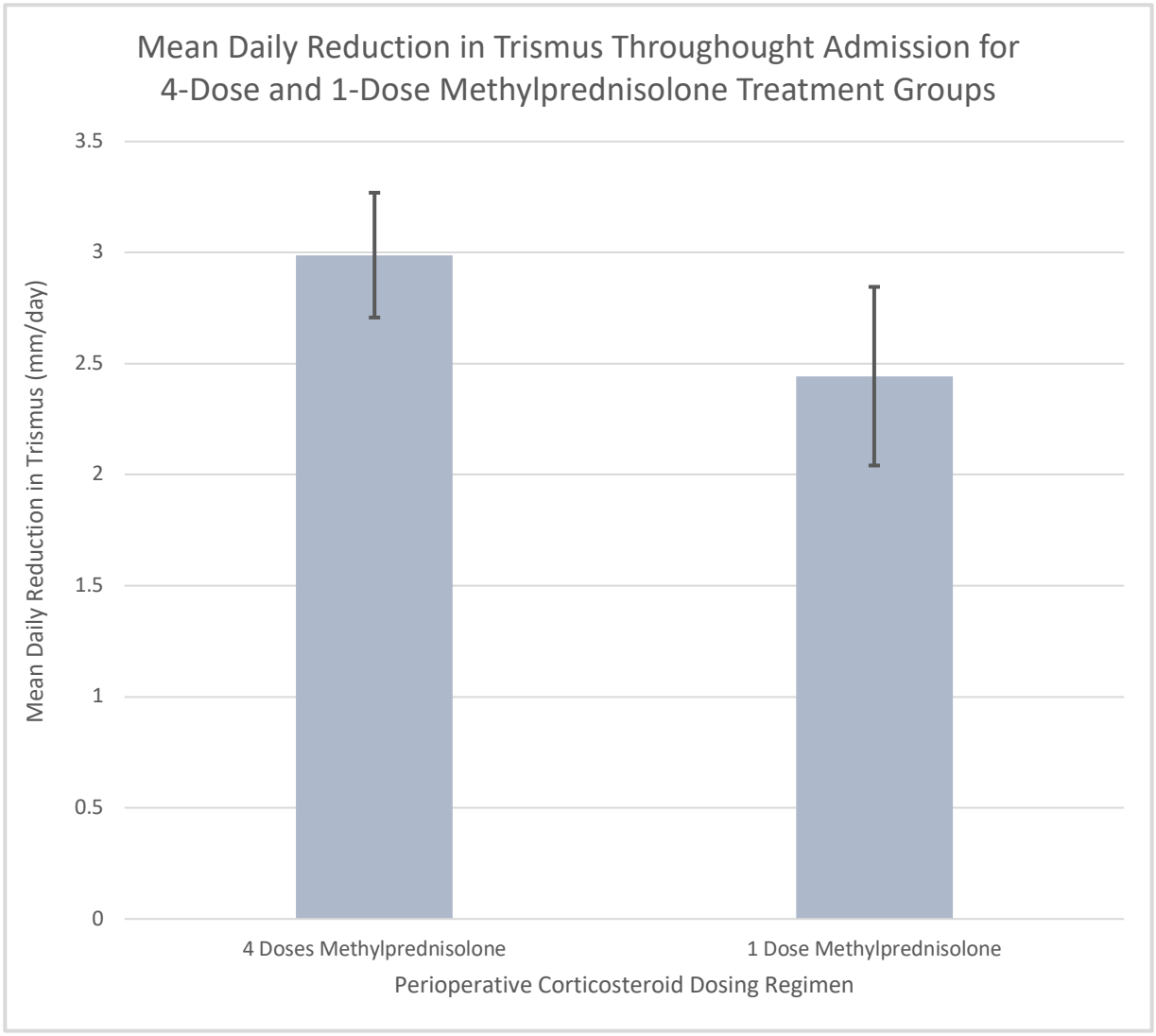
Mean Daily Reduction in Trismus Throughought Admission for 4-Dose and 1-Dose Methylprednisolone Treatment Groups
Mean Daily Reduction in Trismus (mm/day)
3.5
3
2.5
2
1.5
1
0.5
0
4 Doses Methylprednisolone
1 Dose Methylprednisolone
Perioperative Corticosteroid Dosing Regimen

Table Legends

Table 1. Relative potency and duration of action of synthetic glucocorticoids. Duration of action: S-short (8-12hr half-life), I-intermediate (12-36hr half-life), L-long (36-72hr half-life). In: Goodman LS, Brunton LL, Chabner B, Knollmann BC: Goodman & Gilman's pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011.

Table 2. Relative genomic and non-genomic glucocorticoid potencies indexed to prednisone. In: Lipworth BJ: Therapeutic implications of non-genomic glucocorticoid activity. The Lancet 356: 87, 2000.

Tables

Table 1

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

Table 2