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COMPARISON OF PREOPERATIVE METHYLPREDNISOLONE AND IBUPROFEN ON MANDIBULAR ANESTHESIA EFFICACY

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DEDICATION

To Nicol, my beloved wife, who has spent half of our marriage supporting my academic adventures, and my two beautiful children, Anika and Ryden, who have followed me all around the world.

DISCLAIMER

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ABSTRACT

Comparison of Preoperative Methylprednisolone and Ibuprofen on Mandibular Anesthesia Efficacy

Jeffrey M. Clark, D.D.S., 2021

Thesis directed by: CAPT Susan E. Hinman, D.D.S., M.S., Program Director, Endodontics, Naval Postgraduate Dental School

Introduction: Effective pain control is vital to the practice of modern dentistry. Mandibular pulpal anesthesia is commonly achieved using an inferior alveolar nerve block (IANB). Irreversible pulpitis however, can reduce IANB success to as low as 20%. This high failure rate has been attributed to the inflammatory process. Both nonsteroidal anti-inflammatory medications (NSAIDs), and corticosteroid medications have been reported to increase IANB success in inflamed tissues. One clinical trial demonstrated the superiority of a steroid medication over NSAIDs in non-inflamed tissues. To date, no study has compared these two medications in inflamed pulp tissue. Objective: This prospective, double-blind, randomized clinical trial will compare IANB success in patients with symptomatic irreversible pulpitis when given ibuprofen or methylprednisolone prior to initiating endodontic treatment. **Methods**: Subjects meeting inclusion criteria were enrolled and baseline pain level was recorded using a 0-100mm visual analog scale (VAS). They then received an identical appearing encapsulated medication of either 800mg ibuprofen or 40mg methylprednisolone. After forty-five

minutes, 54mg of 2% lidocaine, 1:100,000 epinephrine was administered by IANB. Fifteen minutes later subjects were questioned for lip anesthesia. If lip anesthesia was achieved, the procedure was initiated. If not, subjects were excluded from data collection. If pain occurred during treatment, subjects rated their pain level on a VAS. Supplemental anesthesia was administered for pain rated greater than mild (51-100mm). A final VAS pain score was recorded 48 hours after treatment to compare post procedure pain control. **Results**: Subject enrollment is ongoing. Three subjects were enrolled with one failed block and one protocol deviation. Statistical analysis was not completed. **Conclusion**: No conclusions have been reached due to limited enrolment.

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LIST OF ABBREVIATONS

IANB	Inferior Alveolar Nerve Block
VAS	Visual Analogue Scale
NSAID	Non-steroidal Anti-inflammatory Drugs
SIP	Symptomatic Irreversible Pulpitis

CHAPTER 1: Introduction

Successful anesthesia and pain management during endodontic treatment is considered essential. For the mandibular dentition, the most commonly used anesthetic technique is the inferior alveolar nerve block (IANB). Unfortunately in many cases, this technique does not provide successful anesthesia adequate to perform endodontic treatment. Supplemental techniques such as buccal infiltration or intraosseous delivery of local anesthetic is often required to complete endodontic treatment with minimal pain.[1] A successful block is often evaluated by observing numbness of the lower lip on the side of the block injection, this is due to the nerve endings terminating distal to the deposition of local anesthetic on the nerve trunk. Failure of the IANB is defined as pulpal sensation in the presence of profound lip numbness. Failure rates of the conventional IANB have been reported between 38% and 81% in clinical studies. [2,3]

IANB success is further reduced in the presence of pulpal inflammation. Clinically this is found in patients who exhibit symptomatic irreversible pulpitis (SIP). The clinical presentation of SIP is demonstrated by sharp pain, often in response to thermal stimulation, often lingering for 30 seconds or longer after stimulus removal. [4] This condition marks the tipping point where further insult will result in necrosis of the pulp and therefore requires endodontic therapy. [5] Clinical studies have shown that SIP can decrease the success rate of the IANB. [6]

A prominent theory that accounts for the higher IANB failure in teeth with irreversible pulpitis relates to the presence of inflammatory mediators in the pulp.[7] The pulpal inflammatory response to bacterial invasion modulates and amplifies pain perception through the production of mediators and cytokines that lower pain thresholds.

Of particular interest are prostaglandins, formed from arachidonic acid found in cell membranes, and produced by the action of cyclooxygenase enzymes. Prostaglandin E3 (PGE2) is known to be involved in the development and amplification of pain.[7,8] The increased sensitization of nociceptors as a result of pulpal inflammation adversely affects the effect of local anesthetics.[9]

When applying this knowledge clinically, oral premedication with anti-inflammatory drugs, either steroidal or non-steroidal, has shown the ability to modulate success rates of the IANB in both symptomatic and asymptomatic patients.[10-13] However, to date no study exists that directly compares the two classes of medications in patients with symptomatic teeth and the impact of these medications on the IANB success rate.

The primary objective of this study was to compare 800 mg ibuprofen to 40mg methylprednisolone administered orally 1 hour prior to endodontic treatment on the efficacy of an IANB with 68mg of 2% lidocaine and 0.034 mg of epinephrine in patients with symptomatic irreversible pulpitis. Our second objective was to observe the medications' effects on supplemental anesthesia, if needed. The third objective was to observe the effects of this single preoperative dose of either a steroid, or NSAID, on post-operative pain. Our null hypothesis is that there is no difference in success rates between patients who were administered NSAID's or steroid medications prior to treatment.

CHAPTER 2: Materials and Methods

Materials and methods adapted from Neal, R. 2020 Thesis Manuscript

This Walter Reed National Military Medical Center (WRNMMC) Institutional Review Board (IRB) approved study was completed by the Naval Postgraduate Dental School (NPDS) Endodontics Clinic. The clinic is a referral base clinic. All scheduled and/or emergency (sick-call) patients undergo a thorough clinical and radiographic examination. An analysis using clinical statistics from a recent systematic review helped establish the power of our study. At a 95% confidence interval, it is estimated that 80% of the steroid group will have successful anesthesia versus 60% for the NSAID group. We have adjusted the per group subject number to 50, totaling 100 subjects.

To qualify for this study, each subject had a tooth that fulfilled the inclusion criteria for a clinical diagnosis of symptomatic irreversible pulpitis: a vital mandibular posterior tooth actively experiencing pain, a prolonged response to cold testing using Green Endo-Ice (1,1,1,2 tetrafluoroethane; Hygenic Corp, Akron, OH), and had not taken any analgesics within the past 8 hours. Exclusion criteria were as follows: any person under the age of 18 years, allergies or sensitivities to ibuprofen or methylprednisolone, allergies or sensitivities to local anesthetics or sulfites, pregnant or nursing, prescribed long term steroid medication, history of a serious medical condition preventing routine dental treatment, or diagnosed with a medical condition that is specifically contraindicated for steroid medication or use of NSAIDs. Subjects with no response to cold testing, presence of peri-radicular pathology (other than a widened periodontal ligament), or the lack of vital coronal pulpal tissue upon endodontic access, were also excluded from the study.

Patient Data Collection Sheet

Subject #: _____

Preoperative Pain:

Visual Analog Scale (VAS): Please indicate on line below your current pain level.

_____

No Pain Worst Pain

Pain felt during treatment after initial anesthetic delivery:

Visual Analog Scale (VAS): Please indicate on line below your current pain level.

_____

No Pain Worst Pain

Pain felt during treatment after buccal supplemental anesthetic delivery:

Visual Analog Scale (VAS): Please indicate on line below your current pain level.

If yes, indicate below:

_____

No Pain Worst Pain

Pain felt during treatment after intraosseous anesthetic delivery:

Visual Analog Scale (VAS): Please indicate on line below your current pain level.

If yes, indicate below:

_____

No Pain Worst Pain

Figure 1. Patient Data Collection Sheet

After written informed consent was obtained, the subject rated their pain level prior to administration of an analgesic on a visual analogue scale (VAS). The VAS used was 100mm in length with no identifying marks as to not unduly influence the patient. After

the subject marked their pain level, the mark was measured and placed into one of the following categories: no pain (0 mm), mild pain (> 0mm to 50mm), moderate pain (> 50mm to 75mm), and severe pain (75mm or greater). Subjects rated their pain on this scale at specific timeframes during treatment dependent upon when anesthetic success was achieved.

Two oral medications were compared in this study: 800mg ibuprofen and 40mg methylprednisolone. The medications were blinded to the subject and provider in four identical capsules. Medications were compounded by the Investigational Pharmacy Department at WRNNMC. A third party enrolled each subject into the study and administered the medication. Forty-five minutes after oral administration of the blinded medication, the anesthesia procedure commenced. All injections were administered by one of three board certified endodontic staff members. Prior to the injection, the anesthetic injection site was dried with a 2 x 2 gauze, then 20% benzocaine topical anesthetic gel was placed at the site using a cotton tip applicator and left for 1 minute. Standard IANB and long buccal nerve block (LBNB) injections were administered with an aspirating syringe and a 27-gauge, 1 ¼ in. needle. Each cartridge of anesthetic used contained 34mg of 2% lidocaine with 0.017mg of epinephrine, and measured 50mm in length from the end of the aluminum cap to the stopper. A line was drawn at 25mm on every cartridge to designate the halfway point. Each subject received 2 full cartridges of anesthetic in total with 1.5 cartridges given as an IANB and 0.5 cartridges given as a LBNB.

After anesthetic delivery, the subject remained in a semi-supine position for fifteen minutes. The subject was questioned for lip anesthesia at five-minute intervals for

up to fifteen minutes. If after fifteen minutes anesthesia was not achieved, the block was considered missed. The subject was given more anesthetic to obtain profound anesthesia, however, data collection was terminated for that subject. If profound lip anesthesia was achieved, endodontic treatment commenced. Teeth were isolated with a rubber dam and endodontic access was initiated (60 minutes elapsed since taking blinded medication). Subjects were instructed to raise a hand to alert the dental team if they felt pain during the endodontic procedure. The goal of treatment was a thorough pulpal debridement of each canal. If pain occurred, the procedure was immediately stopped, and the patient rated their pain level on a VAS scale. The success of the IANB was defined as the ability to access and instrument the canal(s) without pain (VAS score of 0) or mild pain (VAS score of 1 - 50mm).

For those who rated their pain as moderate or severe during treatment, the rubber dam isolation was removed, and a supplemental buccal infiltration injection was administered using a 27-gauge short needle and a cartridge of 68mg 4% articaine with 0.017mg epinephrine. This anesthesia was placed in the buccal alveolar mucosa at the depth of the apex (apices) of the tooth under treatment. Rubber dam isolation was reapplied five minutes after the supplemental injection and endodontic access was continued. The supplemental injection was considered a success if endodontic access, initial file placement, and canal debridement were completed without pain (VAS score of 0) or mild pain (VAS score of 1 - 50mm). Once again, if the subject indicated pain during access or instrumentation, the procedure was stopped, and the subject rated their pain level on a VAS scale. If the pain level was moderate or severe, the infiltration injection was deemed a failure and an intraosseous injection was given as described by

previous authors.[14] As a last resort, if pain still occurred after the intraosseous injection, an intrapulpal injection was given. If an intrapulpal injection was administered, no more VAS scores were obtained, and the patient was given enough anesthesia to complete a thorough pulpal debridement.

If treatment was stopped prematurely, the initial IANB was considered a failure. After full treatment was completed, the subject was given the same VAS assessment. Additionally, after completion of treatment, each subject was given a pain journal and asked to document their pain level six, twelve, twenty-four, and forty-eight hours after treatment. The post-operative pain journal was returned to the provider at the follow up appointment, often for completion of root canal therapy or within two weeks of completion of treatment. [15]

CHAPTER 3: Results

Power analysis determined that a total of 100 subjects, 50 per group, was a sufficient study size. Currently, three subjects have been enrolled into the study. The first subject had a preoperative pain VAS measurement of 100mm indicating the most severe pain level. Following IANB and LBNB injections, the patient achieved profound lip numbness and treatment commenced. The subject's pain level on treatment lowered to moderate; however, a supplemental injection was needed. In addition, the first supplemental injection was deemed a failure and the patient required an intraosseous injection. The subject's VAS pain level remained mild until the completion of pulpal debridement.

Two additional subjects were enrolled in the study since the last report, one who had a "missed block" and the second who had a "deviation from research protocol" that resulted in inadmissible results. The lack of further enrollements is suspected to be the result of COVID-19's impact on patient flow at the treatment facility. No statistical analysis has been performed. This is a long-term clinical study and enrollment will continue until 100 subjects is reached.

CHAPTER 4: Discussion

For this study, we postulated that NSAIDs would be inferior to steroid medications in increasing IANB success rates. Our null hypothesis was that there would be no difference between the two medications. Although there is inadequate data to support or reject our null hypothesis, the current author believes there is not likely to be a statistical difference between the medications at the 1-hour mark. This belief is based on the pharmacokinetics of the medications examined.

Mechanism of action:

Nonsteroidal anti-inflammatory drugs (NSAIDs) are members of a drug class that reduce pain, decrease fever, prevent blood clots, and in higher doses, decrease inflammation. Ibuprofen, (Figure 2.) is a chiral 2-arylpropionic acid derivative non-steroidal anti-inflammatory drug. It is both widely used and well tolerated for its analgesic properties.[16] Ibuprofen is a non-selective cyclooxygenase (COX) inhibitor, which inhibits both COX-1 and COX-2 forms. However, its analgesic, antipyretic and anti-inflammatory effects are primarily achieved through COX-2 inhibition.[17]

As with most analgesics, the initial rise in plasma concentration following oral administration of ibuprofen is a primary factor in determining the time to onset of pain relief .[17] ibuprofen is rapidly absorbed, and both peak plasma concentrations and maximal analgesic onset are achieved within 1.5-2 hours of oral administration.[19,20]

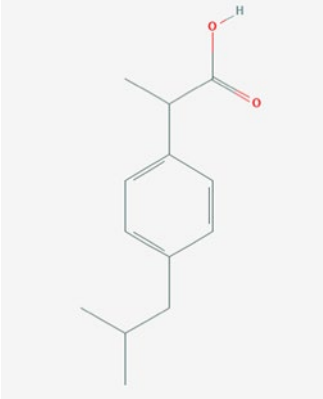

Figure 2. Ibuprofen

Key pharmacokinetic studies have demonstrated a linear dose-response relationship between the amount of drug administered and the area under the serum concentration-time curve (AUC) following single doses of ibuprofen (200-800 mg).[18] In other words, one can expect a more profound effect earlier if a higher dose is administered. There is also a significant correlation between plasma ibuprofen levels and the resultant degree of pain relief, particularly 1 hour after administration. [20,21]

Multiple clinical studies have demonstrated a significant increase in IANB success rates when NSAIDS are given orally prior to treatment. This effect has been shown in both symptomatic[22] and asymptomatic[23] patients. In one study, 600mg ibuprofen given 1 hour prior to injection increased success rates from 32% (placebo) to 78%[22.] When comparing multiple studies in a systematic review, dosages >400mg are required to have an effect on IANB success rates.[24] There is also a potential added benefit to pre-op medications in that supplemental anesthesia success may also be improved, providing an additive effect when multiple anesthetic modalities are used[25] thereby increasing the likelihood of a painless dental procedure.

Glucocorticoids:

Glucocorticoids are steroid hormones with potent anti-inflammatory and immunosuppressant properties. These properties are mediated by both genomic and non-genomic mechanisms. Non-genomic mechanisms function by blocking phospholipase in the arachidonic acid pathway, they have a more rapid onset (seconds to minutes) and

shorter duration of effect (60-90 minutes) then their genomic counterparts.[26] In contrast, genomic mechanisms involve modulation (activation or inactivation) of specific genes that code for anti or pro inflammatory proteins. Because of this, genomic glucocorticoid action is typically characterized by a slower onset due to the time-consuming mRNA transcription and translation process. This process involves many steps and involves a time lag of about 4-24 hours.[27]

Methylprednisolone (Figure 3.) is a glucocorticoid that is both naturally occurring and synthetically available with a dose equivalent of 5x the potency of cortisone acetate.

The plasma concentration of orally administered methylprednisolone r Figure 3. peak at approximately 1.72 hours after oral administration with 90% concentration being achieved at the 1 hour mark.[28] The processes of absorption, distribution, metabolism, and excretion, are affected by a non-linear protein binding pattern.[29]

Glucocorticoids are also lipophilic molecules that can easily diffuse across the cell membrane and bind to the glucocorticoid receptors (GRs) in the cytoplasm.[30] Once inside the cell after passive diffusion, they bind to the GRs in the cytoplasm and go on to modulate nuclear transcription, increasing expression of anti-inflammatory genes and decreasing expression of pro-inflammatory genes.[31,32] This gene activation leads to increased transcription of anti-inflammatory genes such as annexin-1 and IL-10.[33] Additionally, GR represses the activity of many important pro-inflammatory genes by binding to and inhibiting key transcription factors, like nuclear factor kappa B (NFkB),[34] which will then lower tumor necrosis factor α (TNFα), and interleukin 1 beta (IL-1β).

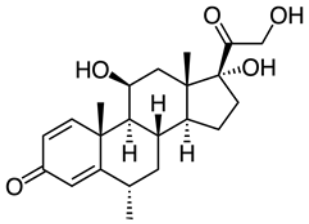

Figure 3. Methylprednisolone

It is unclear the exact mechanisms of the non-genomic actions of glucocorticoids. They affect the physiochemical properties of the cell membrane, either directly or by binding to intracellular or membrane-bound GR's.[35] These effects result in the inhibition of the inflammatory cell function. However, most anti-inflammatory effects of glucocorticoids are due to the transrepression of pro-inflammatory and immune genes.[36] Traditionally, it is believed that arachidonic acid is produced by the action of cytosolic phospholipase A2 (cPLA2) on membrane phospholipids. By binding to its receptor on the cell membrane, epidermal growth factor (EGF) can activate cPLA2 and therefore arachidonic acid production. When bound to glucocorticoid receptors in the cytosol, some components dissociate, blocking phospholipase A2 resulting in blockage of the arachidonic acid production.[36]

A previous randomized clinical trial in asymptomatic patients showed that both ibuprofen and dexamethasone increased success rates of the IANB, however dexamethasone was statistically superior to ibuprofen.[13] Similarly, a meta-analysis comparing multiple medications and their effect on IANB success showed better performance of dexamethasone at increasing the success rate of IANB compared to all other drugs.[37] In comparing NSAID's to steroids, a recent clinical trial found that when delivered via a periodontal ligament injection to patients with symptomatic pulpitis, there was a significant success rate in anesthetic efficacy at the 45 minute mark.[38]

CHAPTER 5: Conclusions

As noted, there are some similarities between steroid and NSAID drugs, however given the significant differences in their mechanism of actions, one should show superiority over the other in a clinical setting. Future data will likely show one of three different outcomes. The first being that 800mg ibuprofen is superior at one hour due to a more profound reduction in pain given its fast acting effect on PGE2. The second potential finding is that they are the same at the one-hour mark given similar non-genomic mechanisms. The third possible scenario is that steroids are simply more effective, both in the non-genomic as well as genomic effects. A final scenario, that is unable to be evaluated by this clinical trial, is that steroids will start to show superiority around 6 hours after administration, once the genomic effects stack with the non-genomic effects. This is where comparing the post-operative pain control becomes a relevant data point for a provider selecting one medication over the other.

In this study, no conclusions can currently been drawn due to the low number of subjects. This project is on-going and data will be provided as subjects are enrolled.

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