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COMPARISON OF PREOPERATIVE METHYLPREDNISOLONE AND IBUPROFEN ON MANDIBULAR ANESTHESIA EFFICACY

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CERTIFICATE OF APPROVAL

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MASTER'S THESIS

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This is to certify that the Master's thesis of

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ABSTRACT

COMPARATIVE EVALUATION OF PREOPERATIVE METHYLPREDNISOLONE OR IBUPROFEN ON ANESTHETIC EFFICACY OF INFERIOR ALVEOLAR NERVE BLOCKS IN PATIENTS WITH SYMPTOMATIC IRREVERSIBLE PULPITIS

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Introduction: Pain management is a critical component for a successful appointment during endodontic procedures. The most common method for delivering mandibular pulpal anesthesia is an inferior alveolar nerve block (IANB). Success rates for achieving adequate pulpal anesthesia range from 25% to 90%. A prominent theory for anesthetic failure is the presence of pulpal inflammation. Symptomatic irreversible pulpitis activates the inflammatory response and increases the production of pain producing neuropeptides and anesthetic resistant sodium channels. Recent clinical trials and systematic reviews have shown an increase in successful anesthesia using a preoperative nonsteroidal anti-inflammatory drug (NSAID). Furthermore, a clinical trial found a greater increase in IANB efficacy using a low dose corticosteroid in comparison to an NSAID in asymptomatic patients. **Objectives:** This prospective, double-blind, randomized clinical trial compared the effectiveness of ibuprofen to methylprednisolone on IANB anesthetic efficacy in patients diagnosed with symptomatic irreversible pulpitis. **Methods:** Patients meeting inclusion criteria were enrolled. Subject baseline pain was recorded using a 0-100mm visual analog scale (VAS). Subjects then received either 800mg ibuprofen or 40mg methylprednisolone (identical capsules formulated in an investigational pharmacy). After forty-five minutes, 54mg of 2% lidocaine, 1:100,000 epinephrine was administered. Fifteen minutes later subjects were questioned for lip anesthesia. If lip anesthesia was achieved, the endodontic procedure was initiated. If not, subjects were excluded from data collection. If pain occurred during treatment, subjects rated their pain on a VAS. Supplemental anesthesia was administered for pain rated greater than mild (51-100mm). **Results:** Subject enrollment is continuing, one subject has completed the study. **Conclusion:** Corticosteroids are more potent

anti-inflammatories than NSAIDs. Their use has been clinically proven to alleviate post-endodontic pain and show promise in increasing IANB efficacy for symptomatic patients.

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I. INTRODUCTION

Managing pain during root canal therapy is a vital component to having a successful clinical outcome (1). Adequate pain control allows the clinician to work efficiently and provides a more comfortable clinical experience for the patient. For patients diagnosed with irreversible pulpitis, obtaining pulpal anesthesia is a challenge (1-11). The inferior alveolar nerve block (IANB) also known as the mandibular block is the most commonly used technique for achieving pulpal anesthesia for mandibular endodontic procedures (12). However, this method does not always result in successful pulpal anesthesia. Previous studies have reported IANB success rates in both symptomatic and asymptomatic patients to be between 25% and 90% respectively (1-6). More specifically, success rates in patients with symptomatic irreversible pulpitis have been observed to be 28% for the first molar, 25% for the second molar, and 39% for the premolars (3). Hence, there is a need to increase the success rate of the IANB for endodontic procedures in symptomatic patients.

There are many proposed reasons for anesthetic failure with the IANB (1, 3, 4, 5, 6, 9, 10, 13). Hargreaves and Keiser discuss these reasons to include anatomical discrepancies, acute tachyphylaxis to local anesthetics, local tissue pH levels, upregulation of tetrodotoxin resistant sodium channels, inflammation effects on pulpal blood flow, and inflammation associated with nociceptor upregulation (6). Further, pulpal inflammation results in high levels of prostaglandin (PG) synthesis causing sensitization of peripheral nociceptors (1-7, 14 -16). PGs are a by-product from the arachidonic acid pathway and are potent inflammatory mediators. Specifically, PGE2, has been found to produce hyperalgesia and clinically shown to be more present in symptomatic teeth versus asymptomatic inflamed pulps (2, 14-16). Due to these findings,

numerous clinical studies have sought to use non-steroidal anti-inflammatory (NSAID) medications to halt the production of PGs.

Parirokh et al. showed in a randomized clinical trial that 600mg ibuprofen and 75mg indomethacin increased the efficacy of the IANB compared to placebo (17). Nogeura-Gonzalez et al. and Shantiaee et al. also reported increased anesthetic success with the use of preoperative NSAIDs (18, 19). A recent systematic review by Nagendrababu et al. concluded that oral pre-medication with NSAIDs increased the success rate of IANBs in patients with irreversible pulpitis, however not to a consistent rate that supplemental anesthetic techniques were not needed to achieve profound pulpal anesthesia (1). Slight to moderate success has been found using strictly analgesics and NSAIDs, therefore it is paramount to continue researching methods to increase the success rate of the IANB block during root canal treatment.

Cortisol is the primary glucocorticosteroid that is secreted by the adrenal cortex (20). Glucocorticosteroids are known to reduce the acute inflammatory response by suppressing vasodilation, migration and phagocytosis of PMN leukocytes, and by inhibiting the formation of arachidonic acid from neutrophil and macrophage cell membrane phospholipids, thus blocking COX and lipoxygenase pathways and the respective synthesis of PGs and leukotrienes (1, 2, 6, 7, 14, 20). Methylprednisolone is a synthetic glucocorticoid with five times anti-inflammatory potency as the bodies naturally occurring hormone, cortisol. These medications act higher on the cascade of inflammatory events than nonsteroidal medications, thus have a stronger and more profound anti-inflammatory effect (14).

Previous studies have used corticosteroids for the purpose of decreasing post-endodontic pain. Jalalzedah et al. and Pochapski et al. reported preoperative corticosteroids lowered post treatment pain in comparison to placebo and NSAIDs (21, 22). Suneelkumar et al. recently

completed a systematic review on the administration of preoperative corticosteroids to lower post-operative endodontic pain. Their findings showed a statistical difference in pain relief up to 48 hours post endodontic procedures compared to placebo (23).

The concept of using a preoperative steroid medication has been influenced by these post-operative studies and the successful results of preoperative NSAIDs (17). One study has addressed the effect of preoperative corticosteroid medication on the effectiveness of the IANB. Shai et al administered 0.5mg dexamethasone or 400mg ibuprofen preoperatively before conducting an IANB and compared results versus a placebo group. Their results showed premedication with dexamethasone significantly increased the success rate of IANBs in mandibular molars over the placebo group, however the patients in this study were asymptomatic prior to treatment (24).

The use of corticosteroids to provide potential increased effectiveness for the IANB needs further investigation. To the best of our knowledge, there have been no studies directly comparing a preoperative corticosteroid with a clinical proven dose of ibuprofen for anesthetic efficacy. Therefore, the primary aim of this prospective, randomized, double-blind study was to compare the effect of oral premedication of ibuprofen and methylprednisolone on anesthetic efficacy of IANB with 68mg of 2% lidocaine with 0.034 mg of epinephrine in patients with symptomatic irreversible pulpitis. With published studies and systematic reviews confirming ibuprofen's effectiveness on increasing the efficacy of the IANB, we hypothesize that oral methylprednisolone will increase the efficacy of anesthetic solution by 20% more than ibuprofen. Due to the low success rate of the mandibular block when inflammation is present, supplemental anesthesia is often administered. The second objective was to examine the

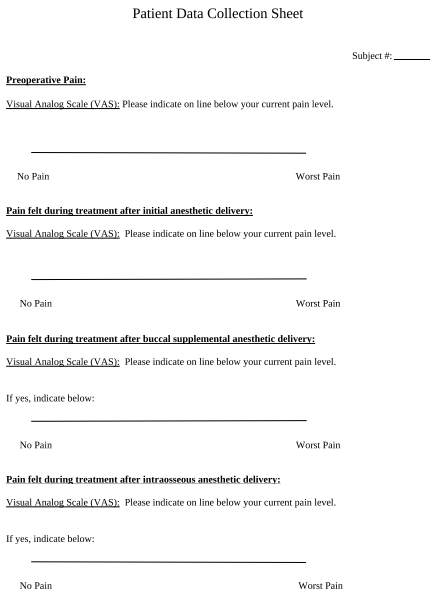
medication's effects on supplemental anesthesia if needed. The third objective is to examine the effects of this single, preop dose of either a steroid or NSAID on post-operative pain.

II. MATERIALS AND METHODS

This Walter Reed National Military Medical Center (WRNMMC) Institutional Review Board (IRB) approved study was completed by the Naval Postgraduate Dental School (NPDS) Endodontic 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 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 periradicular pathology (other than a widened periodontal ligament), or the lack of vital coronal pulpal tissue upon endodontic access were also excluded from the study. Thus, confirming the clinical diagnosis of irreversible pulpitis.

After written informed consent was obtained, the subject rated their pain 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, the mark was measured and placed into one of the following categories: No pain was at 0 mm, mild pain was > 0mm to 50mm, moderate pain was > 50mm to 75mm, and severe pain was defined as 75mm or greater. Subjects' rated their pain on this scale at specific timeframes during treatment dependent upon when anesthetic success was achieved.



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

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, an IANB injection and long buccal nerve block (LBNB) were given to each subject. 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 for 1 minute using a cotton tip applicator. Standard IANB and LBNB injections were administered with a 27-gauge, 1 ¼ in. needle attached to an aspirating syringe. Each cartridge of anesthetic used contained 34mg of 2% lidocaine with 0.017mg of epinephrine.

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. Each cartridge was measured in millimeters from the end of the aluminum cap to the stopper. This distance was found to be 50mm in length, therefore at the 25mm mark on every cartridge a line was drawn dividing the anesthetic cartridge in half. All injections were administered by one of three board certified endodontic staff members.

After anesthetic delivery, the subject remained in a semi-supine position for fifteen minutes. The subject was questioned for lip anesthesia in five-minute intervals for up to fifteen minutes. If after fifteen minutes, an absence of anesthesia was perceived, the block was considered missed. The subject received 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 informed 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 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).

Rubber dam isolation was removed for those who rated their pain as moderate or severe during treatment. A supplemental buccal infiltration injection was administered in the buccal alveolar mucosa near the apex (apices) of the tooth under treatment utilizing a 27-gauge short needle and a cartridge of 68mg 4% articaine with 0.017mg epinephrine. All injections were given by one of three board certified endodontic staff members. 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 was 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 on a VAS scale. If pain was moderate or severe, the infiltration injection was deemed a failure and an intraosseous injection was given as described by previous authors. 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, each subject was given a pain journal after completion of treatment. They were asked to note their pain six, twelve, twenty-four, and forty-eight hours after treatment. The journal was returned to the provider at the follow up appointment for completion of root canal therapy.

III. RESULTS

A total of 100 subjects, 50 per group, was determined sufficient after a power analysis was performed. Currently, one subject has been enrolled into the study. This subject had a preoperative pain VAS measurement of 100mm indicating the most severe pain. 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 proceeded to an intraosseous injection. The subject's VAS remained mild and was able to complete a pulpal

debridement comfortably. No statistical analysis has been performed. This is a long-term clinical study and will continue subject enrollment until 100 subjects is reached.

IV. DISCUSSION

Lip anesthesia is known to be a classic sign that the IANB was effective. However, the results of numerous clinical trials dispute this claim (1-5, 8, 13, 17-19). Hargreaves et al. discuss the origins of lip anesthesia as a cardinal sign of profound anesthesia (6). Local anesthetics block the myelinated Aß and Ad fibers yet seem to affect the unmyelinated C fibers at much lower concentration (6). A-fibers due to myelination respond more rapidly and sharply than slower unmyelinated C-fibers which are far more numerous than the myelinated A fibers in the dental pulp. C-fiber pain is more associated with dull, throbbing pain and are more recognized as a sign of pulpitis (6, 25, 26).

The inflammatory process may play a role in upregulating neuropeptides resulting in a decrease of successful pulpal anesthesia. Fouad discussed the increased production of neuropeptides and their role in propagating pulpal inflammation. During times of pulpal inflammation known inflammatory neuropeptides such as substance P (SP) and calcitonin gene-related peptide (CGRP), have been shown to be increased due to the bacterial front produced from carious lesions (26, 27). The uptake of neuropeptides lends credence to our theory of using a potent preoperative anti-inflammatory medication which would decrease the production of these mediators to increase anesthetic efficacy. Additionally, tetrodotoxin resistant (TTX) sodium channels have been shown to be present in higher numbers in inflamed tissues. The TTX sodium channels have the ability to resist local anesthetic solutions decreasing efficacy for the IANB (6, 26). These channels more than double in the presence of PGE2, a pro-inflammatory

mediator known to be upregulated during pulpal inflammation as a result of the arachidonic acid pathway (6, 26).

Nagendrbabu et al. highlighted the benefits of a preoperative dose of an NSAID in the presence of pulpal inflammation (1). Their study concluded that a clinical dose > 400mg of ibuprofen was needed to have a statistically significant difference on anesthetic efficacy in patients with irreversible pulpitis. Shahi et al. was the first to examine the use of a corticosteroid in comparison to 400mg ibuprofen and placebo in an asymptomatic patient population. Their findings found a 13% increase in IANB success using a low dose of dexamethasone (0.5mg). Their results are promising for the treatment of irreversible pulpitis, however, the subjects were asymptomatic (24). This study is focused on the treatment of symptomatic irreversible pulpitis, one in which an influx of inflammatory mediators such as SP, CGRP and PGE2 results in hyperalgesia and peripheral sensitization causing a decrease in IANB success rates (6, 8, 26). Decreasing the amount of these pro-inflammatory mediators should result in more effective pulpal anesthesia.

Fowler et al. proved that obtaining pulpal anesthesia in symptomatic patients is more difficult than asymptomatic subjects (3, 9). Their study showed an initial success rate from 25% - 39% for the IANB. However, the aim of their study was looking at the success rate of an additional buccal injection of 4% articaine. The addition of a local infiltration supplemental injection resulted in an increase of 13% to 35% success depending on the tooth in question (3). From this finding and the historically low efficacy of the IANB in symptomatic irreversible pulpitis patients, we hypothesized the addition of a preoperative steroid would increase the anesthetic success after the addition of a supplemental injection along with an IANB. Reisman et al. reported a success rate of 25% for symptomatic irreversible pulpitis patients using 34mg of

2% lidocaine with 0.017mg epinephrine. Their success rates increased to 80% with one intraosseous supplemental injection and 98% success with two intraosseous injections using 3% mepivacaine (28). To date, there has been no study evaluating the effectiveness of preoperative steroid medications on efficacy of supplemental anesthesia techniques. Therefore, it is felt the addition of our secondary objective would provide valuable clinical data.

Oral surgery and endodontic pain models using preoperative corticosteroids have shown clinically proven success at decreasing postoperative pain (21-23, 29). A systematic review by Suneelkumar et al. reported a statistically significant difference up to 48 hours post treatment in the corticosteroid group after endodontic procedures (23). Shahi et al. found that a low dose corticosteroid increased anesthetic efficacy for those diagnosed with asymptomatic irreversible pulpitis (24). The pain reduction success using corticosteroids coupled with the clinically proven dosage of greater than 400mg ibuprofen to increase IANB efficacy lead us to the hypothesis. It is predicted that a more potent preoperative anti-inflammatory medication would increase the efficacy of the IANB more than a clinically proven dose of ibuprofen in a symptomatic irreversible pulpitis population.

V. CONCLUSIONS

Several clinic trials along with a recent systematic review have shown an ibuprofen dosage > 400mg can increase the efficacy of the IANB. The outcomes from those studies coincide with the hypothesis that failure of the IANB is due to the inflammatory process and lowering inflammation may increase the efficacy of local anesthesia. In addition, these trials concluded that profound lip anesthesia is not indicative of pulpal anesthesia. The use of preoperative corticosteroids has been shown to alleviate postoperative pain in endodontic models, and this modality shows great promise to help increase efficacy of the IANB and

supplemental anesthesia if needed. The future outcome of this study has the potential to provide a clinically proven adjunct to aid in the efficacy of the IANB in patients suffering from pulpal inflammation.

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