Postoperative Pain After The Use Of A Dexamethasone Rinse As An Irrigant Prior To Obturation

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POSTOPERATIVE PAIN AFTER THE USE OF A DEXAMETHASONE RINSE AS AN IRRIGANT PRIOR TO OBTURATION

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ABSTRACT
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Purpose: The purpose of this randomized, double-blind pilot study was to determine the effect of dexamethasone on post-operative pain when used as an intracanal rinse prior to obturation.

Materials and Methods: Nine adult volunteers consented to enroll. They presented to the Marquette University School of Dentistry Endodontic Department with a diagnosis of irreversible pulpitis. Patients recorded their baseline pain levels on the numering rating scale (NRS). Patients were randomly assigned to either experimental or control group. Patients in the experimental group received 4 mg/mL dexamethasone solution as a final rinse prior to obturation were as patients in the control group received saline as a final rinse. Patients recorded their pain levels at 3, 6, 12, 24, and 48 hours post-operatively. Means and standard deviations were calculated. Treatment effects were analyzed using repeated measures ANOVA. Statistical significance was set at $p<.05$.

Results: Eight patients returned the participation forms. Pain reduction after endodontic treatment was statistically significant (p=0.039). There was no significant difference in post-operative pain between the control and experimental groups (p-0.789).

Conclusion: The patient sample size was not large enough to state any conclusions with confidence. However, endodontic treatment remains an effective means of reducing post-operative pain.

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INTRODUCTION

Pain of odontogenic origin has long been a source of anxiety and fear amongst the general population (Sohn & Ismail, 2005). This fear is so great amongst certain individuals that it actually serves as a barrier to dental treatment (Nixdorf et al, 2010a; Sohn & Ismail, 2005). Odontogenic pain has also been a common source of frustration amongst dentists whom have difficulties in completely relieving their patient's pain (Nobuhara et al, 1993). The ability to relieve such terrible pain amongst patients has been inconsistent, with many patients continuing to experience discomfort after dental treatment is provided (Nixdorf et al, 2010a). No treatment within the dental profession is as intimately associated with the fear of pain as is root canal therapy. This perception is so prevalent that stating something is "worse than a root canal" is a common way of describing terribly painful experiences (Wong & Lytle, 1991). A recent public poll sought to emphasize the unpopularity of members of congress by comparing their favorability ratings to root canals (Public Policy Polling, 2013). The ability to predictably treat pulpal and periapical diseases in a manner that seeks to minimize or even eliminate post-operative discomfort experienced by patients could help improve the image of dentistry within the public realm (Seltzer & Naidorf, 2004a).

LITERATURE REVIEW

Post-operative pain

A substantial amount of research has been published investigating the prevalence of post-operative discomfort after the initiation, continuation, and completion of endodontic therapy. The American Association of Endodontics defines flare-ups as "an acute exacerbation of asymptomatic pulp or peridradicular pathosis after the initiation or continuation of root canal treatment" (Glossary of Endodontic Terms, 2012). Tsesis et al (2008) evaluated the frequency of flare-ups secondary to endodontic therapy through meta-analysis of six studies that included 982 patients. The analysis showed an 8.4% frequency of flare-ups (2008). Nixdorf et al (2010a) published a meta-analysis and systematic review to estimate the presence of odontogenic pain after at least six months following completion of root canal therapy. The analysis included 26 studies and 2,996 teeth qualified for the final analysis. The frequency of persistent odontogenic pain was estimated to be at 5.3% after six months post-treatment (95% CI: 35-7.2%). The authors stated that this is likely a more conservative estimate and that the true figure may be higher, reflecting the widespread occurrence of post-operative pain.

One of the challenges facing clinicians is that many patients present with dento-alveolar pain due to a non-odontogenic source, yet they are treated with conventional dental treatments, including root canal therapy. Nixdorf et al (2010b) sought to determine the presence of non-odontogenic pain after at least six months following completion of root canal therapy. They conducted a meta-analysis of 10 qualifying studies including 1,125 teeth It was determined that possibly up to half of all cases of persistent tooth pain

(3.4%; 95% CI: 1.4-5.5%) may be caused in part by non-odontogenic pain.This highlights the importance of proper diagnosis within the dental profession to prevent unnecessary irreversible dental treatments such as root canal therapy and eventually in many cases, extractions. Improved diagnosis and referral for treatment of pain of non-odontogenic origin would ultimately help decrease the frequency of reported cases of post operative discomfort secondary to endodontic therapy. This in turn could contribute to improved public perceptions regarding discomfort associated with endodontic therapy (ElMubarak et al, 2010).

The presence of post-operative pain can become especially problematic when it is caused by neuropathic pain. The International Association for the Study of Pain defines neuropathic pain as "pain initiated or caused by a primary lesion in or dysfunction of the nervous system" (Merskey & Bogduk, 1994). This type of pain can develop as a result of damage to local neural structures during the root canal procedure itself (Nixdorf et al, 2010a). The damage causes somatosensory changes in the nerves, which manifests as a constant, burning, and deep ache at the site of treatment with the absence of any clinical signs of pathology. The greatest obstacle that this presents is that this condition is not responsive to analgesics, surgery, or any other dental procedures. This painful condition causes great distress to the patients and much confusion amongst their dental providers. Neuropathic pain has been reported to affect 3% - 12% of patients after endodontic therapy (Oshima et al, 2009). The frequency of neuropathic pain after endodontic procedures is higher than that of any other dental procedure (Oshima et al, 2009). Oshima et al investigated a cohort of sixteen patients and found that neuropathic pain was more likely in females (13 of 16), with a predilection for the maxilla (14 of 16). It was found

that tricyclic antidepressants were effective in relieving pain in 68.8% of their patients (11 of 16). However, 25% (4 of 16) of the patients did not report any relief. In order to minimize the risk of neuropathic pain following endodontic treatment, utilization of best endodontic treatment practices, including avoiding overinstrumentation and over extension of obturation materials is critical (Seltzer & Naidorf, 2004a). Improved practice and techniques may eventually reduce the frequency and development of neuropathic pain secondary to endodontic treatment. (Oshima et al, 2009).

There are numerous, well-documented studies that identify predictors of post-operative pain. These predictors are significant in educating both practitioners and patients. ElMubarak et al (2010) investigated a cohort of 234 patients. They found that patients who undergo root canal therapy with a history of pre-operative pain have a 15.9% incidence of post-operative pain within 24 hours post-treatment, compared to a 7.1% incidence in those with no reported pre-operative pain. It is important to note that numbers of patients evaluated for post-operative pain are too small to attach great value pre-operative as a predictive factor. Rather this study demonstrates that endodontic treatment is an effective means of relieving pain, with patients having an 89% risk of pain free after treatment. The authors found a statistically significant difference in the incidence of post-operative pain between vital teeth, 7.8%, and non-vital teeth, 13.7%. In a meta-analysis published in 2011, Pak & White confirmed that the incidence of post-operative pain was greatest in patients who presented with pre-operative pain. Thus it appears that in order to affect any meaningful change in the incidence of post-operative pain within endodontics that the target population for any pain research be patients with

existing pre-operative pain, because they are at greater risk of developing post-operative pain (Pak & White, 2011).

Pulp Physiology and Inflammation

The understanding of pulp physiology and the body's inflammatory processes within the context of the human dental pulp is critical to the development of effective therapeutic approaches to reducing post-operative pain after root canal treatment (Kim 1990). The pulp is very unique in the human body in that the physical environment of the dental pulp is a low-compliance environment through encasement by dentin (Ingle, Bakland, & Baumgartner, 2008). The pulp consists of loose connective tissue that contains nerves, blood vessels, lymph vessels, interstitial fluids, and a wide array of immune and connective tissue cells. Odontoblasts form the border between the pulp and dentin. Fibroblasts are located throughout the pulp that function in maintaining the fibrous extra cellular matrix of the pulp (Ingle, Bakland, & Baumgartner, 2008).

Blood flow to the pulp is provided by very small arterioles, approximately 100 μm in diameter that enters through the apical foramen. Blood from the arterioles are distributed through an extensive network of branching capillaries, nearly 10 μm in diameter, which provides an efficient pathway for the distribution of nutrients. This system is so efficient that every minute the pulp is able to replace the entire blood volume within the vasculature five to fourteen times. Lymph vessels that are located in the central part of the pulp is the only mechanism to remove proteins that leak from the blood vessels, and this becomes of critical importance during reversible pulpitis (Oehmke et al 2003). It is important to note however that there is no source of collateral circulation to the pulp, a fact that has significant consequences in the presence of inflammation (Ingle, Bakland, & Baumgartner, 2008).

There are both autonomic and sensory nerves present in the dental pulp. Sympathetic autonomic nerves have been found to have a regulatory effect on pulpal blood flow, with stimulation causing vasoconstriction of the arterioles. There are two types of sensory nerve fibers: A-fibers and C-fibers. Nearly 90% of pulpal A-fibers are A-delta fibers, which are myelinated, fast conducting, low threshold nerve fibers that are unable to survive in hypoxic environments. The remaining 10% of pulpal A-fibers are A-beta fibers that provide propioceptive feedback. C fibers are unmyelinated, slow conducting, and high threshold nerve fibers that are able to survive in hypoxic environments. Responses to A-delta fibers are characterized by an immediate and sharp, sometimes stabbing-like pain, were as responses to C fibers are characterized by a prolonged dull type of pain (Kim 1990).

External irritants initiate the inflammatory process in the pulp. These irritants can be mechanical irritants such as the friction and heat that is generated when a bur cuts on tooth structure. These irritants could also be chemical, which includes bacteria, bacterial by-products, and even chemical rinses such as concentrated phosphoric acid utilized during cavity preparation. However, the penetration of bacteria and their by-products are by far the most common cause of inflammation to the pulp (Siqueira & Barnett, 2004). The inflammatory process in the pulp is the same as in the rest of the body, and is mediated by the same cells and pathways, with the only difference being the pulp's low-compliance environment (Ingle, Bakland, & Baumgartner, 2008).

Dendritic cells present in the pulp release interleukin-8 (IL-8), which serves as a powerful chemotactic agent for other inflammatory cells, including neutrophils, macrophages, and mast cells (Siqueira & Barnett, 2004). Histamine, a potent vasodilator,

is released from mast cells, resulting in vasoldilation of the arterioles and leakage of the venules. This leads to a further increase in inflammatory infiltrate in the pulp as well as their chemical mediators. There are two main consequences as a result of this increase in infiltrate, both of which are synergistic: Increase in tissue pressure, and increase in inflammatory infiltrate (Caviedes-Bucheli et al, 2008). The first is that the increased osmotic pressure, a result of the increased protein concentration released from inflammatory cells within the pulp, quickly leads to an increase in tissue pressure. The low-compliance environment of the pulp prevents the dissipation of the increased tissue pressure. As a result, pulpal blood flow is decreased. In high-compliant tissues, increased blood flow allows the removal of inflammatory mediators and cells, thus limiting any excessive damage to the local site. As a result of the pulp's decreased blood flow, there is instead a rapid accumulation of inflammatory cells and mediators, which only leads to greater vascular damage (Heyeraas 1985). This vicious cycle eventually leads to tissue necrosis.

The second main consequence is the cascade of pro-inflammatory mediators and their subsequent effects on pulpal tissue throughout the progression of the inflammatory process. These mediators are released from multiple cells and include in part: histamine, serotonin, prostaglandins, leukotrienes, platelet activating factor (PAF), substance P (SP), and a wide host of enzymes that activate several different pro-inflammatory pathways (Siqueira & Barnett, 2004). Histamine and serotonin are released from mast cells and platelets respectively, yet both act on local vasculature to cause increased permeability through the contraction of the blood vessels' smooth muscle (Seltzer & Naidorf, 2004b). Prostaglandins and leukotrienes are very important pro-inflammatory chemical mediators

that orginate from the same precursor, arachidonic acid. Cycloxygenase enzymes convert arachidonic acid to prostaglandins and thromboxanes and lipoxygenase convert arachidonic acid to leukotrienes (Seltzer & Naidorf, 2004b). These pathways are diagrammed in figure 2.

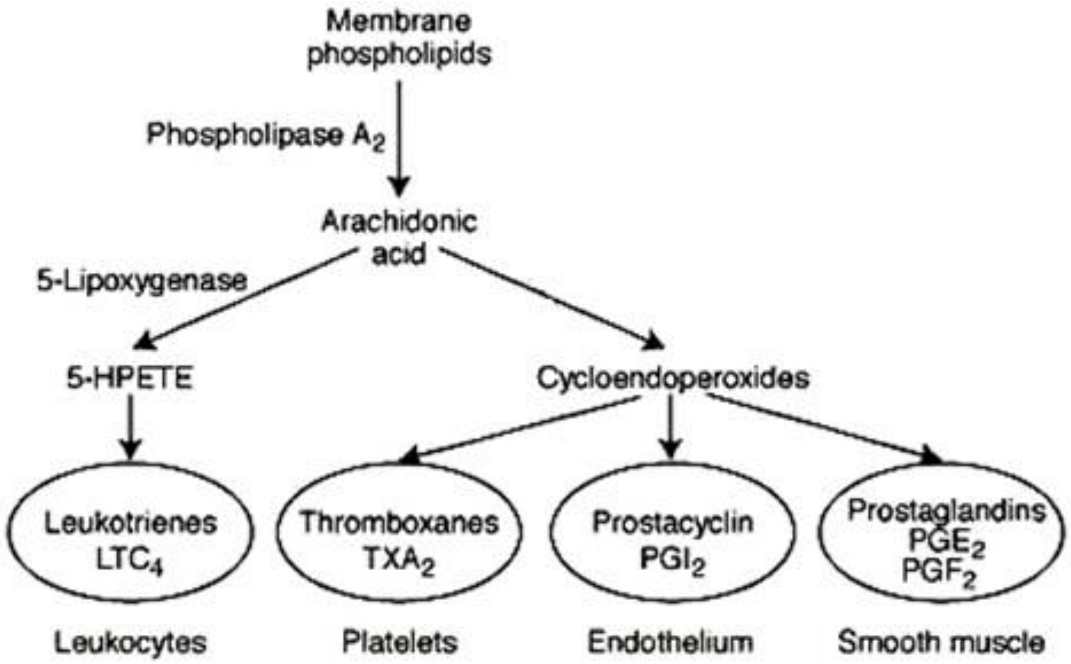

Figure 1 - Arachidonic acid pathway leading to formation of multiple inflammatory mediators (Yudcovitch).

Prostaglandins function to cause vasodilation in local vessels, promote chemotaxis of inflammatory cells, and sensitize the receptors of pain fibers to stimulation by other mediators such as bradykinin (Kim 1990). Leukotrienes are from amongst the most potent chemotactic agents, attracting neutrophils and macrophages that produce extensive tissue and cellular damage through the release of degradative enzymes such as lyzozymes (Siqueira & Barnett, 2004). Leukotrienes also have profound effects on vascular permeability and increase pain through prolonged stimulation of nerve fibers.

Platelet activating factor is released from various immune cells and acts as a chemotactic agent, acts on blood vessels to increase vascular permeability, and acting on other cells to increase the production of other chemical mediators such as serotonin and leukotrienes (Siqueira & Barnett, 2004). SP is a pro-inflammatory neuropeptide that is released by C-fibers upon stimulation and causes vasodilation, increased vascular permeability, and pain by lowering the threshold of sensory nerves (Tuncer et al, 2004). Calcitonin gene related peptide, CGRP, is another neuropeptide released by C-fibers upon stimulation that acts in a similar fashion as SP (Caviedes-Bucheli et al, 2004). The actions of these chemical mediators directly and indirectly cause pain at the site of inflammation. This is done directly through lowering the excitability threshold of the A-delta and C-fibers or indirectly by way of an increase in edema and tissue pressure. Thus it can be seen that the accumulation of pro-inflammatory mediators in the dental pulp quickly leads to a cycle of increased vascular permeability, pain, and ultimately tissue necrosis (Kim 1990). This cycle is aptly diagrammed in Figure 3.

Many recent studies have demonstrated increased levels of inflammatory mediators in inflamed pulpal tissues. Bowles et al (2003) measured the concentration of SP in normal and inflamed pulps through the insertion of micro-dialysis probes into the pulp. The concentrations of SP were eight times higher in teeth

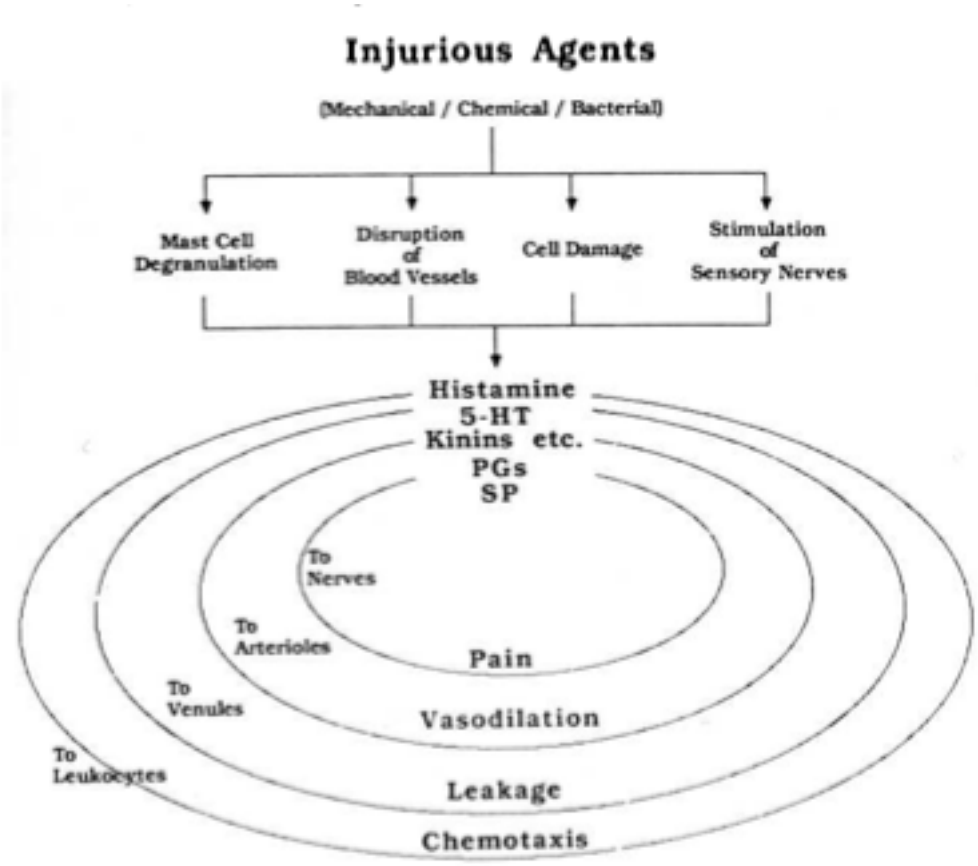

Figure 2 - The role of inflammatory mediators in inflammation (Kim 1990).

clinically diagnosed with irreversible pulpitis in comparison to those teeth diagnosed with normal pulps. Tuncer et al found elevated levels of SP in inflamed periradicular tissues, highlighting the role that it plays in the spread of inflammation from the pulp to the periradicular tissues (2004). Lepinski et al (2000) used the same microdialysis probe technique as Bowles et al to evaluate pulpal concentrations of bradykinin, a potent pain mediator, in teeth with a clinical diagnosis of irreversible pulpitis as compared to normal pulps. Bradykinin concentrations were thirteen times greater in teeth with irreversibile pulpitis as compared to normal pulps. Karapanou et al (2008) obtained gingival crevicular fluid samples from teeth diagnosed with irreversible pulpitis as well as adjacent and contralateral teeth with normal pulpal tissues to evaluate the concentration

of IL-8, an important inflammatory chemotactic agent. It was found that interleukin-8 was significantly elevated in the gingival crevicular fluid of those teeth with irreversibile pulpitis. Caviedies-Buchelli et al (2004) found significantly higher levels of CGRP in pulpal tissues collected from teeth with irreversible pulpitis as compared to normal teeth. A recent article by Yingchun et al (2013) evaluated the expression of EphA7 receptors, a tyrosine kinase found on the membranes of inflammatory cells, in teeth with normal pulps and teeth with irreversible pulpitis. Higher expressions of the receptors were found in inflamed pulps as compared to normal pulps. All of these recent high-level clinical studies suggest an active role of inflammatory mediators in pulpal inflammation.

Post-operative pain develops when the integrity of the periapical tissues is compromised. This can occur during endodontic treatment from mechanical irritants such as hand instruments and obturation materials protruding beyond the minor foramen. Chemical irritation can occur if any of the solution is extruded beyond the apex. Sealers used in obturation are often both mechanical and chemical irritants since many commercially available sealers are cytotoxic (Siqueira & Barnett, 2004). In response to the tissue irritation, an inflammatory response is initiated, leading to an influx of inflammatory cells and mediators as described above, ultimately resulting in post-operative pain.

The Use of Glucocorticosteroids in Dentistry

Disruption of the inflammatory cycle has long been the focus of pain research. The primary target sites for pharmacological approaches have been two classes of enzymes: phospholipase, which synthesizes arachidonic acid from phospholipids, and cyclooxygenase, which synthesizes prostaglandins. Steroidal anti-inflammatory drugs (SAID), also known as glucosteroids, are a class of drugs that function by inhibiting phospholipase A2, thus reducing the production and concentrations of prostaglandins and leukotrienes (Seltzer & Naidorf, 2004b). Non-steroidal anti-inflammatory drugs (NSAIDS), are a class of drugs that function by inhibiting cyclooxygenase enzymes, which reduces prostaglandins but does not affect leukotriene production (Seltzer & Naidorf, 2004b).

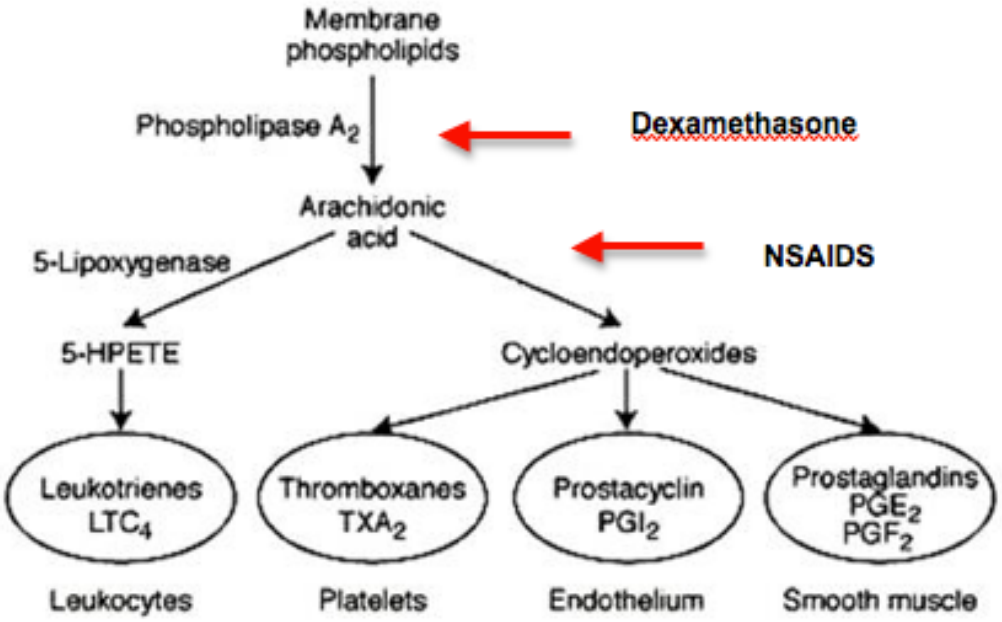

Figure 3 - Pharmacologic targets in the arachidonic acid pathway (Yudcovitch).

Histology has been used frequently to evaluate the direct anti-inflammatory effects of corticosteroids on periapical inflammation and pathology. Metzger et al (2002) studied the effect of dexamethasone on the size of periapical lesions in rats. Bone resorption is modulated by inflammatory cytokines, thus they hypothesized that pharmacological modulation of bone resorption is possible. Periapical lesions were induced in molars of rats in two groups, a control group and an experimental group administered intramuscular injections of dexamethasone. None of the rats in the experimental group developed any abscess or overt sign of infection. Histologic evaluation of the periapical lesions of both groups showed that lesions in the dexamethasone group were significantly smaller than those of the control group. This suggested that the systemic administration of dexamethasone inhibited at least partially, the development of inflammatory periapical lesions. It is possible that dexamethasone had an inhibitory effect on osteoclasts. The authors found that in the experimental dexamethasone group, osteoclasts were more likely to undergo apoptosis, ultimately reducing the number of osteoclasts and limiting the potential for greater resorption.

Nobuhara et al (1993) also used rats to observe any histologic changes due to the application of dexamethasone in inflamed periapical tissues of molars. The distal roots of vital and non-vital first molars were over-instrumented with hand files, followed with the deposition of either saline or dexamethasone via buccal infiltration. The amounts of neutrophils for each specimen were counted at three time points: 6, 24, and 48 hours, and at three different locations within the periodontal ligament: adjacent to the apical foramen, the middle of the ligament, and adjacent to the cancellous bone. For both vital and non-vital cases, the dexamethasone groups demonstrated significantly less neutrophil

infiltrate at 48 hours at the apical portion of the periodontal ligament as well as the middle of the ligament space. Neutrophils are the hallmark cells of acute inflammation, and any potential method to locally decrease neutrophil concentrations may have profound impacts on clinical symptoms following endodontic treatment.

One of the effects of periapical inflammation is the presence of neural sprouting into the periodontal ligament, leading to increased sensitivity upon stimulation of the periodontal ligament. Holland (1996) sought to determine if systemic dexamethasone affects neural sprouting. Twenty ferrets had root canal treatment completed on mandibular canines, with the experimental group administered oral dexamethasone at the time of treatment. After three months, the ferrets were killed and specimens were prepared for histological evaluation. It was found that innervation density in the apical region, as well as the total innervation density of the periodontal ligament, were significantly lower in the dexamethasone group as compared to the control group.

Isett et al (2003) conducted a double-blind, randomized clinical study to investigate the effect of methylprednisolone (depo-medrol) on pulpal concentrations of PGE_2 and IL-8. Forty patients with diagnoses of irreversible pulpitis participated. After being anesthetized, patients were given either intraosseous methylprednisolone or saline. The teeth were extracted anywhere from 24 hours to 72 hours after the intraosseous injection. The pulp tissues were extracted from the teeth and the concentrations of the PGE_2 and IL-8 determined via enzyme immunoassay. The pulpal concentrations of PGE_2 were significantly reduced at 24 hours post injection, but not at seventy-two hours.

Much clinical research also has been produced on the use of SAIDS and their effect on inflammation and postoperative pain (Shariar et al, 2013; Marshall & Walton,

1984; Liesinger et al, 1993; Jalalzadeh et al, 2010; Chu et al, 2006; Ehrmann et al, 2003; Negm et al, 2001). Various modes of administration have been used, ranging from intramuscular injections to intra canal medications (Shariar et al, 2013; Marshall & Walton, 1984; Liesinger et al, 1993; Jalalzadeh et al, 2010; Chu et al, 2006; Ehrmann et al, 2003; Negm et al, 2001). A recent study by Jalalzadeh et al (2010) administered a prednisolone pill 30 minutes before treatment to both vital and non-vital teeth in patients completed in one visit. 40 patients participated in this double blind study with patients divided equally between the placebo group and the prednisolone group. Prednisolone resulted in a statistically significant reduction in post-endodontic pain at 6, 12, and 24 hours following treatment. Marshall and Leisenger (1993) carried out a double blind study evaluating the effect of 4 mg dexamethasone i.m. on post-operative pain in patients with both vital and non-vital teeth. Fifty patients were included in the placebo controlled experiment. Pain levels were recorded at 4 hours, 24 hours, and 48 hours post-operatively. Patients in the experimental group had significantly lower pain levels at 4 hours post-operatively compared to the placebo group. Rogers et al (1999) investigated the analgesic effects of a dexamethasone rinse in symptomatic vital cases in treatments completed in two visits. Forty-eight patients participated and were divided into four groups: placebo pills to be taken post-operatively, oral ibuprofen to be taken post-operatively, dexamethasone (4 mg/ml) intra canal rinse, and ketorolac intra canal rinse. The patients recorded their pain levels at 6, 12, 24, and 48 hours post-operatively. Dexamethasone provided statistically significant pain relief at 12 hours as compared to placebo, but the difference between dexamethasone and ketrolac and ibuprofen was not significant statistically.

Ehrmann et al (2003) sought to evaluate whether Ledermix, a corticosteroid and antibiotic paste, reduced the incidence of post-operative pain in necrotic teeth. Two hundred and twenty one patients were randomized to treatments: ledermix, calcium hydroxide (CaOH), and no medication. Patients in the Ledermix group had consistently less post-operative pain at all observed time points as compared to patients in the CaOH and placebo groups (2003).

In 2001, Negm et al (2001) published a double blind, randomized study evaluating the efficacy of dexamethasone as an intra-canal medicament in the treatment of inter-appointment pain in patients undergoing root canal therapy on vital teeth. Post-operative pain levels were evaluated up to 48 hours. 480 Patients who needed endodontic therapy received either the corticosteroid-antibiotic medicament, or a placebo. Over 93% of the patients assigned to the steroid group had complete relief of pain within the first 24 hours, compared to only 22% in the placebo group. The most significant factor in this study was the large size of participants in each group, with over 248 patients in the experimental group and 232 patients in the control group. A weakness in the Negm study is that the SAID and antibiotic were mixed into one medicament, making it difficult to draw conclusions about the efficacy of either component alone. It would have been more appropriate to have two experimental groups: a SAID group, and an antibiotic group.

The purpose of this prospective, randomized, double blind clinical trial was to determine the effect of dexamethasone on post-operative pain in patients with irreversible pulpitis when used as an intracanal rinse prior to obturation in treatment completed in one visit.

MATERIALS & METHODS

The research design was based on a study previously executed by Mahajan (2012). Second year endodontic residents screened potential participants at the Endodontic Clinic at Marquette University School of Dentistry in Milwaukee, Wisconsin. The candidate's medical history was evaluated through their written health history in addition to oral examination. A candidate was enrolled if they met the following criteria:

Inclusion Criteria:

- Older than 18 years of age;
- Being a patient of record;
- Vital tooth with pulpal diagnosis of symptomatic irreversible pulpitis;
- A pre-operative pain score of at least a four on the numeric rating scale, henceforth known as NRS;
- Treatment completion in one visit;
- Potential to achieve canal patency as determined on pre-operative radiographs
- The candidate's ability to understand and provide informed consent.

Exclusion Criteria:

- Did not sign the consent form
- History of significant medical history, classified as class II or higher by the American Society of Anesthesiologists classification;
- Nursing or pregnant patients;
- Past history of peptic ulcer or gastrointestinal bleeding;
- High risk for renal failure or impairment;

- Presence of allergy or hypersensitivity to non-steroidal anti-inflammatory drugs or corticosteroids;
- Radiographic evidence of periapical pathology;
- Recent intake of anti-inflammatory drugs, antibiotics, or narcotics;
- Presence of adjacent, symptomatic teeth.

The Marquette University Institutional Review Board approved the study (Protocol HR-2195, see Appendix), and written informed consent was obtained from each patient prior to enrollment in the study. Participants were compensated for their time and effort through mail delivery of a $25 VISA® gift card. Pulpal and periapical tests were conducted to determine the pulpal and periapical diagnoses. A preoperative radiograph was taken to rule out periapical pathology. In addition, a comprehensive clinical examination was completed to rule out intra/extraoral swelling, presence of a sinus tract, or other major pathology.

Prior to anesthetizing the treatment area, patients were asked to rate their pain on a numeric pain intensity scale otherwise know as a numeric rating scale (NRS) (Figure 1). The scale was from 0, being no pain, to 10, being the worst possible, unbearable, excruciating pain. The NRS score was considered the baseline pain level of the patient.

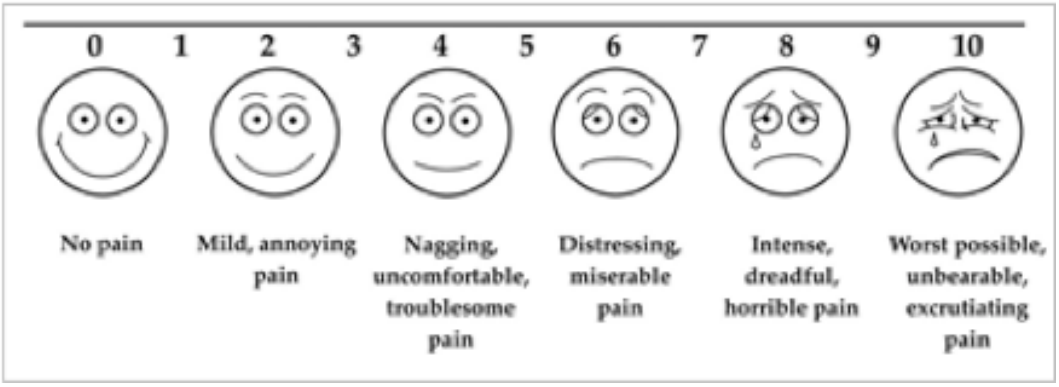

Figure 4 - The numeric rating scale was by patients to determine their pain levels.

Eligible patients were randomly assigned by a research assistant, without knowledge of the clinical investigator, to one of two groups:

- Group 1 was the experimental group that received the dexamethasone rinse in addition to standard of care therapy;
- Group 2 was the control group that received the saline rinse in addition to standard of care therapy.

Randomization tables were generated with the aid of the (pseudo) random number generator in Microsoft® Excel® for Mac 2011 (Microsoft Corp., Redmond (WA)). A formula was set to randomly select an integer between 1 and 30 without replacement.

At the initiation of treatment, patients were anesthetized using 1.7- 5.1 mL of 2% lidocaine with 1:100,000 epinephrine (Xylocaine; AstraZeneca LP, DENTSPLY, York (PA)) via local infiltration or inferior alveolar nerve block, depending on tooth location. Prior to beginning treatment, anesthesia was confirmed by retesting the tooth with Endo-Ice® (Coltene Whaledent Group, Cuyahoga Falls (OH)). After confirmation of complete anesthesia, a rubber dam was placed, the occlusion was adjusted and the tooth was accessed. The working length of the root canal instruments was determined and the

canal(s) were prepared with hand and rotary instruments. Each canal was prepared to at least a size #20 hand file, along with 5.25% sodium hypochlorite (NaOCl) irrigation. A modified crown-down technique was employed to enlarge the canal in the coronal, middle and apical thirds using RaCe (Brasseler USA, Savannah (GA)) and EndoSequence (Brasseler USA, Savannah (GA)) rotary files.

The modified crown-down technique is a technique in which the coronal third of the canal is instrumented first with large tapered rotary files. Afterwards, the apical third is instrumented with rotary files, beginning with smaller sized files and increasing in size until the master file is reached. Throughout the process, the middle third of the canal is instrumented as well.

After the chemo-mechanical cleaning was completed, a final irrigation with 5.25% NaOCl, 17% ethylenediaminetetraacetic acid (EDTA), and 2% chlorhexidine (CHX) was performed. This was followed by ultrasonic agitation using a size #15 ultrasonic K-file (Satelec, Merignac, France). Then, the canal was dried with sterile paper points. At this point, the research assistant gave the practitioner an unlabled 1 mL tuberculin syringe containing a clear solution that was used to rinse the canals. In Group 1, the solution was 1mL of 4 mg/mL dexamethasone sodium phosphate aqueous solution (Luitpold Pharmaceuticals, Shirley (NY)), and in Group 2 the solution was 1mL of 9 mg/mL sodium chloride in H_2O (Luitpold Pharmaceuticals, Shirley (NY)). Patency of the canals was rechecked at this point with a hand file of size #10 or greater. The solution was then agitated with a size #15 ultrasonic K-file for 30 seconds. The canals were dried again with sterile paper points.

Obturation was completed by vertical condensation with Brasseler EndoSequence .04 ISO sized gutta-percha or .06 ISO sized gutta-percha (Brasseler USA, Savannah (GA)) and AH Plus sealer (DeTrey, Dentsply, Ballaigues, Switzerland). A sterile cotton pellet was placed in the pulp chamber and the access opening was sealed with Cavit temporary filling material (Cavit G; 3M ESPE, Seefeld, Germany).

After completion of the endodontic treatment, patients were given post-operative forms that included rescue medication instructions, explanation of possible adverse events, and pain level score collection instructions. As rescue medication, all patients received 4 tablets of 600mg ibuprofen each, to be taken only if pain levels reached or exceeded 6 on the NRS. In addition, if pain was not manageable, patients were informed to contact the principal investigator by phone. Patients were instructed to report also any swelling, fever, or persistent infection. For data collection, patients were requested to record NRS values at exactly 3, 6, 12, 24, and 48 hrs post-operatively. They were also instructed to record the amount of rescue medication and when it was taken. Patients were given stamped, self-addressed envelopes to place the form once completed. Patients were contacted approximately forty-eight hours post operatively by the principal investigator to remind the patients to mail the data collection forms. Upon receipt of the envelope, the research assistant recorded the data, and the principal investigator mailed the gift card as compensation to the patient's address. The research data was unblinded to the principal investigator at the end of the experiment.

Statistical Methods

The sample size of necessary root canal treatments was estimated based on the following: the study design (two parallel groups, 5 measurement points for each patient), a desirable and clinically relevant effect size, type I error rate of 5%, and type II error rate of 10%. Figure 4 shows the sample size estimates as a function of various study design (2 parallel treatment groups, 5 data collection time points) and statistical parameters (type I error, type II error, effect size). Given these premises, the goal was to enroll 30 patients.

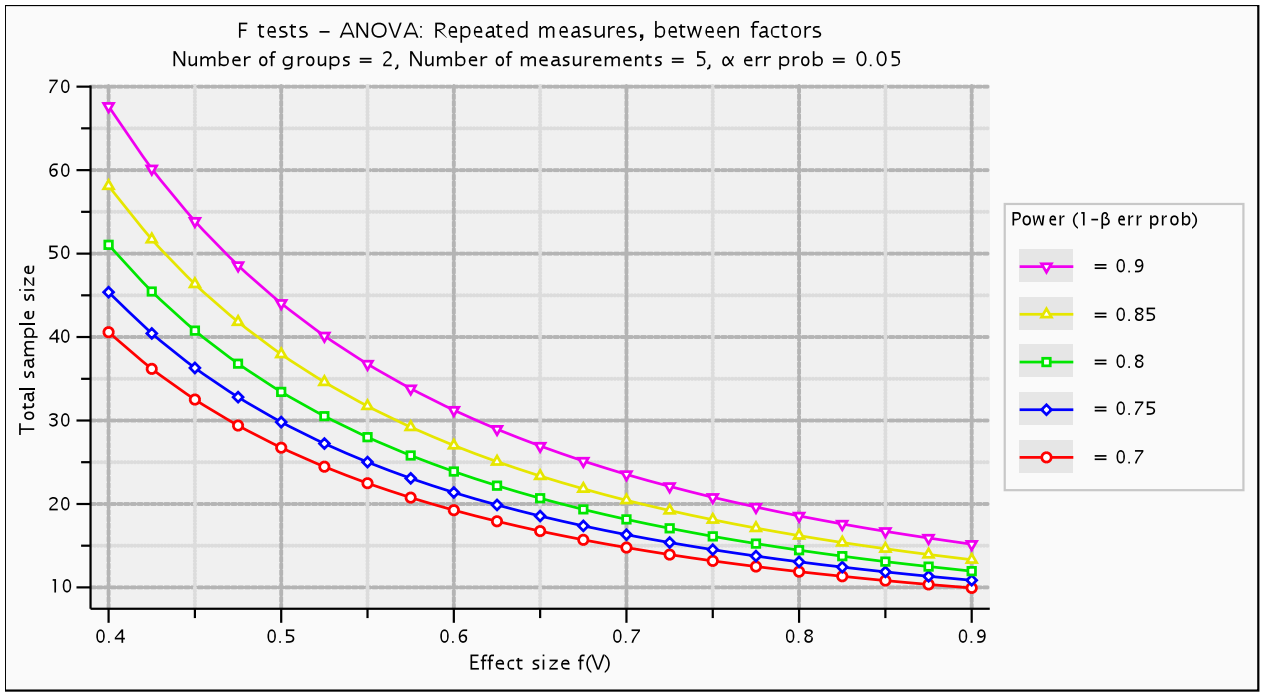

Figure 5 - Sample size as a function of size and power.

Statistical analyses included computation of means, s.d. and 95% confidence intervals. In addition, a repeated measure analysis of variance was executed to investigate statistical within- and between-subjects trends and to generate information that could be used for the planning of larger clinical studies. The patient was used as a unit for all

statistical calculations. The sample included 8 patients (N_{test} = 5, $N_{control}$ = 3). Treatment (Test, Control) was the independent variable. Time (baseline, 3 hrs, 6 hrs, 12 hrs, 24 hrs, and 48 hrs) was the repeated factor. NRS was the dependent variable. Microsoft® Excel® 2010 (Microsoft Corp., Redmond, WA) and SPSS (Version 20, IBM Corporation, Chicago, IL) were used for data analyses.

RESULTS

Nine patients, three males and six females with an average of 36 years of age consented to participate in the study. Eight patients completed the pain evaluation forms and returned the forms by mail; the ninth patient did not submit her pain evaluation form. Of the remaining eight patients, the teeth that were treated included four molars, three anteriors, and one premolar. Three patients were assigned to the control group and five to the experimental group. Patients in the control group reported an average preoperative pain score of 6.7 ± 2.1 (mean ± 1 s.d.). Patients in the experimental group reported an average preoperative pain score of 7 ± 1 (mean ± 1 s.d.). The difference in the baseline preoperative pain levels between both groups was not statistically significant (p=0.767). The table below shows the pain levels of patients of both groups at all observed time points.

Patient	Baseline	3hrs	6hrs	12hrs	24hrs	48hrs	Rescue medication taken
Control Group							
Patient 1	9	4	5	7	6	5	0
Patient 2	5	6	6	6	5	5	3
Patient 3	6	0	1	0	0	0	0
Experimental Group							
Patient 4	8	4	4	2	0	0	2
Patient 5	6	8	4	2	1	1	2
Patient 6	7	7	9	10	9	10	3
Patient 7	8	0	0	0	0	0	0
Patient 8	6	0	0	3	0	0	2

Table 1 – Pain levels for patients over a 48-hour period.

The pain reduction after root canal treatment was statistically significant (p=0.039). Patients in the experimental group reported greater average post-operative discomfort at three hours and less post operative discomfort at all other time points in comparison to the control group. These differences are not statistically significant (p=0.789).

In the experimental group, two patients experienced moderate to severe discomfort at three hours. Of the two patients, one reported moderate pain at six hours, and mild to negligible pain at all other time points. The other patient continued to experience significant pain, after which she contacted the principal investigator two days post treatment complaining of swelling. The patient was seen in the endodontic clinic the following day with mild, intraoral swelling localized around the apex of the treated tooth. The endodontic resident on emergency rotation that day prescribed the patient a seven-day course of 150mg clindamycin. The patient experienced mild palpation sensitivity for six more weeks until symptoms completely resolved. Three of the five patients experienced no post-operative discomfort at 24 hours and 48 hours. This was the only patient to report swelling. No other adverse effects were noted.

In the control group, two of the three patients reported moderate post-operative discomfort at all time points. Only one patient in the control group reported resolution of her symptoms by the end of the observed period.

Six out of the eight patients reported taking the provided 600mg ibuprofen tablets as rescue medication: Four out of the five patients in the experimental group and one out of three patients in the control group.

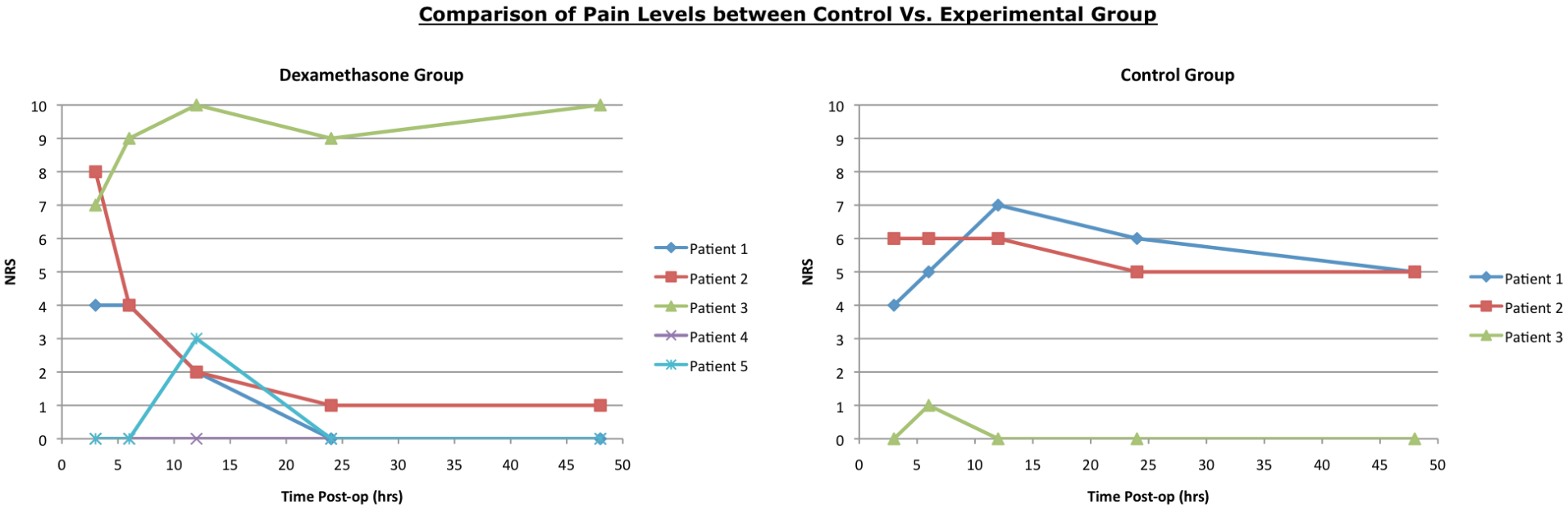

Figure 6 - Reported pain levels for individual patients.

DISCUSSION

The present study was planned to be a continuation of Mahajan's thesis work (2012) on the use of a dexamethasone rinse as an irrigant prior to obturation. Mahajan (2012) found a statistically significant improvement in the post-operative pain experienced by patients in the experimental group. Ten patients participated in Mahajan's study. The purpose of the current study was to enact a few procedural modifications while expanding the patient base.

The greatest limitation in the present study was the low number of participants. After encouraging results from Mahajan's (2012) pilot study, one of the primary aims of this study was to increase the sample size. However, the study concluded with two less participants than the initial study. One possible restrictive requirement may have been the requirement that the treatment be completed within one visit. Oftentimes patients who presented to the emergency clinic were not able to participate because their insurance providers necessitated approval prior to completion of the root canal. Unfortunately there is no data available on how many patients were screened and for what reasons they were excluded from the study. That data would have been beneficial in designing future clinical trials.

The results of this study indicated that standard of care root canal treatment is an effective means to relieve odontogenic pain. The sample size was too small to make any conclusion in regards to the efficacy of dexamethasone on post-operative pain. After the three-hour mark, the average pain levels of the dexamethasone group were lower than the control.

Several modifications were made to the original protocol developed by Mahajan (2012) to improve the clinical relevance of the study. The study was changed from a single blind to a double-blind study through the addition of a placebo rinse. Also, data were no longer reported directly to the primary investigator. In an effort to reduce any potential bias, patients recorded their pain scores and returned the form via mail, after which a research assistant recorded the data. Finally, the pain observation period was extended from 24 hours to 48 hours to determine the effects of dexamethasone over a longer period of time.

Previous studies documented the usage of a steroid medication on either inter-appointment or post-operative discomfort related to endodontic treatments. However, most of these studies evaluated post-operative discomfort during multiple appointments. Chance et al (1987) and Rogers et al (1999) both evaluated post-operative pain after initial treatment. The large clinical trial published by Negm et al (2003) saw treatment completed in three visits, with dexamethasone used as an inter-appointment medicament rather than a final rinse. Liesinger et al (1993) evaluated post-operative discomfort in single visit treatment of vital teeth, however the mechanism of delivery for dexamethasone was through intramuscular injection.

This study focused on single visit treatments due to increasing prevalence amongst endodontists of treatment completed in one visit, particularly when treating cases with irreversible pulpitis. In a survey by Inamoto et al (2002) completed by 156 endodontists, 55.8% completed emergency visits in one appointment. Due to risks of flare-ups, a lesser percentage of endodontists completed necrotic emergency visits in one

apoointment (34.4%). Since the endodontists answered only in response to emergency cases, the real number of single appointment treatment is likely much higher.

Single visit treatments have become more common due to advancements in dental materials, namely the development of nickel titanium files rotary files. Unlike traditional hand instrumentation, rotary instrumentation removes significant amount of debris away from the apex towards the access cavity, reducing the amount of debris that is extruded from the apical foramen into the periapical tissues (Cheung et al, 2009). Nickel-titanium rotary files as well as improved understanding of irrigation have made single appointment treatment much more accessible (Su et al, 2011). Other advantages include greater patient acceptance and cost effectiveness (Su et al, 2011).

Su et al (2011) conducted a systematic review of controlled clinical trials comparing outcome of endodontically treated teeth completed in single visits and multiple visits. They concluded that the healing rate was similar between the two groups and that post-operative pain was significantly lower in the single visit treatment group. Kvist et al (2004) carried out a randomized, clinical trial evaluating the antimicrobial efficacy of endodontic treatment completed in one visit as compared to two-visit treatment in teeth with apical periodontitis. Microbial samples were retrieved from 29% of the one visit group and 36% of the two-visit group, with no significant statistical difference in the antimicrobial efficacy between the two groups. The Su and Kvist studies demonstrate the clinical and anti microbial efficacy of endodontic treatment completed in one visit.

Only teeth with a pulpal diagnosis of irreversible pulpitis were enrolled in the present study. Chance et al (1987) investigated the use of an intra-canal corticosteroid in

both vital and necrotic teeth and its effects on post-operative pain after initial treatment in a randomized, double-blind clinical trial. The frequency of post-operative pain amongst vital teeth was greater in the control group as compared to the experimental group. This difference was statistically significant, p=0.007 (1987). There was no significant difference in post-operative pain in non-vital teeth between the control and experimental groups.

Researchers have utilized many different modes of delivery for corticosteroids. Dexamethasone has been administered through local infiltration, extra oral intra-muscular injections, intra oral intra-muscular injections, oral dosage, and intra canal rinses (Shariar et al, 2013; Marshall & Walton, 1984; Liesinger et al, 1993; Jalalzadeh et al, 2010; Chu et al 2006; Ehrmann et al, 2003; Negm et al, 2001). To limit any possible complications or side effects that may arise from dexamethasone usage, this study used dexamethasone as an intra canal rinse. Dexamethasone has a plasma half-life of 200 minutes and tissue half-life of seventy-five hours (Wayman et al, 1994). Systemic absorption of dexamethasone may produce unwanted actions at other sites of the body such as a decrease in the body's healing response (Wayman et al, 1994). Wayman et al (1994), found that local infiltration of radioactive dexamethasone in the mandibular buccal vestibule of rats was rapidly absorbed in the systematic circulation and deposited throughout the tissues. Within one hour of injection, radioactive dexamethasone was found in the contra-lateral mandible. Although it is difficult to extrapolate conclusions from animal studies, the use of an intra-canal dexamethasone rinse may be an effective means of limiting systematic absorption of the drug.

This study sought to evaluate post-operative pain up to forty-eight hours post-treatment. Liesinger et al (1993) showed that the greatest level of post-operative pain occurred within the first twenty-four hours following treatment. Their study also showed that the greatest therapeutic effects of dexamethasone were observed during this time period. By implementing a 48 hour post-treatment observation period it became possible to fully document the post-operative pain cycle.

One patient in the experimental group did develop localized swelling after treatment was completed. No antibiotics were prescribed for patients who enrolled in the study unless they developed post-operative complications such as swelling, fever, or lymphadenopathy. A Cochrane systematic review by Keenan et al (2006) concluded that there was no evidence that antibiotics provided any analgesic effect in patients with irreversible pulpitis. Rogers et al (1999) suggested that infections secondary to corticosteroid usage may be possible when the inflammatory response is suppressed. However, numerous large studies have previously used corticosteroids without any evidence of fever, swelling, or malaise (Rogers et al, 1999; Negm et al, 2001; Liesinger et al, 1993; Marshall & Walton, 1994; Jalalzadeh et al, 2010).

CONCLUSION

The sample size of this randomized, double blind clinical pilot study does not allow any conclusion to be made with confidence on the analgesic efficacy of dexamethasone as a final rinse prior to obturation. Standard of care root canal therapy for both groups had a statistically significant reduction in post-operative pain, demonstrating the effectiveness of root canal therapy. A much larger sample size is needed to determine if there any possible effects dexamethasone may have on post-operative pain.

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