LOCAL ANESTHETICS IN POST-OPERATIVE ENDODONTIC PAIN

A THESIS
SUBMITTED TO THE FACULTY OF
UNIVERSITY OF MINNESOTA
BY

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IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
MASTER OF SCIENCE

AUGUST 2015

ACKNOWLEDGEMENTS

Dr. McClanahan
It has been an absolute honor to work and study under your guidance. The support and mentoring you've provided is second to none.

Dr. Bowles
Your knowledge, wisdom, and ever-present sense of humor are inspirational.

Dr. Aparicio
Thank you for your support and contribution to this work.

Drs. Baumgardner, Doyle, Edmunds, Ryan, Spitzmueller, and Zucker
Your perspective and advice has been an integral part of this outstanding educational experience.

Drs. Barsness, Roach, and Rodriguez-Figueroa
Thank you for your will and dedication to teaching. I hope to give back to the profession of dentistry with the exuberance that you do.

Drs. Lavasani, Lewis, and Tyler
What an incredible journey it has been. Together we've accomplished so much more than any individual person could dream of.

My other fellow residents, past and present
It has been a pleasure working with each and every one of you. I look forward to our futures together as colleagues.

Alicia, Ling-Hui, Lisa, Marlene, CeCe, Becky, and Jane
Without your help, this ship would have sunk long ago. Thank you for everything you've done along the way.

DEDICATION

I dedicate this work to my parents, my brother, and to Chasidy. Without your everlasting support, none of this would have been possible.

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INTRODUCTION

Pain in the orofacial region, especially odontalgia, is all too common (Riley and Gilbert 2001). A 1993 survey of a United States population found that 12.2% of adults experienced odontalgia in the past 6 months (Lipton et al. 1993). Approximately one-third of all dental emergencies are endodontic emergencies, and as many as 90% of dental emergencies involving pain are pulpal or periapical in origin (Rossman et al. 2006). Management of the dental emergency can be systematically approached using a triad of key points: Diagnosis, definitive treatment (removal of etiology) with proper local anesthesia, and assignment of a drug regimen that contributes analgesic and anti-inflammatory mechanisms (Hargreaves and Keiser 2004).

Pain produces an incentive for the patient to seek dental care. This pre-operative pain can often persist following initiation and/or completion of root canal treatment. More than 40% of patients who underwent chemomechanical root canal preparation reported post-operative pain in the first 24 hours following treatment (Georgopoulou et al. 1986). Even without pain before root canal treatment, an incidence of slight post-operative pain in 28.8%, or moderate to severe post-operative pain in 15.7% following pulpal debridement occurs (Harrison et al. 1983a). A number of studies, however, have demonstrated that the incidence of post-operative pain is considerably higher when patients report pre-treatment pain (O'Keefe 1976; Torabinejad et al. 1988; Walton and Fouad 1992; Mattscheck et al. 2001), and that post-operative pain is most severe within the first 24 hours following treatment (Harrison et al. 1983a; Torabinejad et al. 1994b; Mattscheck, et al. 2001).

Clinical trials have shown that the incidence of moderate or severe post-operative pain following endodontic therapy is strongly correlated with the initial cleaning and shaping procedure rather than with final obturation of the root canal system (Taintor and Ross 1978; Harrison et al. 1983b; Torabinejad et al. 1994a; Walton and Fouad 1992). Pain from a surgical incision or tissue manipulation may occur immediately, but this gives way to inflammatory pain following inflammatory cell recruitment to the injured area over the course of several hours (Gordon et al. 2010).

A higher incidence of post-operative pain may occur in teeth with necrotic versus vital pulpal status. Walton and Fouad (1992) observed a positive correlation with severe post-operative symptoms in patients having a pre-treatment diagnosis of pulpal necrosis and painful apical pathosis.

Previous studies have also suggested that sex differences may play a role in pain perception. In an oral surgery model, it was reported that females presented for treatment with higher baseline pain levels than men (Averbuch and Katzper 2000). In a study by Ng et al. evaluating the incidence of post-operative endodontic pain, females were determined to be a significant prognostic factor (Ng et al. 2004). Other factors that were prognostic determinants of post-operative pain included molar teeth, apical lesions less than 3 mm in diameter, and single-visit treatments. A study by Morin et al. observed that females find post-surgical pain more intense than males, but males are more disturbed than females by low levels of pain that lasts several days (Morin et al. 2000).

To minimize post-operative pain following endodontic treatment opioid analgesics are frequently prescribed, and while effective, can be associated with side

effects such as drowsiness, nausea and vomiting, constipation, and with long term use, tolerance and dependence. Even non-steroidal anti-inflammatory agents have adverse effects such as cardiovascular and peptic ulcers, and cannot be used with all patients. The additional use of long-acting local anesthetics has shown the ability to provide an increased duration of post-treatment analgesia beyond the period of anesthesia (Moore and Dunsky 1983; Dunsky and Moore 1984; Crout et al. 1990; Parirokh et al. 2012; Al-Kahtani 2014). Long acting local anesthetics may also reduce analgesic use and analgesic-related adverse events. Since endodontic treatment by itself often provides substantial pain relief by 24 hours, the use of long-acting local anesthetics represent a logical means for inclusion in the management plan for post-operative pain (Keiser and Hargreaves 2002).

The purpose of this clinical trial was to compare post-operative pain levels following the first stage of two-visit emergency endodontic treatment in patients with either an intermediate-acting local anesthetic (2% lidocaine with 1:100,000 epinephrine) or a long-acting local anesthetic (0.5% bupivacaine with 1:200,000 epinephrine).

HYPOTHESIS

Patients receiving a long-acting local anesthetic (bupivacaine) will report lower postoperative pain levels following emergency endodontic treatment when compared to patients who received emergency endodontic treatment with an intermediate-acting local anesthetic (lidocaine), without regard to post-operative analgesics given.

LITERATURE REVIEW

Tissue Damage and Pain

Clinical pain can be categorized as inflammatory or neuropathic pain. Inflammatory pain generally refers to pain associated with peripheral tissue damage, where neuropathic pain is associated with damage to the nervous system (Woolf and Chong 1993). The most common etiology of pulpal inflammation is microbial infection, while the second most common cause of pulpal inflammation is traumatic injury (Hargreaves and Hutter 2002).

Pain occurs due to direct activation of nociceptive fibers, often by inflammatory mediators. Pain may be expanded due to peripheral or central hypersensitivity caused by posttranslational and transcriptional changes in peripheral nociceptor terminals and dorsal horn neurons (Woolf and Costigan 1999). Sources of pain may be related to a state where the intensity required to initiate a painful response is reduced to a threshold such that a normally innocuous stimulus will result in pain, also known as allodynia. An exaggerated response to a stimulus that would normally be noxious is known as hyperalgesia (Treede et al. 1992; Woolf 1989).

The sensory innervation of the dental pulp includes numerous branches that stem from afferrent myelinated A fibers or unmyelinated C fibers (Byers et al. 2012) Innocuous peripheral mechanical stimuli are generally transmitted by large A-beta primary sensory fibers, while smaller A-delta and C fibers are responsible for transmitting noxious stimuli (Treede et al. 1992; Willis and Coggeshall 2004).

Odontogenic pain generally occurs following a noxious physical stimulus or an influx of inflammatory mediators that activate terminal receptors on afferent C and A-delta fibers (Willis 1985; Woolf and Costigan 1999; Hargreaves and Milam 2001). Slow-conducting, unmyelinated C-fibers comprise more than half of the nerve fibers in human dental pulp, and they are likely responsible for pain that is poorly localized with dull and lingering qualities. Most of the myelinated axons entering the root apex area are fast-conducting A-delta fibers, likely responsible for sharp and brief localized pain (Nair 1995).

Some of the structural features associated with the dental pulp certainly make pulpal pain unique, however, the peripheral mechanisms associated with odontogenic pain share similarities with peripheral pain in the rest of the body (Henry and Hargreaves 2007). The dorsal horn is most often discussed when the central nervous system (CNS) is referred to, however, for orofacial pain, the trigeminal nucleus within the pontine brain stem is the correlate of the dorsal horn. Peripheral afferent impulses travel through the trigeminal ganglion and enter the CNS through the pons, descending along the trigeminal tract in order to reach the trigeminal nucleus where they synapse with second-order neurons (Merrill 2007).

Intrinsic neurons are excited primarily within the superficial lamina of the trigeminal nucleus caudalis by the release of glutamate, an excitatory amino acid, along with neuropeptides (De Biasi and Rustioni 1988). Peptides play an important role in the activation of nociceptors in the spinal system, but their role has also been identified in the dental pulp, some of which include Substance P (SP) (Olgart et al. 1977), bradykinin

(Goodis et al. 2000), neurokinin A (NKA), vasoactive intestinal peptide (VIP), neuropeptide Y (NPY), calcitonin gene related peptide (CGRP) (Uddman et al. 1986), and nerve growth factor (NGF) (Wheeler et al. 1998). Extracellular levels of substance P are positively correlated with inflammation and pain (Byers and Taylor 1993; Traub 1996), and an eight-fold increase in substance P concentrations have been demonstrated in symptomatic pulps diagnosed with irreversible pulpitis (Bowles et al. 2003). Lepinski et al. found an almost 13-fold increase in bradykinin levels in inflamed pulps (Lepinski et al. 2000).

While many inflammatory mediators activate nociceptors, some produce persistent effects or potentiate the effects of other inflammatory mediators. Nerve growth factor concentrations in the inflamed dental pulp can increase by a factor of 8 times compared with the uninflamed pulp (Byers et al. 1994; Wheeler et al. 1998). Injections of nerve growth factor in healthy humans have been shown to evoke persistent pain and allodynia for weeks (Petty et al. 1994; Byers and Narhi 1999). Peripheral afferent fibers respond to nerve growth factor by increasing synthesis of CGRP and substance P, and by sprouting terminal fibers into the inflamed tissue, which may contribute to increased sensitivity in pulpal or periradicular tissues (Byers et al. 1990; Byers 1994; Byers and Narhi 1999).

Prostaglandins contribute to the development of the cardinal signs of acute inflammation, and play a key role in the generation of the inflammatory response (Ricciotti and FitzGerald 2011). Prostaglandin E_2 (PGE_2) has been demonstrated to significantly increase the stimulatory effect of bradykinin in an *ex vivo* bovine dental pulp

model (Goodis et al. 2000). A significant increase in the production of PGE_2 has been detected in inflamed periradicular tissues, especially when pain and/or swelling is present (McNicholas et al. 1991).

A variety of types of receptors and ion channels associated with second-order neurons play a role in modulatory circuits that can facilitate or inhibit pain transmission. If a peripheral inflammatory process produces intense afferent activity and neuronal damage, a central process can begin, leading to increased sensitization, lower response threshold, ectopic discharge, and pain signaling from fibers that typically carry innocuous stimuli, for example, A-beta fibers(Merrill 2007).

Management of Endodontic Pain

Management of endodontic pain should focus on the removal of peripheral mechanisms that cause hyperalgesia and allodynia. This is generally achieved through removal and reduction of bacterial and immunologic factors (Hargreaves et al. 1994; Keiser and Byrne 2011). Endodontic treatments such as pulpotomy or pulpectomy have demonstrated substantial reduction in patient-reported pain compared with pretreatment pain levels (Hasselgren and Reit 1989; Hargreaves 1997; Doroschak et al. 1999; McDougal et al. 2004). Frequently, however, the addition of a pharmacological approach is required to reduce continued nociceptor input using local anesthetics or non-steroidal anti-inflammatory drugs (NSAIDs), and suppression of central hyperalgesia may be achieved with drugs such as NSAIDs or opioids (Keiser and Byrne 2011).

Local Anesthetics

The use of effective local anesthesia is critical in endodontics, as treatment cannot be performed without adequate pain control. The use of local anesthesia was introduced in 1884 when Karl Koller used cocaine as an anesthetic during ophthalmic surgery (Ruetsch et al. 2001). Following a prominent history of toxicity, addiction, and sometimes fatal effects associated with the use of cocaine as a local anesthetic, Alfred Einhorn introduced procaine in 1904 as a safer, less addicting alternative. It was soon learned, however, that the vasodilatory effects of procaine caused a profound drop in blood pressure, allowing the anesthetic to travel widely from the site of injection. This was overcome by the combination of procaine with the α-adrenergic vasoconstrictive properties of epinephrine (Ring 2007).

The chemical structure of early local anesthetics such as cocaine and procaine contain an ester linkage, which is responsible for a high incidence of allergic reactions. The most common forms of local anesthetics used in dentistry today contain an amide linkage, which carries a far lower risk for allergenicity. Lidocaine was introduced in the 1950's and has become the prototypic dental anesthetic in North America due to its excellent efficacy and safety (Moore and Hersh 2010). In 1963 bupivacaine was introduced as an amide local anesthetic possessing a long duration of action, primarily due to its lipid solubility and protein-binding characteristics (Covino and Vassallo 1976).

Local anesthetics can generally be categorized into three types based on their duration of action: short-acting (approximately 30 mins of pulpal anesthesia), intermediate-acting (approximately 60 mins of pulpal anesthesia), and long-acting (over

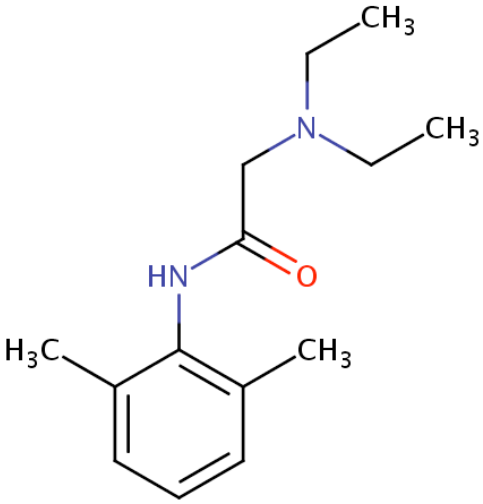
90 minutes of pulpal anesthesia). The duration of anesthesia achieved clinically with each local anesthetic depends, however, on the route of administration (i.e. block versus infiltration) (Reader et al. 2011).

Bupivacaine (with 1:200,000 epinephrine), for example, is considered a long-acting local anesthetic, and studies have shown an average of 4 hours of pulpal anesthesia following inferior alveolar nerve block (Fernandez et al. 2005). Using the same anesthetic as infiltration for anterior teeth, it demonstrated a shorter duration of action than lidocaine (with 1:100,000 epinephrine), which is generally classified as having an intermediate duration of action (Danielsson et al. 1985; Gross et al. 2007).

Another factor affecting the duration of a local anesthetic is the addition (or absence) of a vasoconstrictor. This addition delays the systemic absorption of the anesthetic solution, reducing the risk for toxicity, but also prolonging the local duration of anesthesia. Epinephrine is the agent most commonly used for this purpose, due to its alpha-1 agonistic action (Becker and Reed 2006). Solutions containing 1:100,000 epinephrine are popular, however, research has shown that concentrations higher than 1:200,000 epinephrine do not provide faster onset or greater duration when used for inferior alveolar blocks (Dagher et al. 1997; Tofoli et al. 2003).

Clinically relevant local anesthetics used in dentistry are comprised of an amine on one end with an ester or amide intermediate chain linked to a lipophilic aromatic ring on the other end. The aromatic ring improves the lipid solubility of the compound. The more lipid soluble a molecule is, the more readily it can diffuse through nerve sheaths

and neural membranes. Lipid solubility correlates with the potency of the local anesthetic (Becker and Reed 2006).



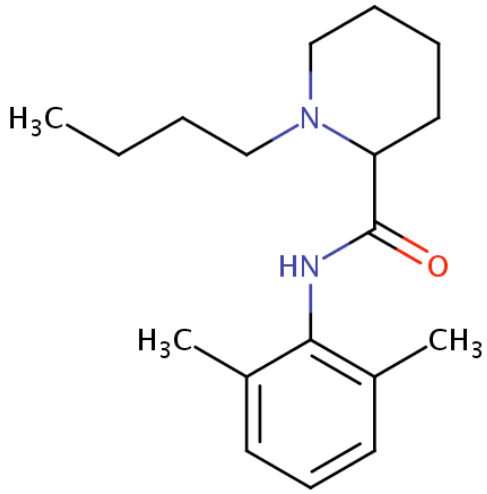


Fig. 1a Chemical Structure of Lidocaine **Fig. 1b Chemical Structure of Bupivacaine**

The terminal amine may exist in either a charged (quaternary) or an uncharged (tertiary) form. While the aromatic ring determines the degree of lipid solubility, the terminal amine acts as a switch that alters the molecule to exist in either a water-soluble (charged) conformation or a lipid-soluble (uncharged) conformation. Prior to injection, the anesthetic exists in the quaternary, water-soluble form. This charged conformation of the molecule is unable to penetrate the neuron, and must first be converted to the uncharged tertiary form. The onset of local anesthesia is dependent on the proportion of molecules that convert to the uncharged form when exposed to physiologic pH. The pK_a,

or ionization constant refers to the pH at which fifty percent of the molecules exist in the charged, water-soluble form and fifty percent in the uncharged, lipid-soluble form. Once the lipid soluble form exists, it can diffuse through the neural sheath and neural membranes, where it targets ion channels.

Voltage-gated ion channels, including potassium (K^+), calcium (Ca^{2+}), and sodium (Na^+) channels, are transmembrane, pore-forming proteins that allow the selective passage of certain ions in a voltage-dependent manner. The activation of Na^+ channels is critical in the initiation and propagation of action potentials (nerve impulse). When a transient generator potential is created by the activity of other ion channels, the opening of the voltage-gated Na^+ occurs. As Na^+ ions enter the axon, depolarization occurs. If a depolarizing threshold is reached, the result is initiation of an action potential. Therefore, drugs such as local anesthetics that block sodium channels (e.g. lidocaine, mepivacaine, bupivacaine, articaine) play a critical role in dental therapeutics (Henry and Hargreaves 2007).

A dramatic increase in the expression of voltage-gated sodium channels has been demonstrated in the inflamed dental pulp, which can lead to a significant impact on the transmission of action potentials from the pulp and periradicular regions (Henry et al. 2009; Luo et al. 2008; Wells et al. 2007).

Sodium channels can be classified according to their susceptibility to tetrodotoxin (TTX), where they may be considered either TTX-sensitive or TTX-resistant (Arbuckle and Docherty 1995). A majority of TTX-resistant channels are found primarily on nociceptors (Wells et al. 2007). Furthermore, these afferent fibers are sensitized by

prostaglandins (Gold et al. 1996) and it has been suggested that TTX-resistant channels are relatively resistant to local anesthetics (Roy and Narahashi 1992; Scholz et al. 1998).

In a study comparing the ability of lidocaine and bupivacaine to reduce firing frequency in both TTX-sensitive and TTX-resistant sodium channels, the two anesthetic solutions were equally effective for TTX-sensitive channels, however, bupivacaine showed greater efficacy in TTX-resistant channels (Scholz et al. 1998).

Local anesthetics may contribute to the treatment of odontogenic pain through additional mechanisms. G protein-coupled receptors (GPCRs) are the target of many classes of drugs (e.g. opioids, catecholamines), but local anesthetics have also shown the ability to modulate certain classes of these receptors (Reader et al. 2011). The G-alpha-q class of GPCRs includes receptors activated by bradykinin. Studies have suggested that local anesthetics can inhibit these receptors, thereby blocking the actions of a major hyperalgesic agent (Hollmann et al. 2004).

Studies have demonstrated analgesia that lasts well beyond the period of anesthesia when long-acting local anesthetics are used (Moore and Dunsky 1983; Dunsky and Moore 1984; Crout et al. 1990; Keiser and Hargreaves 2002), and prolonged alteration in GPCR function might help explain this phenomenon(Reader et al. 2011). In a periodontal surgery model, it has been observed that the administration of a block injection with a long-acting local anesthetic such as bupivacaine can provide analgesia for up to 10 hours, and that reports of perceived pain may be reduced at periods as long as 48 hours after administration (Crout et al. 1990). In more recent clinical trials, patients with irreversible pulpitis who received bupivacaine prior to endododontic treatment

reported significantly lower levels of pain after 12 hours and used fewer analgesics when compared to patients receiving lidocaine (Parirokh et al. 2012; Al-Kahtani 2014).

While long-acting local anesthetics have demonstrated prolonged anesthesia/analgesia when administered by mandibular nerve block, the same may not be true for maxillary infiltration. When the use of long-acting local anesthetic infiltration in maxillary endodontic surgery was examined, soft tissue anesthesia lasted significantly longer, however, pain experience and analgesic intake did not differ from that of patients receiving lidocaine (Meechan and Blair 1993). In a study comparing the duration of pulpal anesthesia achieved with bupivacaine and lidocaine when delivered by maxillary infiltration, it was concluded that bupivacaine did not fulfill the concept of a long-acting local anesthetic (Gross et al. 2007).

Research has suggested that central sensitization can be reduced or inhibited by the administration of a long-acting local anesthetic before and/or immediately after surgery (Gordon et al. 1997; Kaurich et al. 1997; Gordon et al. 2002). By blocking the activation of nociceptors, not only is anesthesia provided but, by reducing the potential for central sensitization, analgesia is provided as well (Keiser and Hargreaves 2002).

Modification of the dosage of a local anesthetic may be required due to certain systemic diseases or disorders. Patients with severe cardiac conditions, including unstable angina pectoris, recent myocardial infarction or stroke (within the past 6 months), severe hypertension, or uncontrolled congestive heart failure, should not receive a local anesthetic containing a vasoconstrictor, and should consult with a physician before treatment (Naftalin and Yagiela 2002).

Even relatively small amount of epinephrine, when delivered by nerve block or intraosseous injection, have shown the ability to cause increases in heart rate (Goldstein et al. 1982; Replogle et al. 1999), systolic blood pressure, and cardiac output (Goldstein et al. 1982).

Inadvertent intravenous injection or large doses of local anesthetic can lead to acute toxicity and CNS depression (Finder and Moore 2002; Naftalin and Yagiela 2002). Although rare, systemic effects from local anesthesia may include tremors, seizures, hypotension, and respiratory arrest (Finder and Moore 2002; Dernedde et al. 2004). To minimize the risk for adverse effects, the clinician must always aspirate before delivering an injection, and should use dosages within accepted guidelines (Reader et al. 2011).

Local anesthetics have the potential to interact with certain medications, so it is critical to perform a thorough review of each patient's medical history(Naftalin and Yagiela 2002). Potential drug-drug interactions occur primarily with the vasoconstrictors in local anesthetic formulations, and the use of anesthetic formulations without vasoconstrictors may be indicated (Reader et al. 2011).

Analgesics

Non-narcotic Analgesics

Non-narcotic analgesics are one major class of drugs for the management of endodontic pain both preoperatively and postoperatively. The primary approach with these drugs is to block inflammatory mediators that sensitize or activate pulpal nociceptors. This category includes NSAIDs as well as acetaminophen (Khan and

Hargreaves 2012). These drugs are classically believed to produce analgesic effects through peripheral mechanisms, however, the CNS is now thought to be an additional site of action (Malmberg and Yaksh 1992; Svensson and Yaksh 2002). It has been shown that NSAIDs prevent the production of prostaglandins by inhibition of the enzyme cyclooxygenase (COX) (Vane 1971; Smith and Willis 1971).

Prolonged pain following a surgical procedure may develop as result of sensitization, beginning with an increased expression of proinflammatory cytokines and COX enzymes, leading to an increased production of prostanoids 2 to 4 hours post-operatively (Woolf and Chong 1993). For many years COX was thought to be a single constitutive enzyme present in most tissues, however, COX activity has been found to be increased by certain inflammatory states and can be induced by inflammatory cytokines (Raz et al. 1988; Fu et al. 1990; Masferrer et al. 1992; Sano et al. 1992). Further research has suggested the existence of two isoforms of COX, a constitutive enzyme present in tissues such as the stomach and kidneys (COX-1), and another form of COX associated with inflammation (COX-2) (Kujubu et al. 1991; Sirois and Richards 1992; Xie et al. 1991).

Although traditional commercially available NSAIDs are effective, gastrointestinal and renal toxicity limits their use, due to non-selective inhibition of pro-inflammatory prostaglandins produced by COX-2, as well as physiologically important prostaglandins produced by COX-1 (Seibert et al. 1994). In more recent years, selective COX-2 inhibitors were introduced, showing the potential for both analgesic and anti-inflammatory benefits with reduced gastrointestinal irritation (Dionne 1999; Khan and

Dionne 2002). Major concerns over the safety of selective COX-2 inhibitors have arisen following the recognition of prothrombic adverse effects associated with these drugs. The demonstration of increased risk for prothrombic events following long-term use of rofecoxib, a selective COX-2 inhibitor, led to withdrawl of the drug from U.S. market in 2004 (FDA 2004).

Ibuprofen is often considered the prototype of NSAIDs, and its efficacy and safety profile have been well documented (Dionne et al. 1983). In a post-extraction oral surgery model, 400 mg ibuprofen demonstrated superior efficacy over 25 mg ketoprofen, 1000 mg acetaminophen, or placebo (Olson et al. 2001).

Many NSAIDs have shown greater efficacy when compared with traditional acetaminophen or opiod combinations such as acetaminophen with codeine (Dionne 1986; Troullos et al. 1986). In conjunction with endodontic treatment such as pulpectomy or pulpotomy, NSAID therapy alone has been shown to be sufficient in many cases, however, when additional analgesia is needed, opiods or acetaminophen may serve as an important adjunct (Hargreaves and Keiser 2004).

Studies have proposed that COX-3, a variant of the COX-1 enzyme is the primary site of action of acetaminophen (Chandrasekharan et al. 2002; Schwab et al. 2003; Kis et al. 2004), but more recent studies have indicated that the action of acetaminophen is more likely through the effects of an active metabolite on CNS cannabinoid receptors (Anderson 2008). Acetaminophen can be used for pain relief alone or in combination with NSAIDs or narcotics. In a clinical trial examining post operative pain following pulpectomy, the combination of 1000 mg acetaminophen with 600 mg ibuprofen

demonstrated significantly greater pain relief versus 600 mg ibuprofen or placebo over an eight hour observation period (Menhinick et al. 2004).

Acetaminophen is considered safe when taken at normal doses but may cause liver toxicity at higher doses, and it has become the most common cause of acute liver failure (Larson et al. 2005). A majority of a normal dose of acetaminophen is conjugated in the liver, forming inactive metabolites. A small portion is metabolized to form N-acetyl-p-benzoquinone imine (NAPQI). NAPQI is highly toxic, but is typically converted by glutathione into nontoxic compounds. If a large dose of acetaminophen saturates the main route of metabolism, increased amounts of NAPQI are formed. If glutathione becomes depleted NAPQI can accumulate, leading to liver injury (Keiser and Byrne 2011).

Opioid Analgesics

Opioids are effective analgesics for moderate to severe pain, and they are often used in dentistry in combination with acetaminophen or other NSAIDs. Most clinically available opioids activate mu opioid receptors in the brain, inhibiting the transmission of signals to higher brain regions. Opioid use is generally limited by their side effects, which can include nausea, emesis, dizziness, drowsiness, constipation, and respiratory depression. Oderda et al. analyzed data from almost 61,000 patients given opioid analgesics for post surgical analgesia, and found an incidence of adverse drug events that were at least moderate in severity of approximately 3% (Oderda et al. 2003).

Pre-emptive Analgesia

Pre-operative administration of anti-inflammatory and analgesic drugs have been examined with the rationale that they may reduce the input from peripheral nociceptors, thereby blocking the development of hyperalgesia. A significant decrease in postoperative pain levels has been suggested with preoperative administration of NSAIDs (Dionne 1986; Jackson et al. 1989) or acetaminophen (Moore et al. 1986). More recent research, however, has indicated that pretreatment with analgesics may not significantly reduce postoperative pain below that achieved with endodontic treatment alone (Attar et al. 2008), unless the analgesic regimen is continued beyond the initial dose.

Pain Measurement

Pain is an unpleasant sensory and emotional experience. It is a phenomenon consisting of multiple dimensions having sensory, cognitive, and motivational components, and it can be very challenging to objectively assess all the attributes of pain (Kumar et al. 2002). In order to appreciate the subjective nature of the pain experience from one patient to the next, subjective methods of measurement such as the Visual Analog Scale (VAS), Heft Parker Scale, or Categorical Scale may be useful.

The Categorical Scale consists of four points ranging from “no pain” to “severe pain,” and asks the patient to choose the point that best represents their current level of pain. Although simple, it has been demonstrated that the Categorical Scale is a reliable

and reproducible method for measurement of pain in clinical trials (Averbuch and Katzper 2004).

The VAS is a widely used method for measuring the intensity of pain following surgery. This scale asks patients to place a mark on a 100 mm horizontal line representing their current level of pain, where 0 mm represents no pain and 100 mm represents a maximum level of pain. Following a critical review of some of the available objective and subjective methods for pain measurement, the VAS was established as methodically sound, conceptually simple, easy to administer, and unobtrusive to the patient (Coll et al. 2004). Further research has demonstrated that the VAS is reproducible and unaffected by gender (Goddard et al. 2004).

The Heft Parker Scale was developed as a way to combine categorical descriptive words with a VAS-type horizontal line. This scale consists of a 170 mm horizontal line with 8 irregularly spaced descriptive words. The patient is asked to place a mark on the horizontal line that represents their current level of pain. Heft and Parker designed this scale with the intention that patients would make categorical judgments based on their understanding of the words and that the categorical ratings are not simply an ordinal index (Heft and Parker 1984).

MATERIALS AND METHODS

The protocol for this study was approved by the Institutional Review Board (IRB) at the University of Minnesota and can be identified by IRB code number 1311M45821. Patients presenting to the University of Minnesota School of Dentistry with pain diagnosed as endodontic in origin were screened for inclusion into the study.

Patients presenting to the Endodontic clinic were pre-screened by being asked to score their current pain level using a Verbal Numeric Rating Scale (VNRS) (Holdgate et al. 2003). The VRNS requires a verbal response by the patient ranging from zero to ten with zero indicating 'no pain' and ten indicating 'worst pain imaginable.' Patients reporting moderate or severe tooth pain (>3 out of 10 on the VNRS) were invited to participate in a research study evaluating post-endodontic pain. If the patient consented to be included in the study and met the following inclusion criteria with none of the exclusion criteria, they were eligible to participate in the study.

Inclusion Criteria

Potential subjects for this study included healthy adults between 18 and 65 years of age, with an ASA class I or II ranking based on medical history. The patients were considered candidates if they presented for endodontic treatment with a pre-treatment VNRS score greater than or equal to 3 out of 10. All patients exhibited symptoms associated with irreversible pulpitis, pulpal necrosis, previously initiated treatment, or

previous endodontic treatment. Patients exhibited an apical diagnosis of normal apical tissues, symptomatic apical periodontitis, asymptomatic apical periodontitis, acute apical abscess, or chronic apical abscess. Finally, all patients were required to have the ability to read and understand the consent forms, and to understand and complete the provided pain questionnaires. To ensure the subjects' understanding of the consent, they were asked questions to assess their understanding of what they were being asked to do, such as:

1. Please describe in your own words the purpose of the study
2. To make sure you understand what is expected of you, please expain what you are being asked to do in the study
3. What more would you like to know?

Exclusion Criteria

Patients with documented allergies or intolerance to any of the proposed test medications or local anesthetic preparations, patients who were pregnant, patients who were currently on a pain medication for an unrelated condition, patients who had taken any pain medication within the last 4 hours, patients who were unwilling/unable to complete the pain scales for the first 48 hours following treatment, patients with a history of liver or kidney disease, and/or patients who were unable to understand and complete the consent form were excluded. Participants also had the option to terminate their participation in the study at any time.

All endodontic treatment was performed by 8 graduate endodontic residents at the University of Minnesota School of Dentistry. Prior to initiation of endodontic treatment each study participant was provided with a pre-packaged envelope which contained:

1. 1 consent form (Appendix 1).
2. 1 HIPAA Authorization to Use and Disclose form (Appendix 2).
3. 1 Patient Information form to be completed by both the treatment provider and the patient (Appendix 3).
4. 8 pain questionnaires (Appendix 4). Each questionnaire included a Categorical scale, Visual Analog Scale (VAS), and a Heft Parker scale. A questionnaire was to be filled out by the participant pre-operatively, immediately post-operatively, 1 hour following a first dose of a randomized pain medication, 1 hour following a second dose of the randomized pain medication, and at breakfast, lunch, dinner, and at bedtime the following day. The values of Categorical scales ranged from 0 (no pain) to 3 (severe pain). The VAS scales were 100 mm in length while the Heft Parker scales were 170 mm in length. Patients were requested to mark their perceived pain level on the provided scales and for the VAS and Heft Parker Scales, the marks were measured using a millimeter ruler to convert them to numerical scores.
5. 2 paired local anesthetic cartridges, each containing either 1.7 mL 2% lidocaine with 1:100,000 epinephrine (Novocol Pharmaceutical, Cambridge, Ontario, Canada) or 1.8 mL 0.5% bupivacaine with 1:200,000 epinephrine

(Novocol Pharmaceutical, Cambridge, Ontario, Canada) to be used to achieve anesthesia prior to treatment. The local anesthetic type included with each patient envelope was randomized, recorded, and cartridge labels were concealed with opaque masking tape during prior envelope assembly so that neither the treatment provider nor the patient were aware of the local anesthetic type to be administered. The identity of the local anesthetic used in each treatment was not disclosed to the principal investigators until the end of the study. Randomization was performed for anesthetic type rather than for each individual cartridge, such that both cartridges included in the envelope would be of the same type (e.g. lidocaine plus lidocaine or bupivacaine plus bupivacaine).

6. Detailed written instructions outlining how and when to complete the questionnaires, medication time intervals, and protocols in the event of an emergency.
7. Contact information for the principle investigators and a second entity outside of the School of Dentistry, should questions arise regarding the study.
8. A pre-stamped, self-addressed envelope with which the patient was given the option to either return the questionnaires by mail or to deliver the forms in person at their next visit.

Thirty-one eligible patients signed the consent form, which outlined the procedures and possible risks associated with the study. Prior to initiation of endodontic treatment, the following demographic data was recorded:

1. Contact information
2. Gender
3. Age
4. Tooth number to be treated
5. Pre-operative pulpal and apical diagnosis based on the definitions in the American Association of Endodontists Glossary of Terms, 2012
6. Specific procedure(s) to be completed

The first pain questionnaire was completed by each participant before administration of local anesthetic in order to establish pre-treatment pain levels. The entire volume of each of the two blinded local anesthetic cartridges were administered, and adequate time was given for the anesthetic to take effect. Sufficient anesthesia for treatment was suspected when the patient experienced resolution of their pre-treatment symptoms, and in cases of irreversible pulpitis, when a #2 cotton pellet saturated with tetrofluoroethane refrigerant spray (Endo Ice, Coltene-Whaledent, Cuyahoga Falls, OH) placed against the tooth surface produced no response. In cases where anesthesia was determined to be inadequate after administration of the two blinded cartridges included with the patient envelope, up to 1.7 mL of 2% lidocaine with 1:100,000 epinephrine was

administered as a supplement, however, this was rarely necessary. No patients required more than 1 additional cartridge of supplemental anesthetic, and sufficient local anesthesia was obtained in all participants prior to initiation of treatment. The volume of any supplemental anesthesia administered was recorded for consideration when analyzing the data. The tooth to be treated was isolated with a rubber dam. Endodontic access was performed, followed by identification and instrumentation of all canals, including removal of existing obturation materials in cases of previous endodontic treatment. The minimum canal preparation size that was considered acceptable for inclusion in this study was to a #25 file or, in cases of previous endodontic treatment, to a minimum of size #35 with removal of existing obturation materials. Canals were instrumented to within 0.5 to 1.0 mm of the apex, as determined by the combination of an electronic apex locator (Root ZX II, J. Morita USA, Irvine, CA) and digital periapical radiographs (Carestream Dental, Atlanta, GA). Nickel-titanium rotary files (K3XF, SybronEndo, Orange, CA; Vortex Blue, Dentsply, York, PA; or ProTaper, Dentsply, York, PA) were used to enlarge canals, with a 5.25% sodium hypochlorite irrigation solution used between files. Canals were dried using sterile paper points and calcium hydroxide intracanal medicament (Ultracal, Ultradent Products Inc, South Jordan, UT) was placed into canals using a syringe. A sterile cotton pellet was placed in the pulp chamber, and a Cavit (3M, St. Paul, MN) temporary restoration was used to seal the endodontic access.

For the purpose of standardization, all endodontic treatments performed in this study were carried out in two stages (a subsequent visit was required to complete the treatment), and only data related to the first stage of treatment was considered.

Following completion of the first-stage endodontic treatment, the participant was asked to complete the second pain questionnaire to establish immediate post-operative pain levels.

A prescription written for the IRB study number was presented to an independent pharmacy (IDS Pharmacy; University of Minnesota), which was then filled according to a randomized reference code known only to the IDS pharmacy. The prescription was provided in a sealed paper bag containing two vials marked 'Dose #1' and 'Dose #2,' with dose #1 to be taken one hour post-operatively (when the patient returns home) and dose #2 to be taken four hours following the first dose. Within the medication vials were one of the following randomly assigned drug regimens:

1. **Dose #1** - Anaprox DS 550 mg (naproxen sodium), **Dose #2** – Placebo
2. **Dose #1** – Placebo, **Dose #2** – Placebo
3. **Dose #1** – Ibuprofen 800 mg, **Dose #2** – Ibuprofen 800 mg
4. **Dose #1** – Ibuprofen 800 mg + hydrocodone 5 mg/acetaminophen 325 mg, **Dose #2** Ibuprofen 800 mg + hydrocodone 5 mg/acetaminophen 325 mg

The appropriate randomized drugs were provided in a generic form so that neither the patient nor the treatment provider were aware of the identity of the medication. The IDS pharmacy provided a 24-hour phone service number in case of an emergency situation where the drug code could be un-blinded for the treatment provider/patient. Otherwise, the identity of the drugs associated with the reference code were not disclosed

to the principal investigators until the end of the study. In the present study, no situation requiring un-blinding of the drug or inter-appointment emergency treatment occurred.

Participants were instructed to take dose #1 of the assigned medication approximately one hour post-operatively (after returning home). One hour after taking dose #1, participants completed the third pain questionnaire. Dose #2 of the assigned medication was to be taken four hours following the first dose. One hour after taking dose #2, participants completed the fourth pain questionnaire. The remaining four questionnaires were completed at breakfast, lunch, dinner, and bedtime the following day. In the event of any complications with the test medications, or in the event of any adverse symptoms/side effects, patients were encouraged to call the principle investigators. Patients who elected to take additional pain medication or pain medications other those provided in the study were to indicate this on the questionnaires and were excluded from the study. Upon completion of the questionnaires, patients were to return the forms in person at the subsequent visit, or by mail using the pre-stamped, self addressed envelope.

RESULTS

A total of thirty-one patients were enrolled in this clinical trial from February 2014 through April 2015. Ten patients were unable to complete the study because they could not be reached following the 48-hour trial period and/or because they failed to return the pain questionnaires. No patients were excluded due to the inability to achieve sufficient local anesthesia under the previously described research model. Furthermore, no patients were excluded based on the need for emergency inter-appointment treatment or the use of additional pain medications within the 48-hour trial period. Therefore, data from twenty-one patients was available for analysis.

First, comparability between the two local anesthetic groups was evaluated according to baseline characteristics. Table I compares the distribution of gender, age, and pre-operative pain as recorded on the Categorical scale, the VAS, and the Heft Parker scale (HP).

Table I. Patient Baseline Characteristics

Group	n	Gender (f:m)	Mean Age (years)	Mean Initial Categorical Scale	Mean Initial VAS	Mean Initial HP
Lidocaine	11	7:4	35.0	2	53.0	94.2
Bupivacaine	10	4:6	41.1	2.4	57.9	102.7

Comparability between the two anesthetic groups was evaluated based on the distribution of vital (irreversible pulpitis) vs. non-vital (necrotic, previous treated, previously initiated) pre-operative pulpal status (Table II), apical diagnosis (Table III),

and arch (maxilla vs. mandible; Table IV). The distribution of these characteristics between the two groups was similar.

Table II. Vital vs. Non-vital Pulpal Status by Study Group

Group	Vital	Non-vital	n
Lidocaine	5	6	11
Bupivacaine	4	6	10

Table III. Apical Diagnosis by Study Group

Group	SAP	AAP	AAA	CAA	Normal	n
Lidocaine	9	1	1	0	0	11
Bupivacaine	8	0	2	0	0	10

SAP = symptomatic apical periodontitis; AAP = asymptomatic apical periodontitis;
AAA = acute apical abscess; CAA = chronic apical abscess

Table IV. Maxillary Teeth vs. Mandibular Teeth by Study Group

Group	Maxillary	Mandibular	n
Lidocaine	9	2	11
Bupivacaine	7	3	10

Next, the effect of the local anesthetic solutions on pain measurements at the various time points was evaluated. The anesthetic-group main effect examines whether the local anesthetic groups differ according to each patient's average pain measurement over the seven post-operative time points (Table V). The two groups showed similar trends.

Table V. Anesthetic-Group Main Effect

Group	Average CS (SEM)	Average VAS (SEM)	Average HP (SEM)
Lidocaine	0.8 (0.1)	15.7 (2.0)	34.9 (3.3)
Bupivacaine	0.9 (0.1)	16.7 (2.6)	33.8 (4.0)

The time main effect examines whether the average pain measurements differ at the seven post-operative time points (Table VI). Pain measurements shows an overall trend where pain increases from the immediate post-operative period until mid-day on day 2, when a decreasing trend in pain measurements is observed.

Table VI. Time Main Effect

Time	Average CS (SEM)	Average VAS (SEM)	Average HP (SEM)
Immediate post-op	0.7 (0.2)	11.2 (3.5)	26.8 (5.5)
1 hr following med #1	1.0 (0.1)	18.8 (3.6)	38.8 (5.3)
1 hr following med #2	0.9 (0.2)	16.0 (4.2)	33.6 (6.5)
Day 2 breakfast	1.0 (0.2)	19.0 (4.8)	41.5 (7.6)
Day 2 lunch	0.9 (0.2)	19.1 (5.2)	39.6 (8.4)
Day 2 dinner	0.9 (0.2)	16.9 (4.7)	36.7 (7.4)
Day 2 bedtime	0.6 (0.2)	12.1 (4.0)	24.0 (6.6)

The group-by-time interaction examines whether the pain measurements between the two local anesthetic groups differ over time (Table VII). A trend in which the bupivacaine group reports lower pain levels when compared to the lidocaine group is observed on the first day, followed by a comparatively higher pain level on day 2. Both local anesthetic groups show a decreasing pain trend near the end of the second day.

Table VII. Group-by-Time Interaction

Time	Lidocaine Avg. VAS (SEM)	Bupivacaine Avg. VAS (SEM)
Immediate post-op	9.0 (3.4)	13.7 (6.6)
1 hr following med #1	23.6 (6.0)	13.6 (3.3)
1 hr following med #2	24.5 (6.9)	6.6 (1.9)
Day 2 breakfast	15.8 (5.3)	22.5 (8.5)
Day 2 lunch	16.0 (5.7)	22.7 (9.1)
Day 2 dinner	12.0 (3.2)	22.3 (9.2)
Day 2 bedtime	9.0 (4.5)	15.6 (7.0)

When the group-by-time interaction is examined by pain measurements as reported on the Categorical scale (Fig. 2), VAS scale (Fig. 3), and Heft Parker scale (Fig. 4), a similar trend for each of the two local anesthetic groups is observed.

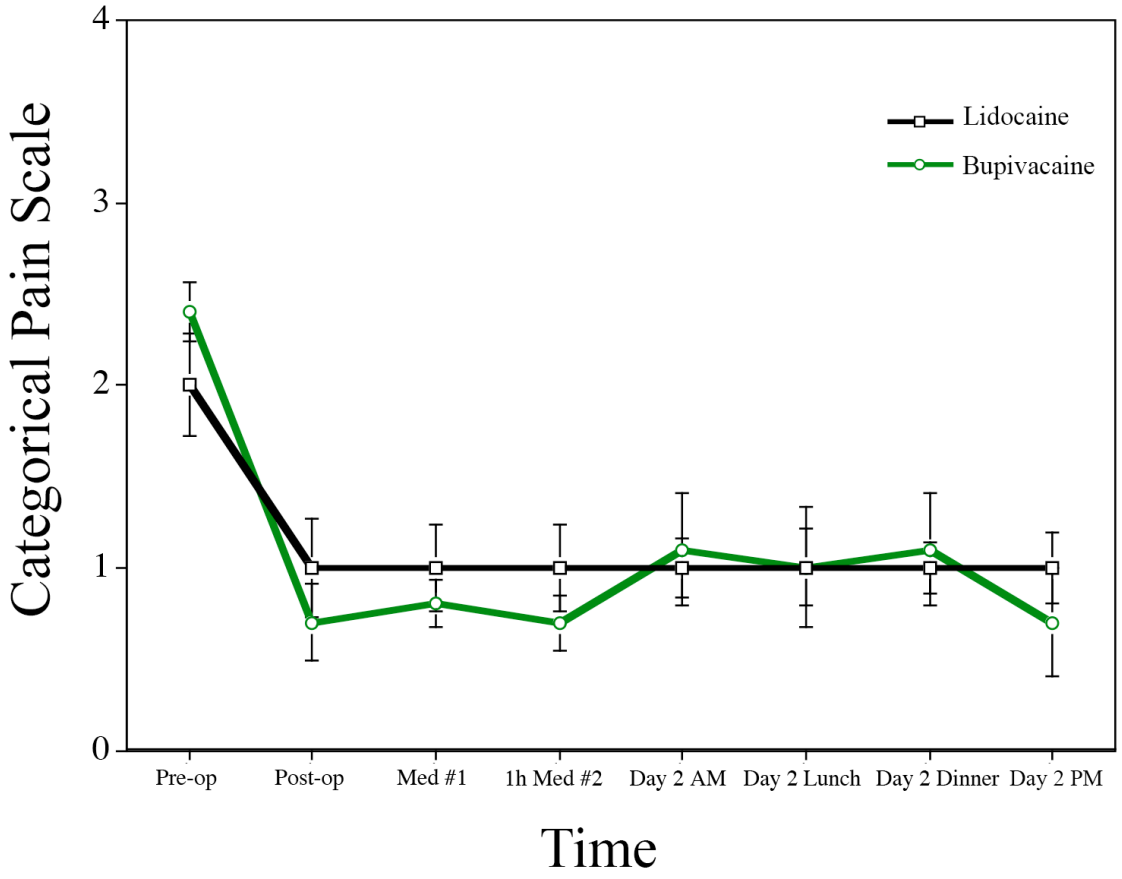


Figure 2. Group-by-Time Interaction – Average Categorical scale reading at each time point.
n = 10-11/group Error Bars = S.E.M.

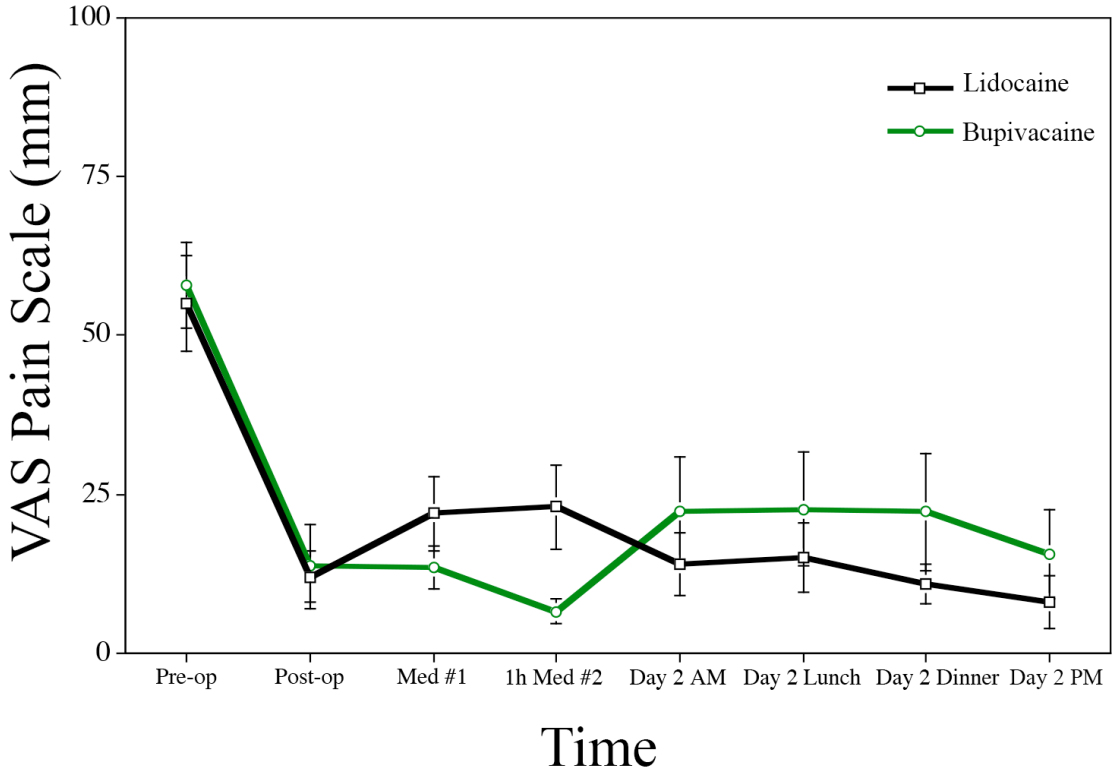


Figure 3. Group-by-Time Interaction – Average VAS reading at each time point n = 10-11/group Error Bars = S.E.M.

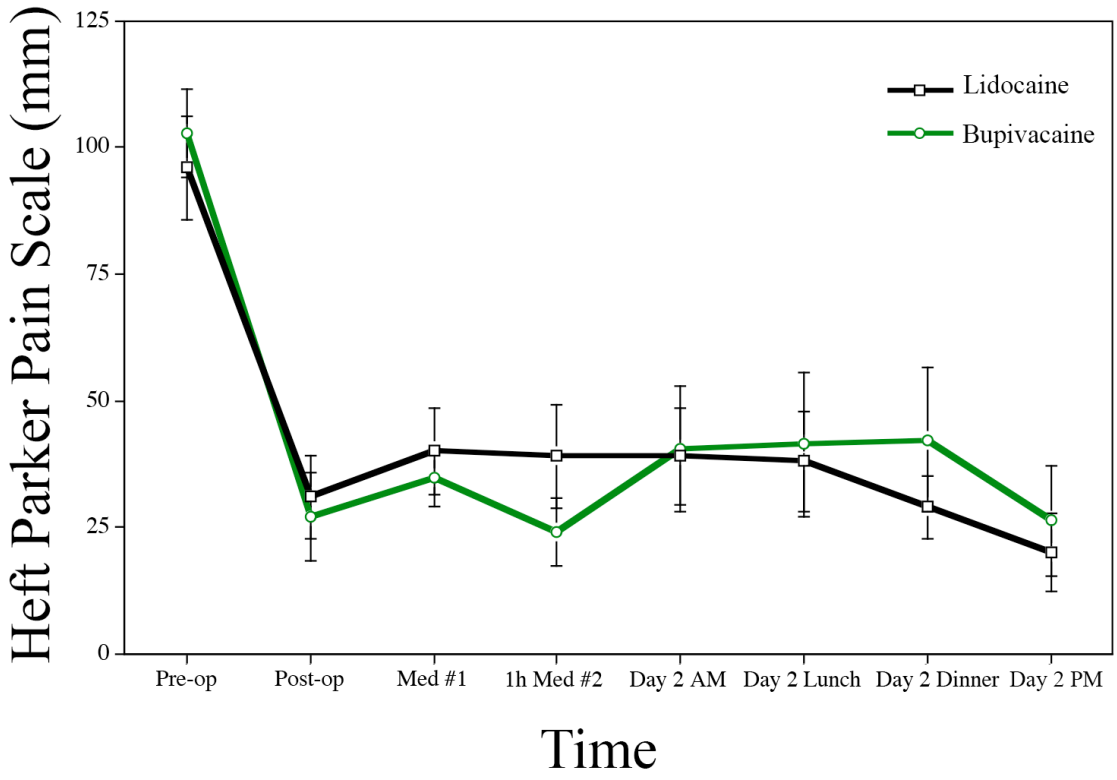


Figure 4. Group-by-Time Interaction – Average Heft Parker scale reading at each time point
n = 10-11/group Error Bars = S.E.M.

Next, we evaluated whether the post-operative pain levels in each treatment group differed when examined by patient sex (Fig. 5). Interestingly, females who received bupivacaine reported higher levels of pain on day 2 when compared with males who received bupivacaine and females who received lidocaine. Conversely, males who received lidocaine reported higher levels of pain when compared with females who received lidocaine and males who received bupivacaine.

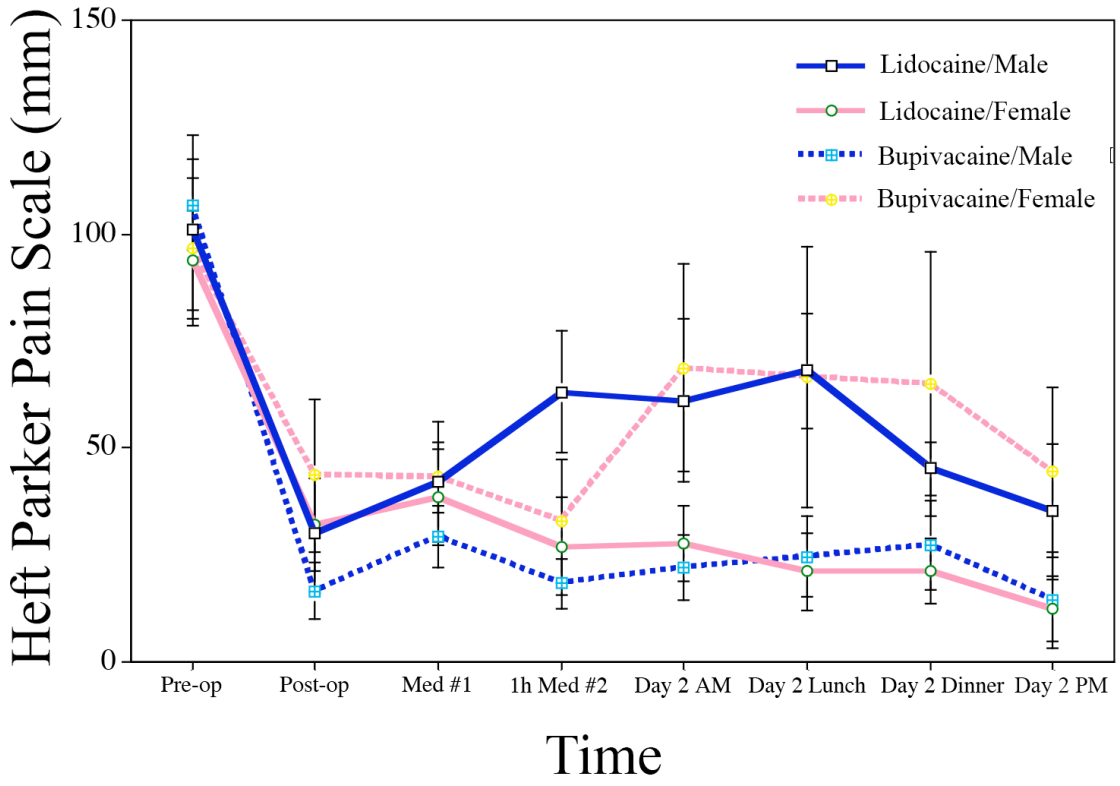


Figure 5. Group-by-Time Interaction for Male vs. Female Patients – Average Heft Parker scale reading at each time point
n = 4-7/group Error Bars = S.E.M.

Finally, the pain measurements were evaluated in a group-by-time interaction with respect to vital (irreversible pulpitis) or non-vital (necrotic, previously initiated treatment, previous treatment) pre-operative pulpal status (Fig. 6). Patients with non-vital pulpal status reported slightly higher pre-operative pain levels, and a reduction in immediate post-operative pain levels occurred in both groups regardless of pre-operative

pulpal status. A trend was observed in which patients with non-vital pulps receiving bupivacaine demonstrated higher levels of pain on day 2.

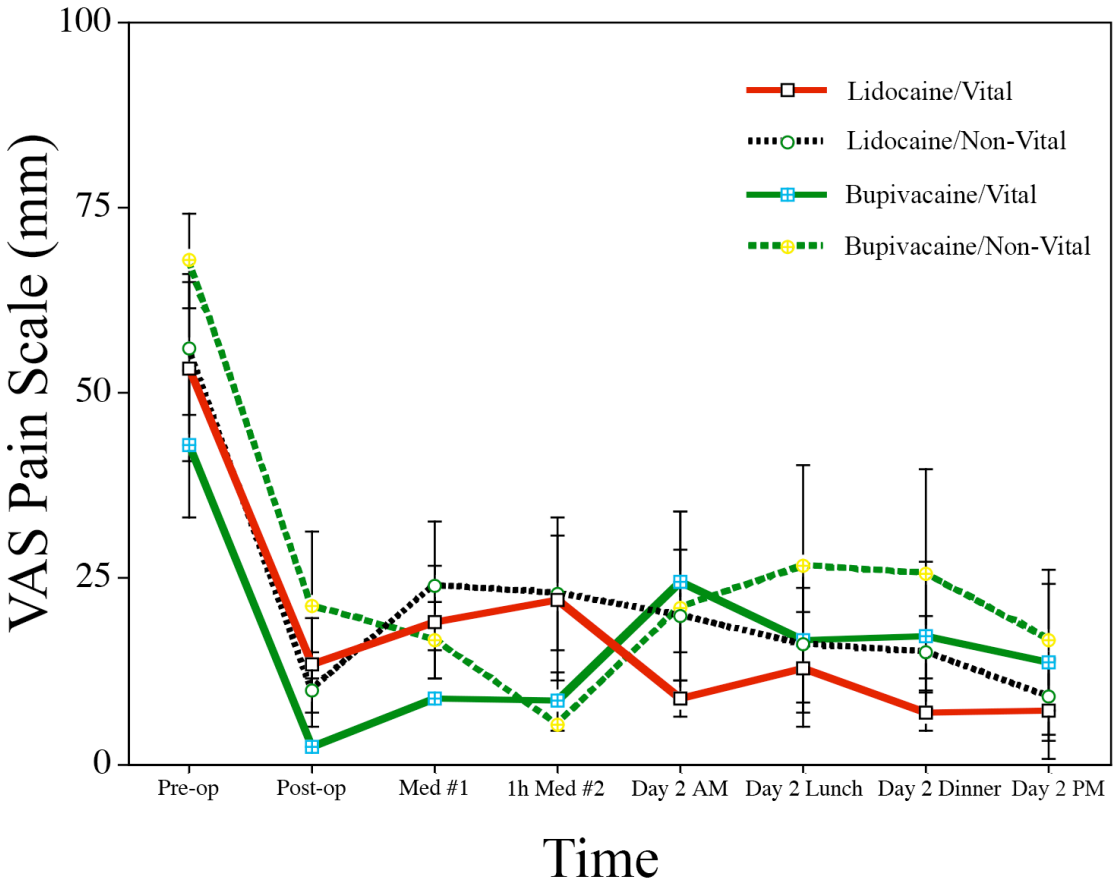


Figure 6. Group-by-Time Interaction for Vital vs. Non-Vital Pulp – Average VAS reading at each time point
n = 4-6/group Error Bars = S.E.M.

DISCUSSION

The ability to deliver endodontic treatment is impossible without the use of effective local anesthesia. Although the focus of endodontic treatment is the removal and reduction of bacterial and immunologic factors from the root canal system (Hargreaves et al. 1994; Keiser and Byrne 2011), many patients report some level of post-operative pain following treatment (O'Keefe 1976; Harrison et al. 1983; Georgopoulou et al. 1986), and that post-operative pain is most severe within the first 24 hours following treatment (Harrison et al. 1983; Torabinejad et al. 1994b; Mattscheck et al. 2001). For these reasons, a flexible analgesic prescription plan has been recommended (Troullos et al. 1986; Keiser and Hargreaves 2002; Hargreaves and Keiser 2004). In addition to the analgesic benefits that can be achieved with drugs such as NSAIDs and opioids, it has been demonstrated that long-acting local anesthetics can provide analgesia that lasts well beyond the initial period of anesthesia (Moore and Dunsky 1983; Dunsky and Moore 1984; Crout et al. 1990; Keiser and Hargreaves 2002).

In this clinical trial, data from 21 patients was available for evaluation. Patients were administered either an intermediate-acting local anesthetic (2% lidocaine with 1:100,000 epinephrine), or a long-acting local anesthetic (0.5% bupivacaine with 1:200,000 epinephrine) prior to initiation of emergency endodontic treatment. A randomized drug regimen consisting of either an NSAID (naproxen sodium or ibuprofen), a combination anti-inflammatory/analgesic (ibuprofen + hydrocodone/acetaminophen), or placebo was provided to simulate a modern clinical

endodontic situation. Lidocaine served as positive control, while bupivacaine was included to investigate its potential analgesic effects.

Although the number of patients included in this clinical trial was too few to perform meaningful statistical analysis, several trends were suggested. First, the group-by-time interaction evaluated whether the pain levels reported between the two local anesthetic groups changed over time. For both the lidocaine and bupivacaine groups, a notable reduction in immediate post-operative pain was observed. Patients in the lidocaine group reported pain levels that increased in time periods following the immediate post-operative period during the first day, while pain levels for the bupivacaine group remained relatively lower during the same period.

The trends observed in this study for the first three post-operative measurement periods are in agreement with previous studies conducted using similar endodontic models, where post-operative pain levels reported by patients receiving bupivacaine were significantly lower in the first 12 hours when compared with patients who received lidocaine (Moore and Dunsky 1983; Parirokh et al. 2012; Al-Kahtani 2014).

However, in the present study, these trends reversed on day 2 (12+ hours), where the bupivacaine group demonstrated increased pain levels while the lidocaine group reported lower levels of pain. These results are in conflict with the results of the aforementioned studies. Moore and Dunsky observed significantly reduced pain levels over a 24-hour post-operative period for patients who received bupivacaine (Moore and Dunsky 1983). Parirokh et al. and Al-Kahtani observed lower pain levels beyond the first 12-hour period in patients who received bupivacaine, but the differences were not found

to be significant (Parirokh et al. 2012; Al-Kahtani 2014). Several differences in the study models, in combination with the low number of subjects in the present study may account for these conflicting results. In the present study, only patients with a current level of spontaneous pain were included (patients that required application of a stimulus to reproduce their symptoms were excluded). Moore and Dunsky did not evaluate pre-operative pain levels, and pre-operative symptoms were not required for inclusion (Moore and Dunsky 1983). Studies by Parirokh et al. and Al-Kahtani included only patients with irreversible pulpitis and absence of percussion symptoms, and Parirokh et al. excluded patients with spontaneous pain. Furthermore, the present study model consisted only of the first-stage of two-visit endodontic treatment (pulpal debridement followed by calcium hydroxide interappointment medication). Moore and Dunsky's study model included single-visit treatment, two-visit treatment, and endodontic surgery. Parirokh et al. and Al-Kahtani performed only single-visit treatment consisting of obturation with gutta-percha and AH-plus sealer, which may have had differing effects on apical tissues from one patient to the next. Finally, a potential problem with the current study was the large proportion of maxillary teeth treated compared to mandibular teeth; Infiltration-type anesthesia rather than nerve block was likely achieved in many of the patients, which may have had a negative affect on the overall duration of anesthesia/analgesia. Parirokh et al. and Al-Kahtani included only mandibular molars anesthetized by administration of inferior alveolar nerve block.

Both local anesthetic groups in the present study showed a decreasing pain trend near the end of the second day, which lends further support to previous evidence that

endodontic post-operative pain is most severe within the first 24 hours following treatment, yet moderately decreased from pre-operative pain levels the patient presented with.

Examination of the group-by-time interaction with respect to sex differences suggested interesting trends. Females in the bupivacaine group reported notably higher pain levels on the second day when compared with females in the lidocaine group and males in bupivacaine group. Conversely, males in the lidocaine group reported notably higher pain levels when compared with males in the bupivacaine group and females in the lidocaine group. These trends suggest the possibility that bupivacaine may be more effective at providing prolonged analgesia in males, however the population in the present study is too small to draw such a conclusion and further research is needed. Furthermore, the impact of the various analgesic regimens administered cannot be ruled out due to the unfortunately small number of subjects included in this study. Nevertheless, the trends observed in the present study for the two local anesthetic groups with respect to sex differences might be explained by the findings of Morin et al. (2000) where females experienced more intense post-surgical pain than males, but males were found to be more disturbed than women by low levels of pain over several days. Therefore, from the present study, the hypothesis could be made that males experienced less adequate analgesia than males in the bupivacaine group resulting pain of greater duration and increased perception of pain.

CONCLUSIONS

From the trends observed in this study, it can be suggested that:

1. The use of a long-acting local anesthetic (0.5% bupivacaine with 1:200,000 epinephrine) may provide extended analgesia in the first day following emergency endodontic treatment when compared to an intermediate-acting local anesthetic (2% lidocaine with 1:100,000 epinephrine).
2. The use of a long-acting versus an intermediate-acting local anesthetic may not result in lower post-operative pain levels at later time periods (during the second day following treatment).
3. Males may benefit more than females from the extended analgesic effects of long-acting local anesthetics.

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APPENDIX 1

CONSENT FORM
Local Anesthesia and Analgesics in Post-Operative Endodontic Pain

You are invited to participate in a research study of the effect of different pain medications and local anesthetics for tooth pain after beginning a root canal. You were selected as a possible participant because you have tooth pain and are in need of root canal treatment for your tooth. We ask that you read this form and ask any questions you may have before agreeing to be in the study.

This study is being conducted by Walter Bowles DDS PhD, Steven Wiswall DDS, and Riley Lewis DDS, Division of Endodontics at the University of Minnesota School of Dentistry. It is funded by the Endodontics division, to examine methods for pain relief after starting a root canal.

Study Purpose

The purpose of the study is to determine the best way to treat tooth pain after starting a root canal, by evaluating your pain level before treatment and after treatment when you are given local anesthetic and pain medication. We will provide regular or long-lasting local anesthesia before starting the root canal, and pain medication after the root canal to determine which method(s) provide the best pain relief.

Study Procedures

If you agree to participate in this study, we would ask you to do the following: Evaluate the amount of tooth pain you are having (mark on pain scales the level of pain you feel) before and after root canal treatment, after taking pain medication, and during the following day. You will be given either local anesthetic or long-acting local anesthetic before the root canal, and you will be given two doses of pain medication to take during the first day. After evaluating your tooth pain level at several time points each day till the end of the day following the root canal, you will then need to mail the forms back to the University in a pre-addressed, postage paid envelope.

The root canal procedure is the standard treatment for this type of tooth pain and the medications given are standard pain medication given to patients reporting tooth pain. Assignment to study groups is randomized and all patients will get anesthetic (local or long acting local anesthetic), take 2 doses of pain medication and fill out pain level forms.

Risks of Study Participation

The study has the following risks: analgesic medication may have a side effect of stomach upset or may cause drowsiness.

Benefits of Study Participation

There is no direct benefit to the patients enrolled.

Alternatives to Study Participation

If you do not wish to participate, you may proceed with local anesthetic and root canal treatment.

Study Costs/Compensation

You will not incur any costs due to research participation. The root canal procedure will be charged in the regular manner. The emergency treatment fee (approximately $175) will not be charged if you decide to participate in the study for your time and inconvenience or, if this fee is covered by other monies, this amount may be credited toward the endodontic treatment fee if you so wish. The emergency fee reduction is pro-rated for partial participation (i.e. if not all pain evaluation forms returned) and will be reduced to approximately half ($85 credit) if only first 2 pain forms are filled out, and $15 credit for each of the pain scales filled out at home and returned (6 other forms given in take home packet $90 credit)

Research Related Injury

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to you or your insurance company. If you think that you have suffered a research related injury, let the study dentists know right away.

Confidentiality

The records of this study will be kept private. In any publications or presentations, we will not include any information that will make it possible to identify you as a subject. Your record for the study may, however, be reviewed by departments at the University with appropriate regulatory oversight. Study information will be recorded in the your medical record stating only the study number and that you were given pain medication. To these extents, confidentiality is not absolute. Study data will be encrypted according to current University policy for protection of confidentiality.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This Web site will not include information that could identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Protected Health Information (PHI)

Your PHI created or received for the purposes of this study is protected under the federal regulation known as HIPAA. Refer to the attached HIPAA authorization for details concerning the use of this information.

Voluntary Nature of the Study

Participation in this study is voluntary. Your decision whether or not to participate in this study will not affect your current or future relations with the University. If you decide to participate, you are free to withdraw at any time without affecting those relationships.

Contacts and Questions

The researchers conducting this study are Walter Bowles DDS PhD, Steven Wiswall DMD, and Riley Lewis DDS. You may ask any questions you have now, or if you have questions later, **you are encouraged to** contact them at *612-624-9900* (Division of Endodontics, University of Minnesota School of Dentistry)

If you have any questions or concerns regarding the study and would like to talk to someone other than the researcher(s), you are encouraged to contact the Fairview Research Helpline at telephone number 612-672-7692 or toll free at 866-508-6961. You may also contact this office in writing or in person at *Fairview Research Administration, 2344 Energy Park Drive, St. Paul, MN 55108.*

You will be given a copy of this form to keep for your records.

Statement of Consent

I have read the above information. I have asked questions and have received answers. I consent to participate in the study.

Signature of Subject_____ Date_____

Signature of Person Obtaining Consent_____ Date_____

APPENDIX 2

HIPAA[1] AUTHORIZATION TO USE AND DISCLOSE INDIVIDUAL HEALTH INFORMATION FOR RESEARCH PURPOSES

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1. Purpose. As a research participant, I authorize [name of PI] and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research project entitled [title of study], Human Subjects Code #1311M45821.

2. Individual Health Information to be Used or Disclosed. My individual health information that may be used or disclosed to conduct this research includes: [List all of the individual health information to be collected for this protocol/study such as demographic information, results of physical exams, blood tests, x-rays, and other diagnostic and medical procedures as well as medical history].

3. Parties Who May Disclose My Individual Health Information. The researcher and the researcher's staff may obtain my individual health information from:

Hospitals:

Clinics: _____

Other

Providers:

Health Plan: _____

_____

and from hospitals, clinics, health care providers and health plans that provide my health care during the study.

4. Parties Who May Receive or Use My Individual Health Information. The individual health information disclosed by parties listed in item 3 and information disclosed by me during the course of the research may be received and used by Walter Bowles DDS PhD and the researcher's staff Also, if I receive compensation for participating in this study, identifying information about me may be used or disclosed as necessary to provide compensation.

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[1] HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information.

5. Right to Refuse to Sign this Authorization. I do not have to sign this Authorization. If I decide not to sign the Authorization, I may not be allowed to participate in this study or receive any research related treatment that is provided through the study. However, my decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

6. Right to Revoke. I can change my mind and withdraw this authorization at any time by sending a written notice to [researcher's name and address] to inform the researcher of my decision. If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

7. Potential for Re-disclosure. Once my health information is disclosed under this authorization, there is a potential that it will be re-disclosed outside this study and no longer covered by this authorization. However, the research team and the University's Institutional Review Board (the committee that reviews studies to be sure that the rights and safety of study participants are protected) are very careful to protect your privacy and limit the disclosure of identifying information about you.

> **7A.** Also, there are other laws that may require my individual health information to be disclosed for public purposes. Examples include potential disclosures if required for mandated reporting of abuse or neglect, judicial proceedings, health oversight activities and public health measures.

[researcher's name and address]

This authorization does not have an expiration date.

I am the research participant or personal representative authorized to act on behalf of the participant.

I have read this information, and I will receive a copy of this authorization form after it is signed.

_____	_____
signature of research participant or research participant's personal representative	date
_____	_____
printed name of research participant or research participant's personal representative	description of personal representative's authority to act on behalf of the research participant

APPENDIX 3

PATIENT INFORMATION
FOR INVESTIGATIONAL DRUG STUDIES PHARMACY

The Investigational Drug Studies Pharmacy needs the following information on all study patients.

PATIENT'S FULL NAME: (first,middle,last)_____

PATIENT'S ADDRESS:

- STREET: _____
- CITY & STATE: _____
- ZIP CODE: _____
- TELEPHONE NUMBER: _____

PATIENT'S SEX: _____ MALE _____ FEMALE

PATIENT'S DATE OF BIRTH (MM/DD/YYYY): __ __/ __ __/ __ __ __ __

PATIENT'S HOSPITAL NUMBER (if one has been assigned): _____

ALLERGIES TO MEDICATIONS:

_____

_____

_____

PRIOR ADVERSE REACTIONS TO DRUGS: _____ NONE _____ YES

IF YES – LIST DRUG AND TYPE OF REACTION EXPERIENCED (i.e. nausea, hives, difficulty breathing, etc.) **WE MUST BE GIVEN PRIOR ADVERSE REACTIONS TO DRUG INFORMATION**

_____

_____

_____

Study Name/IDS #: _____

Study Coordinator/Contact Person: _____

Phone Number: _____

Fax the completed form to the Investigational Drug Studies Pharmacy: 612-273-2176. IDS Pharmacy must have a completed form before any prescriptions can be dispensed.

Please call the Pharmacy, at 612-273-6212, with any questions. Thank You.

APPENDIX 4

(not to scale)

Form #1

UNIVERSITY OF MINNESOTA
Laboratory of Neuropharmacology
School of Dentistry
515 Delaware Street SE
Mpls, MN 55455

STUDY: IDS #4497

PATIENT #_____

DATE:_____

TIME POINT: Pre-op (form #1)

CLOCK TIME:_____

Check the box that best describes the amount of pain that you feel now:

- ☐ 3 = Severe
- ☐ 2 = Moderate
- ☐ 1 = Mild
- ☐ 0 = None

Place a mark on the line to show the amount of ***PAIN*** *that you feel now:*

No Pain ——————————— Pain As Much As It Could Be

Place a mark on the line to show the amount of ***PAIN*** *that you feel now:*

None | Faint | Weak | Mild | Moderate | Strong | Intense | Maximum Possible

Have you taken any medication since the last report? yes /no

Have you experienced any adverse effects or benefits from this medication? yes /no
If yes, please describe.