A COMPARISON OF LIPOSOMAL BUPIVACAINE AND BUPIVACAINE FOR PAIN CONTROL IN UNTREATED SYMPTOMATIC VITAL TEETH

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By

Kristy Lynn Bultema, D.D.S.

Graduate Program in Dentistry

The Ohio State University
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Master's Examination Committee:

Sara Fowler D.M.D., M.S., Advisor

Melissa Drum, D.D.S., M.S.

Al Reader, D.D.S., M.S.

John Nusstein, D.D.S., M.S.

F. Michael Beck, D.D.S., M.A.

ABSTRACT

Studies from medical literature have demonstrated prolonged pain relief and reduction in opioid utilization for up to 72 hours postoperatively in patients that received post-surgical infiltration injections with liposomal bupivacaine. At the present time, there are no studies in dental literature that have investigated liposomal bupivacaine for pain control in endodontics. The purpose of this double-blind, randomized controlled trial was to compare bupivacaine HCl to liposomal bupivacaine for endodontic pain control in untreated symptomatic vital posterior teeth in patients experiencing moderate to severe pain. One hundred adult patients were randomly divided into two groups and received either 4 mL of liposomal bupivacaine (13.3 mg/mL) or 4 mL of 0.5% bupivacaine HCl with 1:200,000 epinephrine by infiltration following injection with 1.8 mL of 2% lidocaine with 1:100,000 epinephrine via infiltration or inferior alveolar nerve block. Patients received a diary for the day of the appointment (day 0) and three days post-injection to record tooth numbness, lip numbness, pain levels and analgesics (non-narcotic and narcotic) utilization. No significant differences were found between treatment groups for tooth numbness, pain, use of non-narcotic and narcotic pain medications. A statistically significant difference in lip numbness was found on day 1 to day 3 for the liposomal bupivacaine group. In conclusion, liposomal bupivacaine did not provide prolonged pain control, nor did it reduce analgesic consumption when used for untreated posterior symptomatic vital teeth.

DEDICATION

To my love, Patrick, your good humor adds amusement to my life, your love brings contentment to my heart, and the comfort you provide calms my spirit. I cherish you and the endless love, strength, friendship, support, and patience you have always, and continue to, provide me. I couldn't have done this without you!

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VITA

2009…….....Bachelor of Arts, Biology
The Ohio State University
Columbus, Ohio

2013……...Doctor of Dental Surgery,
The Ohio State University
College of Dentistry,
Columbus, Ohio

2015……...……Specialization in Endodontics
Post-Doctoral Certificate,
The Ohio State University
College of Dentistry,
Columbus, Ohio

FIELD OF STUDY

Major Field: Dentistry

Specialization: Endodontics

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CHAPTER 1

INTRODUCTION

In the treatment of patients with symptomatic irreversible pulpitis, endodontic debridement (pulpotomy or pulpectomy) by an endodontist is a predictable method to relieve pain. When debridement is not possible, appropriate analgesics, often narcotics, are prescribed (1). However, pain associated with symptomatic irreversible pulpitis is often severe and difficult to bear even with narcotic pain medications. General practitioners often are not equipped to treat patients presenting with symptomatic irreversible pulpitis. Inability to gain profound anesthesia and limited time for instrumentation due to a busy schedule are generally cited as the reasons for not attempting endodontic treatment (1). Strong analgesic medications and antibiotics are often given until the tooth becomes asymptomatic (pulp becomes necrotic) and an appointment is scheduled. Unfortunately, antibiotics have no effect on untreated irreversible pulpitis and contribute to their misuse (2).

Long-acting local anesthetics have been suggested as a way to manage postoperative pain (1). It is well known that a 0.5% bupivacaine solution prolongs the analgesic period (3-7). Bupivacaine in this formulation does not completely eliminate pain or the need for any analgesic medication (4, 8, 9-12). The length of the postoperative pain period must be considered. Many authors have found an initial

decrease in postoperative pain with bupivacaine but decreasing effects throughout the postoperative period (7, 8). The analgesic period of the 0.5% bupivacaine formulation does not usually last long enough to cover the entire extent of postoperative discomfort. A longer-acting formulation of bupivacaine may be able to extend the analgesia during this postoperative period, thus decreasing the need for narcotic pain medications.

Liposomal bupivacaine (Exparel®, Pacira Pharmaceuticals,San Diego, CA) was approved for use by the FDA in 2012. The indication is for a single-dose injection into the involved site to produce postoperative analgesia (13). The formulation is a preservative-free aqueous suspension of multivesicular liposomes containing bupivacaine at a concentration of 13.3 mg/mL (expressed as anhydrous bupivacaine HCl equivalent) (14). A small amount (approximately 3%) is free bupivacaine, which provides immediate numbness, while the remaining drug is released from the liposomes over time (14). The lipids (phospholipids, cholesterol, and triglyerides) are naturally occurring or close analogues of endogenous lipids, and are thus well tolerated and cleared by normal pathways (14). Liposomal bupivacaine is contraindicated in obstetrical paracervical block anesthesia (14). The drug has not been studied in patients younger than 18 years of age. Liposomal bupivacaine should not be given concurrently with lidocaine solutions, at the same site as it may cause immediate release of the liposomal bupivacaine (14). Waiting for 20 minutes before administering liposomal bupivacaine is acceptable (14).

Liposomal bupivacaine has shown promising results in reduction of pain and opioid requirements (14) following medical procedures such as hemorrhoid surgery (15), bunionectomy (16), knee replacement (17-19), and breast augmentation (20-21). There

were no differences in adverse events between liposomal bupivacaine and bupivacaine HCl (22). With use of liposomal bupivacaine, patient satisfaction surveys showed 95% of the patients were extremely satisfied or satisfied with their postoperative anesthesia after hemorrhoidectomy (15).

BUPIVICAINE HCl - PHARMACOKINETICS

Bupivacaine HCl is classified as a long-acting, amide type local anesthetic. Bupivacaine HCl is a weak base with a pKa of 8.1, and pH of 3.0-4.5 in vasoconstrictor-containing solution or pH 4.5-6.0 in plain solution (23). The anesthetic half-life is 2.7 hours. The estimated duration of pulpal anesthesia is greater than 90 minutes and soft-tissue anesthesia ranges between 240 and 720 minutes for 0.5% bupivacaine HCl with 1:200,000 epinephrine. Bupivacaine HCl is four times as potent as lidocaine, mepivacaine, and prilocaine, while less than four times as toxic as lidocaine and prilocaine. When compared to lidocaine, prilocaine, and mepivacaine the vasodilating properties of bupivacaine HCl are greater, however, onset of action is typically longer (6-10 minutes). Like all amide anesthetics, bupivacaine HCl is metabolized in the liver by amidases and excreted by the kidneys (23).

Bupivacaine blocks nerve conduction by reversibly binding to sodium channels located on the nerve membrane. This inhibits the influx of sodium ions, raises the excitation threshold, and prevents depolarization and propagation of impulses along the nerve. In order to penetrate the nerve membrane, the lipid-soluble form of the anesthetic must be present. Once within the membrane, the charged form is needed to

bind to the sodium channels. Under physiologic pH of approximately 7.4, 15% of bupivacaine dissociates into the lipid-soluble form, the form capable of penetrating the neuronal membrane (24). Greater lipid solubility equates to greater potency, as more drug is available to pass freely into the neuronal membrane and effectively decrease nerve conduction. While duration of action is related to increased lipid solubility and potency, the protein binding capacity of the drug is the greatest determinant. The greater the affinity for proteins, the longer the anesthetic will remain bound to the nerve cell (25).

Isolated nerve studies evaluating properties including pKa, lipid solubility, and protein binding have been used to classify local anesthetics as short, intermediate, or long-acting (1). In the case of bupivacaine HCl, its high protein binding (90-95%) and high lipid solubility are reasons for its classification as a long-acting local anesthetic. Pateromichelakis and Prokopiou found that studies on isolated nerves are not precise guides to compare the clinical actions of local anesthetics (1, 26). In fact, studies have found that the duration of action for these classified anesthetics are different when used clinically for various anesthetic administration techniques, i.e., nerve blocks, infiltrations and intraosseous injections (1). Although bupivacaine is classified as long-acting, this is only the case for nerve blocks. The same is not true for maxillary infiltrations, periodontal ligament injections, or intraosseous anesthesia. No studies have been conducted on mandibular infiltrations. Unfortunately, the classification of anesthetics may be misleading when the clinical effectiveness does not always reflect the designated classification of the local anesthetic (1).

EFFICACY - BUPIVACAINE HCl AS A BLOCK

Lidocaine HCl is commonly selected for use with the inferior alveolar nerve block (IANB), however the use of bupivacaine HCl with the IANB has resulted in similar success rates for pulpal anesthesia in mandibular first molars. In fact, administration of bupivacaine HCl by way of the inferior alveolar nerve block may result in slower onset of pulpal anesthesia, prolonged duration of pulpal anesthesia, and increased soft tissue numbness when compared to lidocaine HCl. Fernandez et al found similar success rates for asymptomatic mandibular first molars when comparing 0.5% bupivacaine with 1:200,000 epinephrine to 2% lidocaine with 1:100,000 epinephrine. However, lower success rates were found for second molars, premolars, and lateral incisors (27). Lower success rates were believed, in part, to be a result of the slower onset of bupivacaine HCl. Bupivacaine HCl had an average duration of pulpal anesthesia of 4 hours versus 2 hours and 24 minutes for lidocaine HCl (27).

EFFICACY - BUPIVACAINE HCl FOR TREATMENT OF IRREVERSIBLE PULPITIS

Clinical studies have measured postoperative pain in patients with irreversible pulpitis of mandibular molars after receiving inferior alveolar nerve blocks with either bupivacaine or lidocaine. Parirokh et al found that overall, at all time intervals following treatment, 58.26% of bupivacaine patients and 41.74% of lidocaine patients experienced no pain (28). Patients who received bupivacaine had significantly lower pain scores at 6 and 12 hours postoperatively than those receiving lidocaine, as well as significantly less

use of pain medications (28). Al-Kahtani et al completed a similar study and the results supported the findings of Parirokh (29). Al-Kahtani found that after treatment almost half of the lidocaine patients and nearly two-thirds of the bupivacaine patients experienced no pain. When comparing postoperative pain reduction, patients who received bupivacaine reported significantly decreased pain levels at 6 and 12 hours, while those who received lidocaine had less pain at 24 hours (29).

Su et al investigated the efficacy and safety of bupivacaine versus lidocaine by performing a meta-analysis of sixteen randomized controlled trials (30). Studies comparing 2% lidocaine 1:100,000 epinephrine to 0.5% bupivacaine 1:200,000 epinephrine found that bupivacaine had significantly lower success rates in achieving pulpal anesthesia in vital, uninflamed pulps ($p<0.00001$), while bupivacaine had significantly higher success rates in achieving pulpal anesthesia in inflamed pulps ($p=0.03$). Other significant findings regarding bupivacaine HCl included a lower utilization of postoperative pain medications ($p<0.0001$), longer duration of anesthesia and longer onset time for pulpal anesthesia ($p<0.00001$) (30).

Sampaio et al compared the efficacy of the inferior alveolar nerve block when using either 3.6 mL 0.5% bupivacaine 1:200,000 epinephrine or 2% lidocaine 1:100:000 in patients with irreversible pulpitis in mandibular first or second molars (31). It was found that although all patients reported lip numbness, pulpal anesthesia (measured by lack of response to electric pulp tester) was achieved in only 20% of bupivacaine patients and 42.9% of lidocaine patients. Eighty percent of bupivacaine patients and 62.9% of lidocaine patients reported no to mild pain throughout the instrumentation process. A

significant difference in pulpal anesthesia success was found for lidocaine when compared to bupivacaine. However no significant difference was found with regard to pain reported during the instrumentation process. From these results, it was concluded that neither bupivacaine nor lidocaine, administered by way of IANB, resulted in effective pain control during treatment of mandibular molars with irreversible pulpitis (31).

EFFICACY - BUPIVACAINE HCl FOR INFILTRATION INJECTION

When used for a nerve block, bupivacaine HCl is a long-acting local anesthetic that has been found to decrease postoperative pain as well as analgesic consumption (27). However, when used for maxillary infiltration injections no prolonged pulpal anesthesia resulted (1). Gross et al compared the efficacy of infiltration injections using 1.8 mL 0.5% bupivacaine with 1:200,000 epinephrine and 1.8 mL 2% lidocaine with 1:100,000 epinephrine for maxillary laterals and first molars (32). For maxillary lateral incisors, there were significantly lower pulpal anesthesia success rates (2 consecutive 80 EPT readings) for bupivacaine (78%) than lidocaine (97%). For maxillary first molars, although bupivacaine (64%) had lower pulpal anesthesia success rates than lidocaine (82%), the difference was not determined to be statistically significant as neither agent produced pulpal anesthesia for one hour. Onset of action in maxillary first molars was significantly slower for bupivacaine (7.7 minutes) versus lidocaine (4.3 minutes) (32).

Gross et al also evaluated the duration of soft-tissue numbness and time until return of normal sensation (32). Infiltration with bupivacaine resulted in significantly

longer lip numbness (177 versus 128 minutes) and greater time until return of normal sensation (383 versus 201 minutes) when compared to lidocaine. No difference was found in duration of soft tissue numbness or time until return of normal sensation for maxillary first molars (32). Though lip numbness may be sustained longer than pulpal anesthesia for maxillary lateral incisors, this is of no real clinical advantage. A study conducted by Rosenquist and Nystrom (8) reported that 34% of patients found the increased duration of soft tissue numbness resulting from long-acting anesthetics to be unpleasant for reasons including increased risk of trauma and difficulty eating and/or speaking.

It is known that when bupivacaine HCl is used for the inferior alveolar nerve block, patients may experience prolonged postoperative analgesia. Advantages of prolonged postoperative analgesia include decreased postoperative pain and reduced consumption of analgesics. Meechan and Blair found that the use of long-acting local anesthetics for infiltration injections in the maxilla did not decrease patient postoperative pain or analgesic intake when compared to lidocaine (33). Regrettably, prolonged postoperative analgesia has only been associated with the use of a long-acting local anesthetic administered via the inferior alveolar nerve block.

LIPOSOMAL BUPIVICAINE - PHARMACOKINETICS

Liposomal bupivacaine is a new anesthetic formulation developed with the goal of extending the duration of anesthesia longer than traditional local anesthetics. A single dose infiltration of liposomal bupivacaine is designed to gradually release anesthetic

molecules over the course of 72 hours. Liposomal bupivacaine is an aqueous suspension of both free bupivacaine HCL (approximately 3%) and multivesicular liposomes containing bupivacaine (13.3 mg/mL). The phospholipid components include endogenous components of the human cell membranes, triglycerides, cholesterol, and lipid, making them biocompatible and cleared by normal metabolic pathways (34). Encapsulation of bupivacaine molecules in multivesicular liposomes is different from past technologies such as unilamellar vesicles and multilamellar vesicles. Unlike unilamellar vesicles with a single bilayer and multilamellar vesicles with concentric bilayers, multivesicular liposomes consist of multiple, closely packed, non-concentric vesicles. The tight, honeycomb-like, non-concentric nature of the vesicles allows for rearrangement of vesicles within the liposomes as erosion of the outer surface particles occurs as a result of destabilization from body heat (34, 35). This design is thought to increase stability, while permitting the slow release and increased duration of action of liposomal bupivacaine.

Following administration of liposomal bupivacaine there are two peaks in plasma concentration. Regardless of dose, the first and smaller peak occurs around 1 hour with duration of action of approximately 8 hours (34). A second and larger peak follows between 12-36 hours post-injection. The first peak is the result of systemic absorption of the free bupivacaine within the suspension, while the second peak is a result of the gradual release of bupivacaine from the liposomes. Toxic plasma concentrations are avoided as free bupivacaine HCl concentrations are reduced significantly prior to release of bupivacaine from the liposomes. Once released from the liposomes, bupivacaine

behaves similarly to bupivacaine HCL pharmacokinetically. The rate of systemic absorption is determined by total dose of the administered drug, route of administration and vascularity of the area (36).

Pharmacokinetics and/or physicochemical properties of liposomal bupivacaine, including rate of release and plasma concentrations may be altered with administration of other local anesthetics at the injection site. Co-administration of bupivacaine HCl in a dose greater than 50% that of liposomal bupivacaine dose is contraindicated (34). Co-administration of non-bupivacaine local anesthetics, such as lidocaine HCl, with liposomal bupivacaine can potentially disrupt the multivesicular liposomes. Disruption of the liposomal membranes can cause immediate release of bupivacaine and produce potentially toxic plasma levels of bupivacaine. To prevent this potentially toxic effect, liposomal bupivacaine should be administered at least 20 minutes following administration of non-bupivacaine local anesthetics (14, 37).

LIPOSOMAL BUPIVACAINE - SAFETY

After much research, it has been determined that liposomal bupivacaine is safe for single-dose administration via local wound infiltration and has no greater adverse events than that of plain bupivacaine (36, 38, 39). The most common adverse events reported by the manufacturer include constipation, nausea, vomiting, dizziness, headache, fever, tachycardia, pruritus and somnolence (40). The frequency of adverse events was positively correlated with greater liposomal bupivacaine doses (24). Like most anesthetics, the systemic toxicity is dose-dependent affecting the CNS and the cardiovascular system (37). The toxic plasma concentration range for liposomal

bupivacaine is between 2000-4000 ng/mL. Among four trials (hemorrhoidectomy, bunionectomy, herniorrhaphy, or total knee replacement) the largest dose of 532 mg, which resulted in an average plasma concentration of 935 ng/mL, led to cardiovascular and CNS adverse events. When doses were kept at or below the FDA highest recommended dose of 266 mg, which resulted in an average plasma concentration of 867 ng/mL, no signs of adverse cardiovascular or CNS events were noted (24).

Liposomal bupivacaine is Pregnancy Category C, as it has not been studied in pregnant or nursing patients. Liposomal bupivacaine has not been studied in patients under 18 years of age. Although there is no data showing differences in safety or efficacy for elderly patients, some older patients may be more sensitive to liposomal bupivacaine (37). Since only limited studies have been completed, minimal data exists with regard to safety, efficacy, and proper doses for other surgeries and procedures. Further study of liposomal bupivacaine is recommended before use in other procedures or administration by alternative routes (41).

LIPOSOMAL BUPIVACAINE - DOSE, AVAILABILITY AND STORAGE

Liposomal bupivacaine is recommended for single-dose wound infiltrations with a maximum recommended dose of 266 mg (24, 42). Liposomal bupivacaine is manufactured as an aqueous suspension contained within a 20 mL vial (1.3% undiluted drug) packaged in cartons of ten. Since the 20 mL vial contains no more than the maximum recommended dose of 266 mg, average plasma concentration levels below the toxic plasma concentration range (2,000-4,000 ng/mL) are ensured. Slow administration

into soft tissue with a 25 gauge or larger bore needle is recommended. To avoid disruption of the liposomes and immediate release of bupivacaine, alternative local anesthetics should be administered at least 20 minutes prior to liposomal bupivacaine (14, 42).

Liposomal bupivacaine must be refrigerated between 36 to 46 degrees Fahrenheit. Liposomal bupivacaine should not be frozen or exposed to temperatures greater than 104 degrees Fahrenheit. For up to 30 days, sealed, un-opened vials may remain unrefrigerated at temperatures between 68 and 77 degrees Fahrenheit. Once opened, vials should not be re-refrigerated (14).

EFFICACY - PLACEBO VERSUS LIPOSOMAL BUPIVACAINE

Golf et al and Gorfine et al conducted similar studies to assess the efficacy of liposomal bupivacaine versus sodium chloride placebo and found that liposomal bupivacaine provided a prolonged period of pain relief, reduction in opioid analgesic use, and longer time to first opioid administration (15, 16, 40).

In a randomized, multicenter, double-blind phase 3 clinical study Golf et al compared liposomal bupivacaine to placebo for pain prevention after bunionectomy (16). A total of 193 patients randomly received 0.9% sodium chloride placebo (N=96) or 120 mg liposomal bupivacaine (N=97) by way of wound infiltration prior to surgical wound closure. Pain intensity was measured from time 0 to 72 hours postoperatively using a numeric rating scale (NRS) and the efficacy was evaluated by area under the curve (AUC). Patients receiving liposomal bupivacaine had significantly lower pain intensity

scores (AUC for NRS) at 24 hours ($p=0.0005$) and 36 hours ($p<0.0229$) when compared to those receiving placebo (16).

Golf et al found that during the first 24 hours, patients receiving liposomal bupivacaine had significantly greater ($p<0.0404$) avoidance of opioid rescue medication than patients receiving placebo (7.2% versus 1%). In fact, during the first 24 hours patients receiving liposomal bupivacaine only consumed 3.8 tablets of oxycodone/acetaminophen versus 4.7 tablets consumed by patients receiving placebo. The median time to first opioid use was delayed significantly ($p<0.0001$) in patients receiving liposomal bupivacaine rather than placebo (7.2 versus 4.3 hours). Patients receiving liposomal bupivacaine reported being pain free with NRS scores of ≤ 1 at 2, 4, 8, and 48 hours. The percentage of patients that did not take opioid rescue analgesics after receiving liposomal bupivacaine versus placebo was found to be statistically significant at 8, 12, 16, and 24 hours. It was not found to be statistically significant at 36, 48, or 60 hours post-injection (16).

Using a randomized, double-blind, multicenter, parallel-group placebo-controlled phase 3 study Gorfine et al compared the efficacy and duration of postoperative pain relief achieved from a single dose of liposomal bupivacaine or sodium chloride placebo after hemorrhoidectomy (15). Patients received either 300 mg liposomal bupivacaine or 0.9% sodium chloride. For 72 hours following surgery, patients rated pain on NRS and first use of opioid and amount consumed was recorded. Gorfine et al demonstrated a reduction in pain throughout the 72-hour postoperative period with pain intensity scores

that were significantly lower for liposomal bupivacaine than that of the placebo (141.8 versus 202.5, $p<0.0001$) (15).

Patients receiving liposomal bupivacaine showed significant reduction in time to first opioid use and diminished use of opioid analgesics when compared with placebo. The number of patients who required no opioid analgesics was significantly greater for the liposomal bupivacaine group versus placebo at every measured time point within 72 hours postoperatively (14% versus 10%, $p<0.0008$). The median time to first opioid use was greater for liposomal bupivacaine group (14.3 hours) compared to placebo group (1.2 hours) ($p<0.0001$). Furthermore, more patients in the liposomal bupivacaine group remained opioid free at 24 hours to 72 hours than in the placebo group (59% versus 28%, $p<0.0008$). Of the patients that consumed opioids within the first 72 hours, the mean total consumption was less for liposomal bupivacaine than the placebo (22.3 mg versus 29.1 mg, $p\leq0.0006$) (15).

EFFICACY - BUPIVACAINE HCl VERSUS LIPOSOMAL BUPIVACAINE

A randomized, double-blind, dose-ranging controlled study conducted by Bramlett et al compared wound infiltration of liposomal bupivacaine to bupivacaine HCl for postsurgical analgesia in total knee arthroplasty (18). Various doses of liposomal bupivacaine (133, 266, 399, and 532 mg) or bupivacaine HCl (150 mg with 1:200,000 epinephrine) were infiltrated deep into the knee tissues of 138 patients with the goal of determining appropriate dosing. Following surgery, patients received a single dose of a non-steroidal anti-inflammatory drug and managed pain with 1000 mg acetaminophen

three times daily for 96 hours postoperatively. As needed, morphine was administered via a morphine patient controlled analgesia (PCA) pump until patients could take orally administered oxycodone/acetaminophen. Bramlett et al found that in comparison to bupivacaine HCl, there was no statistically significant difference between mean area under the curve (AUC) of numeric rating scale (NRS) scores when patients were active for all liposomal bupivacaine groups ($p>0.05$). While not statistically significant, the mean AUC of NRS scores when active were lower than the bupivacaine HCl group for the 266 mg, 399 mg, and 532 mg liposomal bupivacaine groups through days 2, 3, and 5. When at rest, 532 mg liposomal bupivacaine was associated with statistically significantly greater analgesia compared to bupivacaine HCl. Numeric Rating Scores for 532 mg liposomal bupivacaine group were significantly lower than bupivacaine HCl for all time points throughout days 1 and 5 ($p<0.05$). At rest, the mean AUC for NRS scores were significantly lower on days 2 through 5 for the 532 mg groups and demonstrated a dose-response trend. Unlike many studies, the difference in the mean consumption of opioid analgesics for the liposomal bupivacaine groups was not statistically significant when compared to bupivacaine HCl. The power of these results were limited due to being a Phase II clinical trial with small numbers in each treatment group. However, Bramlett et al believed the efficacy of the 532 mg dose, its similar frequency of adverse events compared to smaller doses, and its potential to expand the duration of anesthesia from under 12 hours to up to 5 days compared to bupivacaine HCl warranted further evaluation with larger treatment groups (18).

Smoot et al investigated the extent and period of analgesia attained with liposomal bupivacaine compared to bupivacaine HCl for bilateral, submuscular mammoplasty (44). A randomized, double-blind, multicenter study was performed on 136 patients. Patients were administered either 600 mg of liposomal bupivacaine or 200 mg of bupivacaine HCl with 1:200,000 epinephrine throughout the implant pockets. For 72 hours postoperatively, patients were provided with acetaminophen 1000 mg to be taken three times daily and supplemental oxycodone as needed. Comparison of the mean AUC for NRS of active patients resulted in no statistically significant difference between liposomal bupivacaine and bupivacaine HCl, however, authors noted the study was underpowered. The total amount of opioids consumed through 24 hours and 48 hours postoperatively were statistically significantly lower for liposomal bupivacaine. From the results, Smoot et al concluded that liposomal bupivacaine aided in reduction of opioid analgesic consumption and was seemingly more efficacious than bupivacaine HCl (44).

Bergese et al utilized pooled data from 10 Phase II and Phase III double-blind, randomized liposomal bupivacaine clinical trials to provide an overview of the efficacy of liposomal bupivacaine 72 hours postoperatively by way of meta-analysis. The cumulative pain scores from five different surgical studies (hemorrhoidectomy, breast augmentation, bunionectomy, total knee arthroplasty, or hernia repair) involving single-dose wound infiltration were compared and analyzed. A total of 823 patients were exposed to liposomal bupivacaine in doses that ranged from 66 mg to 532 mg, while 446 patients were exposed to bupivacaine HCl in doses that ranged from 75 mg to 200 mg, and 190 patients received 0.9% sodium chloride placebo. In the analysis of cumulative

pain (AUC of NRS-A and NRS-R), 16 of the 19 treatment arms analyzed showed liposomal bupivacaine to be associated with lower pain scores throughout the first 72 hours. Of the 17 treatment arms comparing liposomal bupivacaine to bupivacaine HCL, 6 treatment arms and 5 treatment arms had pain scores that were statistically significantly lower than bupivacaine HCl groups at 24 and 72 hours, respectively ($p<0.05$) (45, 46).

The time to first opioid analgesic consumed was pooled across 9 of the studies. The median time until use of first opioid analgesic for liposomal bupivacaine was significantly longer (9.3 hours) than bupivacaine HCl (6.4 hours, $p=0.03$) and placebo (3.6 hours, $p<0.0001$). The proportion of patients avoiding use of opioid medication throughout the 72 hour postoperative period was only significantly lower for the phase III trial (NCT00890721), which compared liposomal bupivacaine to placebo for hemorrhoidectomy (45, 46).

Further analysis of the data demonstrated the total postsurgical consumption of opioid rescue medication to be less for patients receiving liposomal bupivacaine. In fact, the greatest reduction in opioid consumption was related to the highest doses of liposomal bupivacaine (266 mg and 532 mg). At 24 hours, two bupivacaine HCl and two placebo-controlled studies showed statistically significant reduction in opioid consumption. While at 72 hours, one bupivacaine HCl and one placebo-controlled study demonstrated significant reduction in opioid consumption (45, 46).

Six of 10 studies analyzed included assessment of patient satisfaction of postsurgical pain relief. Of these 6, only one study demonstrated statistically significantly better patient satisfaction, which also happened to be the only study of the 6

that compared liposomal bupivacaine to a placebo. In this study, 24 hours after surgery, 95% of patients receiving liposomal bupivacaine 266 mg dose were "satisfied" or "extremely satisfied" with their postoperative pain control as opposed to only 72% of the placebo group ($p=0.0007$). The remainder of the other studies, which compared liposomal bupivacaine to bupivacaine HCl, showed no statistically significant between-group differences (45, 46).

Liposomal bupivacaine was found to be well-tolerated amongst the 823 patients exposed over the course of the 10 studies, and the adverse events for liposomal bupivacaine were similar to that of bupivacaine HCl. At least one adverse event was reported in 62% of liposomal bupivacaine patients, 75% of bupivacaine HCl patients and 42% of the placebo patients. Nausea, vomiting, and constipation were the most commonly reported adverse events, which are also adverse events that are frequently reported in patients taking opioid analgesics. Bergese et al noted that with increasing bupivacaine HCl and liposomal bupivacaine doses the incidence adverse events increased (45, 46).

From the meta-analysis of the 10 Phase II and Phase III trials, Bergese et al concluded that treatment with liposomal bupivacaine was safe and effectively decreased postoperative pain in soft tissues, delayed first opioid consumption, and reduced total amount of opioid analgesics consumed within 72 hours postoperatively (45,46).

CHAPTER 2

MATERIALS AND METHODS

One hundred adult patients participated. All were emergency patients of the Ohio State University College of Dentistry and in good health (ASA Class I or II) as determined by a health history and verbal questioning. Exclusion criteria were the following: subjects who were younger than 18 years; history of significant medical problem (ASA class III or higher); patients who had taken CNS depressants or any analgesic medication within the last 6 hours; pregnancy; or inability to give informed consent. Any female patients who were unsure of their pregnancy status were offered a urine pregnancy test (Osom®, Genzyme Diagnostics Corp, San Diego, CA). The Ohio State University Human Subjects Review Committee approved the study, and written informed consent was obtained from each patient (Appendix C). All patients also completed a HIPPA research authorization form (Appendix D).

To qualify for the study, each patient had a vital mandibular or maxillary posterior tooth (molar or premolar), was actively experiencing moderate to severe pain at the emergency visit, and had a prolonged response to cold testing with Endo-Ice™ (1,1,1,2 tetrafluoroethane; Hygenic Corp, Akron, OH). Patients with no response to cold testing and radiographic evidence of periradicular pathosis (other than a widened periodontal

ligament) were excluded from the study. Therefore, each patient had a tooth that fulfilled the criteria for a clinical diagnosis of symptomatic irreversible pulpitis.

Patients completed a Corah dental anxiety scale to rate their level of anxiety (Appendix E) (47). Each patient rated his or her initial pain on a Heft-Parker visual analogue scale (VAS) (Appendix F) (48). The VAS was divided into 4 categories. No pain corresponded to 0 mm. Mild pain was defined as greater than 0 mm and less than or equal to 54 mm. Mild pain included the descriptors of "faint", "weak", and "mild" pain. A score greater than 54 mm and less than 114 mm indicated moderate pain and included the descriptor of "moderate" pain. Severe pain was defined as equal to or greater than 114 mm. Severe pain included the descriptors of "strong", "intense", and "maximum possible".

The 50 patients randomly received either liposomal bupivacaine (Exparel®, Pacira Pharmaceuticals, San Diego, CA) or 0.5% bupivacaine HCl with 1:200,000 epinephrine (Marcaine, AstraZeneca LP, Dentsply, York, PA)(control solution) by infiltration. Each of the 50 patients in each group was randomly assigned a six-digit number to blind the experiment. That is, the patient and primary investigator were unaware of which anesthetic solution (bupivacaine HCl or liposomal bupivacaine) was given to them because only the random numbers identified the solutions. A random number generator (www.random.org) was used to generate the random numbers.

Using sterile technique, 4 mL of the appropriate anesthetic solution (bupivacaine HCl or liposomal bupivacaine) was drawn into 5.0 mL sterile, plastic syringes (Becton-

Dickinson & Co., Rutherford, NJ) with a 25-gauge 5/8 – inch needle (Monoject; Sherwood Services, Mansfield, MA) by personnel not directly involved in the study. The syringe was wrapped with opaque tape, and the corresponding six-digit number was written on the tape to effectively blind the anesthetic solutions and recorded on the data sheets and diary. The master list of six-digit random numbers was not made available to the primary investigator (KB).

Prior to administration of the bupivacaine formulations and to ensure patient comfort, all patients were anesthetized with 1.8 mL of 2% lidocaine with 1:100,000 epinephrine (Xylocaine, AstraZeneca LP, Dentsply, York, PA) via infiltration for maxillary teeth or inferior alveolar nerve block for mandibular teeth. Preceding the injection, topical anesthetic gel (20% benzocaine, Patterson Dental Supply, Inc., St. Paul, MN) was applied passively for one minute to the tissue using a cotton tip applicator. A standard aspirating syringe and 27 gauge 22 mm needle were used for all lidocaine injections.

At the moment the needle penetrated the mucosal tissue, "insertion" was stated. Following insertion, "placement" was announced as the needle was positioned to the depth of 1/2-inch for the IANB and at the estimated level of the root apices for maxillary infiltration. Upon reaching the desired needle depth and noting negative aspiration, "deposition phase" was announced and the anesthetic solution was administered over the course of one minute. Following the injection, the needle was removed and the patient recorded the three pain phases of the injection. The patient was questioned for lip, or cheek, numbness every 5 minutes for 20 minutes. If profound lip or cheek numbness was

not felt after 20 minutes, the study was terminated and emergency root canal treatment was rendered after achieving anesthesia (no patients were terminated).

At least 20 minutes following administration of the lidocaine infiltration or inferior alveolar nerve block, topical anesthetic gel was applied, as described above. Patients received an infiltration adjacent to the symptomatic tooth of either the liposomal bupivacaine or bupivacaine HCl using the 5.0 mL syringe and a 25-gauge 5/8-inch needle (Monoject; Sherwood Services, Mansfield, MA). The anesthetic solution given was determined randomly, as described above, and administered for both maxillary and mandibular teeth using the infiltration technique described above. A single operator administered all injections. No endodontic treatment was initiated.

Prior to each injection, the patient was given the instructions to listen for the words "insertion," "placement," and "deposition" and to make note mentally of the level of pain they experienced at that point in time. Following both injections, patients rated the pain of needle insertion, needle placement, and solution deposition of the injection on the VAS (Appendix G and H).

At the conclusion of the appointment, each patient rated their tooth numbness and lip or cheek numbness on a VAS (0 to 100 mm) and pain level on a 170 mm VAS (Appendix I). Each patient was scheduled for a return appointment 4-7 days later to start the endodontic treatment, and was given medications and a patient questionnaire to take home (Appendix J). All patients received twenty 600 mg tablets of ibuprofen and forty 500 mg tablets of acetaminophen. Dose was reviewed and labeled on the bottles Patients

were instructed to take one ibuprofen 600 mg tablet every 6 hours, and two acetaminophen 500 mg tablets every 6 hours as needed for pain. Patients were instructed to take the medications at the same time or separately depending on their preference. Patients were instructed to only take these medications if the anesthetic did not sufficiently control their pain. Patients were instructed to not take any other analgesic medication.

If the ibuprofen and/or acetaminophen given to the patient did not control their pain, the patients were instructed to call an assigned cell phone that was carried by the primary investigator at all times. If after speaking with the primary investigator, it was determined that an escape medication was needed, Norco 5/325 mg (hydrocodone/acetaminophen) was prescribed for the patient. During the data-collection portion of the study, the DEA schedule for acetaminophen/hydrocodone changed from schedule III to schedule II. The change of drug schedule prevented prescriptions from being called into pharmacies. After this change went into effect, to ensure patients access to escape medication, all patients were given a prescription for acetaminophen/hydrocodone upon completion of their appointment. Patients were instructed to contact the investigator prior to filling the prescription and a note was written on the prescription asking the pharmacist not to fill the prescription without first contacting the prescribing doctor. If the patient had significant pain prior to their scheduled appointment that was not relieved by the pain medication, they were seen immediately and endodontic treatment was rendered at that time.

Patients received a diary for the day of the appointment (day 0) and three days post-injection to record any numbness or pain that they experienced and the pain medications (study or escape) taken (Appendix J). On the day of treatment and three days post-injection, patients recorded the time that they perceived that the anesthesia wore off (if it did). Patients recorded pain on the VAS as described earlier. If patients were in pain, they recorded the time of day when the pain began. Tooth numbness and lip or cheek numbness was recorded on VAS (0 to 100 mm). Starting on the morning after their initial appointment, patients recorded the number of pain medications taken within each 24-hour period. The time of day was recorded. There was a place for patients to write comments on the diary.

On the last day of the survey, patients completed a satisfaction survey (Appendix J). The patient was asked to mark a vertical line on a VAS (0 to 100 mm) that best describes their satisfaction with the endodontic treatment. The VAS was divided into 4 categories. Not satisfied corresponded to 0. Somewhat satisfied was defined as greater than 0 mm and less than or equal to 33 mm. Moderately satisfied was defined as greater than 33 mm but less than 66 mm. Completely satisfied was defined as greater than or equal to 66 mm. Patients were required to return all unused medications upon completion of the study to verify diary reports. The patients received $50 at the end of the first appointment. Upon the completion and return of the survey and all unused medications, subjects received an additional $50. The patients returned the survey and all unused medications at their scheduled root canal appointment or at another time determined by

the patient and the investigator. At the scheduled treatment appointment endodontic treatment was initiated using standard methods.

Data was collected and statistically analyzed. Comparisons between the bupivacaine and liposomal bupivacaine groups for age, initial pain, and satisfaction ratings were analyzed using the randomization test. The patients' Corah Dental Anxiety Scales were analyzed using a Mann-Whitney-Wilcoxon test. Comparisons of tooth types were made with a Fisher Exact test. Gender was analyzed using the Chi-square test. Escape drug utilization was analyzed using the Chi-square test; or, if the expected frequencies were less than 5.0, then the Fisher Exact test was used.

Success was analyzed using a Chi-square test and was defined as no or mild pain and no narcotic utilization. Tooth numbness, lip and cheek numbness, and pain response on VAS were analyzed using multiple randomization tests with p-values adjusted by Step-down Bonferroni method of Holm. Binary tooth numbness, lip and cheek numbness, and pain responses were analyzed using multiple randomization tests with p-values adjusted by the Step-down Bonferroni method of Holm. Analgesic utilization in number of tablets was analyzed for total non-narcotic utilization, acetaminophen and ibuprofen utilization, and narcotic utilization using a Mann-Whitney-Wilcoxon test and adjusted with a Step-down Bonferroni method of Holm. Primary and secondary injection pain were analyzed using a Randomization test and adjusted with a Step-down Bonferroni method of Holm. Satisfaction rating was analyzed using a Mann-Whitney-Wilcoxon test. The post-injection questionnaire was analyzed using a Fisher exact test.

With a non-directional alpha risk of 0.05 and assuming an escape-drug utilization rate of 20% (49) a sample size of 50 patients per group would be required to demonstrate a difference in utilization rate of ±30% with a power of 0.89. For VAS pain scores, assuming a standard deviation of 50.3 (49), a difference of ±30 mm could be detected with a power of 0.84 with 50 patients per group. This sample size would also allow recognition of a difference of ±3 tablets in pain medication use, assuming a standard deviation of 4.3 tablets (49), with a power of 0.93.

CHAPTER 3

RESULTS

A total of 100 patients were enrolled in this study. Table 1 shows the preliminary data, including total subjects, jaw, gender, age, initial pain, Corah Dental Anxiety Scale ratings, and tooth type, for the bupivacaine and liposomal bupivacaine treatment groups. With 50 subjects in each group, the 100 subjects were divided evenly between the bupivacaine and liposomal bupivacaine groups. In the bupivacaine group, 24 (48%) of the teeth were maxillary and 26 (52%) were mandibular. In the liposomal bupivacaine group, 25 (50%) of the teeth were maxillary and 25 (50%) were mandibular. In terms of tooth type, the bupivacaine group contained 43 (86%) molars and 7 (14%) premolars, while the liposomal bupivacaine group contained 39 (78%) molars and 11 (22%) premolars. In the bupivacaine group, 64% of the patients treated were female and 36% were male. In the liposomal bupivacaine group, 52% of the patients treated were female and 48% were male. The mean age for the bupivacaine and liposomal bupivacaine groups was 34 $\pm$ 10 years and 33 $\pm$ 11 years, respectively. All participating subjects were experiencing equal to or greater than moderate pain on the 170 mm Heft Parker VAS. The mean initial pain for the bupivacaine group was 136 $\pm$ 27 mm and 135 $\pm$ 23 mm for the liposomal bupivacaine group. The median scores from the Corah Dental Anxiety Scale were 9 for the bupivacaine group and 10 for the liposomal bupivacaine group.

There were no statistically significant differences between bupivacaine and liposomal bupivacaine groups for any of the preliminary data (Table 1).

Table 2 reports the success of bupivacaine and liposomal bupivacaine treatment groups. Success was defined as no or mild pain with no narcotic utilization throughout the post-treatment period. Seventeen of the 48 (35%) patients in the bupivacaine group and 10 of the 47 (21%) patients in the liposomal bupivacaine group experienced defined success. There was no statistically significant difference in success between treatment groups.

Table 3 and Table 4 show the crude odds ratio and adjusted odds ratio. The crude odds ratio for success based on treatment group was 0.493 with a 95% confidence interval of 0.195 to 1.246. The adjusted odds ratio accounted for the effects of potential confounding variables (treatment group, gender, jaw, and tooth type) for bupivacaine and liposomal bupivacaine treatment groups. The adjusted odds ratio for success based on treatment group was 0.44 with a 95% confidence interval of 0.166 to 1.167. Group, gender, jaw, and tooth type had no significant effects on success.

Table 5 and Figure 1 display tooth numbness as rated on a 100 mm VAS for each group by day. Table 6 reflects binary (yes/no) tooth numbness responses for each group for day 0A through day 3. From the tables it can be seen that immediately following the injection of the study drug regimen, the majority of the patients felt tooth numbness day 0A. Table 5 shows that on day 0A, the mean VAS rating for tooth numbness was 87 mm for both groups. Table 6 demonstrates binary 'Yes' response to tooth numbness was 49/50 (98%) for the bupivacaine and 50/50 (100%) for the liposomal bupivacaine group.

By day 0B, mean tooth numbness VAS ratings had decreased to 37 ± 39 mm and 42 ± 39 mm for bupivacaine HCl and liposomal bupivacaine, respectively. Binary 'Yes' response day 0B had decreased to 23/48 (48%) for bupivacaine HCl and 25/47 (53%) for liposomal bupivacaine. Both of the VAS ratings and binary 'Yes' responses continued to decrease throughout the three days post-treatment with mean tooth numbness VAS ratings decreasing on day 3 to 11 ± 30 mm and 11 ± 24 mm for bupivacaine HCl and liposomal bupivacaine, respectively, and binary 'Yes' responses day 3 decreasing to 5/48 (13%) for bupivacaine HCl and 7/47 (15%) for liposomal bupivacaine. Figure 1 illustrates the largest decrease in post-treatment tooth numbness from day 0A to day 0B and the gradual decline in tooth numbness for both groups. No significant differences were noted between tooth numbness for the bupivacaine and liposomal bupivacaine groups from day 0 to day 3.

Table 7 and Figure 2 display lip numbness as rated on a 100 mm VAS for each group by day. Table 8 reflects binary lip numbness responses for each group by day. Subjects in the bupivacaine and liposomal bupivacaine groups reported the most lip numbness day 0A with 89 ± 21 mm for the bupivacaine group and 89 ± 15 mm for the liposomal bupivacaine groups. Binary 'Yes' responses were 100% (50/50) for both groups. Figure 2 demonstrates the general trend with lip numbness being the greatest day 0A, sharply declining by day 0B, and then slowly declining over days 1 through 3. The lowest VAS ratings (3 ± 14 mm for bupivacaine HCl and 8 ± 18 mm liposomal bupivacaine) and lowest binary 'Yes' responses (0% bupivacaine HCl and 15% liposomal bupivacaine) were reported on day 3. The gap between trend lines for days 1

through 3 helps to visualize the statistically significant difference in lip numbness experienced on days 1 through 3 by patients in the liposomal bupivacaine group. The difference in lip numbness reported by the liposomal bupivacaine group was about 17 mm on the VAS on day 1, 11 mm on day 2, and 5 mm on day 3. No statistically significant differences in lip numbness were found for day 0A and day 0B.

Table 9 and Figure 3 display pain as rated on a 170 mm VAS for each group by day. Table 10 displays binary pain responses for each group by day. In our study, no statistically significant difference in the pain throughout the three day post-treatment period was reported. In general, patient pain levels decreased greatly by day 0A with 96% (48/50) of the bupivacaine group and 88% (44/50) of the liposomal bupivacaine group reported 'No' binary pain response. Overall, the lowest pain scores were reported day 0A (8 ± 18 mm for bupivacaine HCl and 16 ± 25 mm for liposomal bupivacaine groups) and increased approximately 41 mm for both bupivacaine and liposomal bupivacaine groups day 0B. Figure 3 demonstrates how the pain levels increased from day 0A to day 0B and then remained steady between mild and moderate pain (49-59 mm for bupivacaine HCl and 49-63 mm for liposomal bupivacaine) through post-treatment day 3.

Table 11 reports total non-narcotic (ibuprofen and acetaminophen) analgesic utilization in mean number of tablets taken post-treatment day 0-1 to day 3 for bupivacaine and liposomal bupivacaine groups. No statistically significant differences were found between bupivacaine HCl and liposomal bupivacaine for total analgesic utilization day 0-1 to day 3. The most non-narcotic analgesics were taken day 0-1, with five tablets for both groups, and continued to decrease through day 3 to 3 tablets.

Figure 4 illustrates the total number of non-narcotic medications (ibuprofen and acetaminophen) in mean number of tablets taken by group and by day. For both groups, medication use was highest day 0-1 and continued to fall through day 3.

Table 12 shows acetaminophen and ibuprofen utilization in number of tablets for day 0-1 to day 3 for bupivacaine and liposomal bupivacaine groups. No statistically significant differences were found between bupivacaine HCl and liposomal bupivacaine for acetaminophen and ibuprofen utilization day 0-1 to day 3. The mean number of both ibuprofen and acetaminophen tablets were greatest day 0-1 and steadily decreased for each through day 3.

Figure 5 illustrates the amount of ibuprofen and acetaminophen utilized by day in mean number of tablets by group. No more than 3 tablets of either medication were taken on a given day. Overall, the most tablets were taken day 0-1 and declined through day 3 for both ibuprofen and acetaminophen.

Table 13 displays the number and percentage of patients by treatment group who required narcotic medication for pain control at least once during the post-treatment period. Narcotic utilization was similar between groups with only 23% (11/48) of bupivacaine patients and 33% (15/46) liposomal bupivacaine patients requiring escape medication.

Figure 7 illustrates the number of patients by group who utilized narcotics during the post-treatment period. Narcotics were utilized most in the liposomal bupivacaine group (33%). Overall for both groups, most patients did not require narcotics to manage pain.

Table 14 reflects narcotic utilization in number of tablets by group for day 0-1 to day 3. No statistically significant differences were found between bupivacaine HCl and liposomal bupivacaine for narcotic utilization in number of tablets day 0-1 to day 3. In general, the mean narcotic utilization was less than 1 tablet per day for both groups.

Figure 6 depicts the mean number of tablets of narcotic medication utilized by group and by day. The average number of tablets taken each day was less than 1, with the greatest amount taken on day 3.

Table 15 reports the number of unscheduled post-treatment emergency visits. Return visits as a result of insufficient pain control that occurred within the three-day post-treatment period were considered unscheduled post-treatment emergency visits. A total of 5 patients returned for unscheduled emergency visits. All 5 patients were in the bupivacaine treatment group.

Table 16 shows primary injection pain as rated on a 170 mm VAS for both groups by jaw and by stage of injection. Primary injection consisted of either maxillary infiltration or mandibular inferior alveolar nerve block with lidocaine. No significant difference was found for maxillary or mandibular injection pain ratings at insertion, placement, and deposition stage for both groups. The mean injection pain rating for maxillary infiltration (51-57 mm) was less than mandibular inferior alveolar nerve block (58-82 mm) for both groups. The mean pain rating for maxillary injections fell within the mild and moderate pain categories, while mandibular injections were categorized as moderate pain.

Table 17 displays secondary injection pain as rated on a 170 mm VAS for both groups by stage of injection. Secondary injection consisted of either maxillary or mandibular buccal infiltration with liposomal bupivacaine or bupivacaine HCl. There was no significant difference between injection pain ratings at needle insertion, needle placement or solution deposition stages of injection between groups. For both groups, injection pain ratings were least painful for needle insertion and most painful for anesthetic deposition; however, all stages of injection fell within the mild pain category.

Table 18 shows primary injection pain by stage of injection and jaw using categorical descriptors from the 170 mm VAS for both groups. The majority of patients in both groups reported between mild and moderate pain during all stages of the injection for both maxillary and mandibular injection stages.

Table 19 shows secondary injection pain by stage of injection using categorical descriptors from the 170 mm VAS for both groups. For the bupivacaine group, the majority of patients experienced either none or mild pain with all stages of the injection, while the majority of patients in the liposomal bupivacaine group experienced mild or moderate pain for all stages of injection.

Table 20 shows patient satisfaction with procedure as rated on 100 mm VAS for bupivacaine HCl and liposomal bupivacaine. There was no statistically significant difference in patient satisfaction between groups. Overall, the both groups were moderately satisfied with the treatment received. The mean satisfaction for bupivacaine HCl was 60 ± 34 mm, while the mean satisfaction for liposomal bupivacaine was 59 ± 31 mm.

Table 21 shows percent satisfaction by category. Varying degrees of satisfaction were reported, however the highest number of respondents, 61% (27/44) of bupivacaine patients and 47% (21/45) of liposomal bupivacaine patients, reported being completely satisfied with treatment.

Table 22 presents patient responses to the post-treatment questionnaire. No statistically significant differences were found in patient responses to questions 1, 3, and 4. However, a statistically significant difference was found between bupivacaine and liposomal bupivacaine groups in response to question 2 regarding whether they were satisfied with the level of pain control achieved while numb. Ninety-eight percent of patients in the bupivacaine group were satisfied, while 82% of the patients in the liposomal bupivacaine group were satisfied with the level of pain control achieved when numb.

CHAPTER 4

DISCUSSION

PRELIMINARY DATA

Analysis of the preliminary data indicated that the bupivacaine and liposomal bupivacaine groups were equal with respect to all variables, including jaw, gender, age, initial pain, Corah Dental Anxiety Scale and tooth type. Similarity amongst the groups ensures that the known effects of the confounding variables on treatment were uniform. Therefore, the differences found between the bupivacaine and liposomal bupivacaine groups could be attributed to the difference in treatment.

SUCCESS

Pain associated with an untreated symptomatic vital tooth is often severe, disruptive, and difficult to manage. Understandably, when a patient presents to an endodontist there is often an expectation of receiving treatment to relieve dental pain. Ultimately, the goal of the endodontist is to eliminate the pain, or at minimum, help to reduce the intensity. Narcotics are often prescribed to aid in achieving this goal. However, these medications have many side effects, and minimizing use is advisable. Therefore, in this study, treatment was considered successful when patients reported experiencing no or mild pain and no narcotic utilization. Low levels of success were

reported in both the bupivacaine and liposomal bupivacaine groups. Thirty-five percent (17/48) of bupivacaine patients and 21% (10/47) of liposomal bupivacaine patients reported experiencing no or mild pain and no use of narcotics. Although 14% more bupivacaine patients experienced success than liposomal bupivacaine patients, the difference in success was not determined to be significantly different even when adjusting for the effect of group, gender, jaw and tooth type (OR=0.493, CI (0.195 to 1.246), p=0.1266). However unlikely, this low success could, in part, be attributed to four missing post-treatment questionnaires, as data for 3 patients in the liposomal bupivacaine group and 1 patient in the bupivacaine group could not be included. More likely, the decreased success can be attributed to the lack of prolonged pain control provided by the anesthetics. The low success rates indicate that liposomal bupivacaine did not have the effect we had hoped it would have when administered via buccal infiltration. Diminished tooth numbness within the first day and increased pain the night of treatment is evidence that liposomal bupivacaine did not provide pain control up to 72 hours as previous studies have demonstrated (15, 16, 40, 45, 46, 50, 51). Instead, both liposomal bupivacaine and bupivacaine had equally poor success with regard to controlling pain. Once the effects of pulpal anesthesia diminished and pain levels increased, patients relied solely on analgesics to manage the pain associated with their symptomatic vital teeth. The study anesthetics proved to be an unreliable method of pain control as reflected by 65% of bupivacaine patients and 79% of liposomal bupivacaine patients reporting pain greater than mild and/or requiring narcotic medication to manage pain during the post-treatment period. The lack of pain control achieved through use of

analgesics further demonstrated the difficulty in managing pain associated with untreated symptomatic irreversible pulpitis and was, in part, the reason for the low overall success rates.

LIP NUMBNESS, TOOTH NUMBNESS AND PAIN RATINGS

Following treatment, patients were asked to record the level of tooth numbness, lip numbness, and pain on both binary (yes/no) and Heft Parker VAS, as well as the amount of pain medications taken in a post-treatment diary. On the day of treatment, patients completed two surveys. The first one was completed immediately following the anesthetic injections to ensure patient comfort prior to leaving and the second one was completed on the night of treatment before going to bed, in an effort to better understand the true duration of anesthesia. For each of the three subsequent days, patients were asked to complete the survey upon waking.

The results of our study indicate that liposomal bupivacaine did not provide extended pulpal anesthesia beyond that of bupivacaine HCl. Over the course of the three day post-treatment period, the level of pulpal anesthesia expressed as "tooth numbness" by the patients decreased steadily with the least amount of tooth numbness reported on day 3. As expected, following the injection regimen, the majority of the patients experienced pulpal anesthesia, which was confirmed by 98% of the bupivacaine HCl group and 100% of liposomal bupivacaine group responding 'Yes' to feeling tooth numbness. By the end of the day of treatment (day 0), tooth numbness VAS ratings and binary responses had decreased by more than half for both groups. Tooth numbness

continued to decrease throughout the three days post-treatment (Figure 1). It should be recognized that the largest decrease in post-treatment tooth numbness occurred within day 0, and is likely the result of waning pulpal anesthesia. For maxillary first molar infiltrations, pulpal anesthesia is known to be of short duration, lasting between 45-50 minutes after administration of 1.8 mL of 2% lidocaine 1:100,000 epinephrine and 25 minutes for 1.8 mL 0.5% bupivacaine 1:200,000 epinephrine (1). The duration of pulpal anesthesia for mandibular inferior alveolar nerve blocks (IANB) is known to be longer. Fernandez et al found that pulpal anesthesia after IANB with 1.8 mL of 2% lidocaine 1:100,000 epinephrine may last up to 2 hours and 24 minutes, and 1.8 mL 0.5% bupivacaine 1:200,000 epinephrine may last 3 to 4 hours (27). The duration of pulpal anesthesia for mandibular buccal infiltrations with bupivacaine HCl and liposomal bupivacaine has not been studied. However, several studies in the dental literature have shown similar efficacy for primary buccal infiltration injections in mandibular molars to that of the inferior alveolar nerve block (52-71). To date, there are no reports in the dental literature that have investigated the duration of pulpal anesthesia for liposomal bupivacaine infiltrations. However, since no significant differences in tooth numbness were noted between bupivacaine HCl and liposomal bupivacaine throughout the three day post-treatment period, the findings of the present study show that liposomal bupivacaine did not extend the duration of pulpal anesthesia beyond that of bupivacaine HCl.

Extent of patient lip and/or cheek numbness was recorded as a representation of soft tissue anesthesia. Extended soft tissue anesthesia has been reported after

administration of bupivacaine HCl and liposomal bupivacaine. Fernandez et al found soft tissue numbness after IANB with 2% lidocaine 1:100,000 epinephrine to last over 3 hours, and over 8 hours for IANB with 0.5% bupivacaine 1:100,000 epinephrine (27). Gross et al evaluated the duration of soft-tissue numbness and time until return of normal sensation for maxillary first molar infiltrations with bupivacaine (32). Soft tissue numbness lasted 135 minutes, while time until return of normal sensation was 213 minutes for maxillary first molars (32). In the current study, all patients experienced lip and cheek numbness immediately following the injection regimen, reporting the greatest level of numbness prior to leaving the appointment, followed by a large decrease in lip and cheek numbness the night of the treatment. Figure 1 demonstrates the continual decline in the level of lip and cheek numbness reported by the patients over the three day post-treatment survey period, with the least amount of lip and cheek numbness felt on day 3. Although both groups reported an overall decline in lip and cheek numbness, the liposomal bupivacaine group had statistically significantly higher lip and cheek numbness experienced on days 1 through 3. However, no statistically significant differences in lip and cheek numbness were found the day of treatment, immediately following the anesthetic injections (day 0A) and the night of treatment (day 0B).

No differences in lip and cheek numbness on the day of treatment, immediately following anesthetic injections (day 0A) and the night of treatment (day 0B), can be explained by the decline in soft tissue numbness as anesthesia wore off. Our results demonstrate that profound soft tissue numbness subsided the most within the first day for both groups. Our results are similar to those of Fernandez et al (27) and Gross et al (32).

Despite the variances in duration of soft tissue anesthesia noted, injection technique, or anesthetic formulation utilized (lidocaine or bupivacaine), soft tissue anesthesia was found to consistently diminish within the day of treatment as reported in our study.

The difference in lip and cheek numbness reported for days 1 through 3 can likely be attributed to the unique pharmacokinetics of liposomal bupivacaine, which is designed to gradually release anesthetic molecules over the course of 72 hours (13). Liposomal bupivacaine is an aqueous suspension of both free bupivacaine HCl (approximately 3%) and multivesicular liposomes containing bupivacaine (13.3 mg/mL). Multivesicular liposomes consist of multiple, closely packed, non-concentric vesicles. The tight, honeycomb-like, non-concentric nature of the vesicles allows for rearrangement of vesicles within the liposomes as erosion of the outer surface particles occurs as a result of destabilization from body heat (34, 35). This design is thought to increase stability, while permitting the slow release and increased duration of action of bupivacaine.

Following administration of liposomal bupivacaine there are two peaks in plasma concentration. Regardless of dose, the first and smaller peak occurs within about one hour with a duration of action of approximately eight hours (34). A second and larger peak follows at 12-36 hours post-injection. The first peak is the result of systemic absorption of the free bupivacaine within the suspension, while the second peak is a result of the gradual release of bupivacaine from the liposomes (34). The second peak is believed to be the cause of the prolonged lip and cheek numbness experienced during days 1 through 3 by patients in the liposomal bupivacaine group.

The difference in VAS lip and cheek numbness reported by the liposomal bupivacaine group was approximately 17 mm on day 1, 11mm on day 2, and 5 mm on day 3. Although this difference was considered statistically significant, one may question how clinically significant a difference this small can truly be. Are there advantages accompanying this soft tissue numbness? Despite prolonged lip and cheek numbness during days 1 through 3, patients in the liposomal bupivacaine group still reported similar pain levels to those in the bupivacaine group (mild and moderate pain). Moreover, 15% of patients commented that they disliked the prolonged soft tissue numbness. Reasons given for their dissatisfaction included disruption of their daily lives, the resultant trauma to their lip or tongue, and interference with speaking and eating as a result of prolonged soft tissue anesthesia. Our results are comparable to the study conducted by Rosenquist and Nystrom, which reported that 34% of patients found the increased duration of soft tissue numbness resulting from long-acting anesthetics to be unpleasant for reasons including increased risk of trauma and difficulty eating and/or speaking (8).

The profound soft tissue numbness felt the day of the anesthetic injections (day 0) is likely the outcome of administration of the initial injections of lidocaine and bupivacaine HCl, not the liposomal bupivacaine. The amount of free bupivacaine present in the liposomal bupivacaine suspension is most likely insufficient and thus incapable of eliciting profound anesthesia. This is supported by patients' reports of post-treatment numbness on the day of anesthetic injections (day 0). However, it is believed that the difference in soft tissue numbness reported on days 1 through 3 was the result of the slow release of bupivacaine from the liposomal packets, as described above. In fact, it is

suspected that in some patients the effects of lidocaine wore off before liposomal bupivacaine was able to release an effective dose, as some patients reported experiencing waves of soft tissue numbness.

Our results show that the dose of liposomal bupivacaine was effective in producing minimally prolonged soft tissue numbness, but not ample enough to provide prolonged pulpal anesthesia or a reduction in pain and analgesic use. Even the soft tissue numbness, although significantly different from bupivacaine, could not be categorized as profound anesthesia. The results of our study clearly demonstrate that the dose of 4 mL (53.2 mg) of liposomal bupivacaine was not effective in providing extended pain control. Ideal dosing for the purpose of pulpal anesthesia and prolonged pain control is yet to be determined. The rate of release of bupivacaine from the liposomes is not known, as it varies by individual. The dose of 53.2 mg used in this investigation is much less than the typical doses, ranging from 120 mg to 532 mg, used in clinical trials and studies from medical literature that have found prolonged analgesia after injection with liposomal bupivacaine (15, 16, 20, 45, 46, 72). Increasing the dose has been shown to increase effectiveness (45, 46). One must ask how much the dose would need to be increased in order to achieve the desired level of pulpal anesthesia and prolonged analgesia, as well as what risks would be involved with such an increase? Sklonik found that when doses were kept at or below the FDA highest recommended dose of 266 mg, no signs of adverse cardiovascular or CNS events were noted (24). This means that our dose (4 mL) could be increased up to 20 mL without experiencing greater systemic adverse events. However in the oral environment, an increase in dose, and thus the volume administered,

would be limited by the soft tissue space available for infiltration. With our administration of just 4 mL, patients left the appointment with visible bullous in their cheeks. Increasing the dose may increase pain of the injection and pain at the site of infiltration. A fix to dose and space limitations may be found in the development and manufacture of a formulation of liposomal bupivacaine specific to dentistry. A dental specific version of liposomal bupivacaine would need to have a concentration greater than the current 13.3 mg/mL. Increasing the bupivacaine concentration would allow for administration of greater doses without increasing the volume of solution. Another means of improving success of liposomal bupivacaine could be through the administration of liposomal bupivacaine via inferior alveolar nerve block (IANB). Currently, liposomal bupivacaine is contraindicated for administration via nerve blocks. However, it could be argued that an IANB is not a true nerve block, but rather a deep infiltration. Therefore, there is potential for increased success using liposomal bupivacaine with the IANB rather than infiltrations, as studies have shown bupivacaine to prolong analgesia and extend pulpal anesthesia when used with IANB (27).

Pain was recorded for the post-treatment period and no significant differences were found between the bupivacaine and liposomal bupivacaine groups (Table 9). In both groups the patient pain levels decreased greatly following the injection regimen to no or mild pain, only to more than double the night of treatment to mild to moderate pain. For the subsequent three days, pain levels remained steady around mild to moderate levels, despite the reduction in analgesic use. Possible explanations for this include a decrease in acute inflammatory response or necrosis of the pulp. Gallatin et al found that when

comparing the effectiveness of intraosseous injection with Depo-Medrol versus placebo in untreated symptomatic vital mandibular teeth 19% of teeth in the placebo group, and 5% of teeth Depo-Medrol group became necrotic over the course of 7 days ($p>0.05$) (73). Nagle et al found that when comparing the effectiveness of penicillin versus placebo on pain control in untreated symptomatic vital maxillary or mandibular posterior teeth 25% of the penicillin group and 20 % of the placebo group became necrotic over the course of 7 days (2). In the present study, pulpal vitality at the emergency debridement appointment was not recorded for the vast majority of patients and not all patients returned between days 4 and 7 for their originally scheduled return appointment (four patients did not return at all), thus, the rate of occurrence of pulpal necrosis for liposomal bupivacaine and bupivacaine could not be determined. Therefore, a direct comparison between our results and those reported by Gallatin et al (73) and Nagle et al (2) could not be made. However, our data record indicates that at least two teeth in the liposomal bupivacaine treatment group were diagnosed with pulpal necrosis upon access at their return appointment. Furthermore, it is possible that the reason the four patients did not return for emergency debridement was due to decreased pain as a result of pulpal necrosis. Necrosis of the symptomatic vital pulp is a possible explanation for the patients that reported no pain throughout the post-treatment period, even after pulpal anesthesia had diminished. Our limited data in combination with the aforementioned rate of necrosis presented by Gallatin et al (73) and Nagle et al (2) supports pulpal necrosis as a possible explanation for decreased pain and drug use in our study.

The return of pain within the day of the anesthetic injections (day 0) is thought to be associated with the loss of pulpal anesthesia, which occurred within the first day for both groups. It is interesting to note that even after pulpal anesthesia had diminished, pain experienced by patients in both experimental groups remained well below the initial level of severe pain reported. This reduction in pain is not thought to be a result of the extended actions of either anesthetic formulation as was reported by other studies (15, 16, 45, 46, 51). Rather, this is more likely due to the patients' ability to manage pain using non-narcotic and narcotic analgesic medications.

There is limited dental research in management of pain in untreated symptomatic vital teeth. The reason for this is likely due to the predictable and effective outcomes of emergency endodontic debridement of the inflamed, symptomatic pulp. However, the aforementioned studies by Gallatin et al (73) comparing Depo-Medrol intraosseous injection with placebo in untreated symptomatic vital mandibular teeth and Nagle et al (2) comparing penicillin with placebo in untreated symptomatic vital maxillary and mandibular posterior teeth helps to give insight into pain and analgesic use associated with this diagnosis. Gallatin et al found that patients who received the placebo (N=21) reported moderate to severe pain on days 1 through 7 postoperatively, with 62% on day 1, 67% on day 2, 62% on day 3, and with an average of 54% on days 4 through 7 (73). In the placebo group, the percentage of patients requiring narcotic analgesics was 48% on day 1, 52% on day 2, 52% on day 3 (73). Nagle et al found that patients who received placebo (N=20) reported moderate to severe pain on days 1 through 7 postoperatively, with 40% on day 1, 45% on day 2, 40% on day 3, and with an average of 56% on days 4

through 7 (2). In the placebo group, the percentage of patients requiring narcotics was 40% on day 1, 45% on day 2, and 40% on day 3 (2). Although limited by the small number of patients enrolled in the studies, the data can act as a baseline to which we may compare our results. In comparison to the moderate to severe pain reported days 1 through 4 in the untreated symptomatic vital teeth, treatment with both liposomal bupivacaine and bupivacaine resulted in less pain. Reported pain levels ranged between mild and moderate on the night of treatment (day 0B) to day 3. Additionally, a reduced number of patients required narcotic analgesics for both bupivacaine (23%) and liposomal bupivacaine (33%) compared to that of the placebo group in Gallatin's study (48-52%) (73) and Nagle's study (40-45%) (2). From this comparison, we can postulate that treatment with liposomal bupivacaine or bupivacaine in untreated symptomatic vital teeth may reduce pain levels and decrease narcotic use more effectively than placebo.

However, when comparing the results of our study to previous clinical trials and medical studies, which evaluated liposomal bupivacaine as compared to placebo or bupivacaine HCl for the ability to provide prolonged analgesia, reduce opioid use, and prolong time to first opioid, mostly dissimilar results were found. Unlike our study, which demonstrated no difference in reduction in opioid use or prolonged pain relief between groups, two studies conducted by Golf et al and Gorfine et al did find liposomal bupivacaine provided prolonged pain relief within the first 72 hours and reduced opioid consumption in patients undergoing bunionectomy and hemorrhoidectomy, respectively (15, 16). However, Golf et al (15) and Gorfine et al (16) compared liposomal bupivacaine to placebo, unlike our study, which used bupivacaine HCl for the control.

Therefore, the differences in our results could possibly be attributed to the differences in control groups.

When evaluating the results of studies that compare liposomal bupivacaine to bupivacaine HCl, conflicting results are reported. The differences may be related to how the studies were analyzed. When looking at individual studies comparing liposomal bupivacaine to bupivacaine HCl, the results were similar to ours and indicated no significant difference in pain control or opioid analgesic use between groups (18, 44, 74). However, in a meta-analysis conducted by Bergese et al, which examined liposomal bupivacaine pooled efficacy data from ten Phase II and Phase III double-blind clinical trials in patients undergoing hemorrhoidectomy, breast augmentation, bunionectomy, total knee arthroplasty, or hernia repair statistically significant differences were found (45). Bergese et al found 17 treatment arms that compared cumulative pain scores for liposomal bupivacaine to bupivacaine HCl, with statistically significant differences in 6 treatment arms through 24 hours and in 5 treatment arms through 72 hours. Statistically significant differences in total postsurgical opioid consumption were found at 24 hours in 2 studies (266 mg liposomal bupivacaine vs. 75 mg bupivacaine HCL and 532 mg liposomal bupivacaine vs. 200 mg bupivacaine HCl) and at 72 hours in 1 study (266 mg liposomal bupivacaine vs. 75 mg bupivacaine HCl) (45). A meta-analysis conducted by Dasta et al used pooled efficacy data from nine double-blind, placebo or bupivacaine HCl-controlled studies that administered less than 266 mg of liposomal bupivacaine and found comparable results with significant reduction in cumulative pain scores at 72 hours and decreased opioid consumption (51). From the results of the two meta-analyses,

Bergese et al (45) and Dasta et al (51) both concluded that treatment with liposomal bupivacaine was safe and effectively decreased postoperative pain in soft tissues, delayed first opioid consumption, and reduced total amount of opioid analgesics consumed within 72 hours postoperatively, regardless of choice of placebo or bupivacaine HCl for control group.

When analyzing the differences in results between medical studies and our dental study, acknowledgement of the even greater differences in type of treatment procedure should be made. These differences are sizable, making comparison challenging. Pulpal pain associated with symptomatic vital teeth has been classified as somatic deep visceral pain. This is different in nature from the somatic deep musculoskeletal pain and somatic superficial cutaneous pain associated with invasive surgical procedures and incisional wounds, respectively. When patients present with a symptomatic vital tooth, the pain is known to be the result of acute exacerbation of a chronic inflammatory condition, while inflammation resulting from surgeries is an acute inflammatory response in response to new trauma. Chronic inflammation and pain is known to cause enhanced excitability of nociceptors and increased activation of transient receptor potential vanillanoid-1, peripheral and central sensitization, and increased expression of tetrodotoxin-resistant (TTX) resistant sodium channels (75-78). These changes may result in hyperalgesia and allodynia, as well as increased difficulty achieving profound anesthesia (78-80). The difference in the degree and duration of inflammation between that of a symptomatic vital tooth and invasive surgery likely contribute to the contrasting results. However, the duration and nature of the pain may not be the only explanation.

An additional contributing factor could be the difference in anesthetic dose. The doses used in the medical studies were much greater than the 53 mg dose used in our study. In fact, the studies that compared liposomal bupivacaine to bupivacaine HCl and reported significant differences in pain scores used doses ranging from 93 mg to 532 mg, while those finding significant differences in opioid utilization had doses of 266 mg and 532 mg (45). When compared to our study, the medical doses were approximately 2 to even 10 times as great as our dose. Furthermore, studies indicated that larger doses of liposomal bupivacaine were associated with greater efficacy (45, 51). Looking at the aforementioned evidence, we may conclude that the relatively small 53 mg dose contributed to the decreased efficacy when compared to medical studies that utilized larger doses of liposomal bupivacaine.

ANALGESIC USAGE

Initially, the present study's protocol included providing the patient with ibuprofen and acetaminophen to manage their pain. It is important to note that patients were instructed to take one ibuprofen 600 mg tablet every 6 hours, and two acetaminophen 500 mg tablets every 6 hours as needed for pain. In an attempt to prevent patient confusion and ensure proper use, the bottles were labeled with instructions for proper use for each drug. Despite these instructions, it was noted that many patients did not take the medications as instructed, or if they did, they may not have recorded their consumption accurately. Some patients circled that they took pain medication, but did not indicate how many tablets of each type. Others took more pain medication than they

were given. Therefore, recorded drug use may vary from actual use, which may limit the value of the data.

If pain was not adequately managed with non-narcotic analgesics, patients were instructed to contact the investigator for a narcotic prescription. The purpose of this part of the protocol was to deter patients from obtaining escape medication unless it was absolutely necessary. There was concern that if all patients received the prescription pain medication at the end of the appointment, some patients would not attempt to initially manage pain without narcotics. This would then skew the results for non-analgesic use and success.

During the data-collection portion of the study, the DEA schedule for acetaminophen/hydrocodone changed from schedule III to schedule II. The change of drug schedule prevented prescriptions from being called into pharmacies. After this change went into effect, to ensure patients access to escape medication, all patients were given a prescription for acetaminophen/hydrocodone upon completion of their appointment. Patients were instructed to contact the investigator prior to filling the prescription to ensure the use of narcotics was warranted and that patients were taking the non-narcotic medications properly. An additional precaution was taken by writing a note on the prescription, asking the pharmacist not to fill the prescription without first contacting the prescribing doctor. This aided in identifying the patients that, despite instructions, attempted to obtain narcotic analgesics prior to contacting the investigator.

Patients were instructed to record the number of tablets of each analgesic medication taken in a table after each day. It is important to note when analyzing

analgesic use that the day of treatment (day 0) and day 1 were combined and reported as day 0-1. Initially, analgesic use was to be analyzed by hour. Soon after data collection began it was determined that patient error in recording times was too great and could not be considered accurate to the hour. Instead, use of analgesic tablets would be analyzed by day. A consequence of this decision was the inability to distinguish between the analgesic use on the day 0 (day of treatment) and day 1 (first post-treatment day). For this reason, analgesic use for these days was combined into day 0-1. This is not of great concern as long as it is recognized that day 0-1 is a longer time period than day 2 and day 3, which could possibly account for the greater total drug use during this period. Furthermore, the amount of analgesics needed on day 0 would likely vary greatly depending on when the patient was seen. Patients seen in the morning of day 0 have greater opportunity within that day to take pain medication than patients treated in the afternoon of day 0. Therefore, including analgesic use from day 0 with values from day 1 helps to minimize variance in pain medication use on day 0 based on appointment time.

Overall, there was no difference between groups with regard to total non-narcotic and narcotic utilization. When looking at acetaminophen and ibuprofen use individually, there was no difference in utilization by group on any day. No difference in analgesic use may be the result of the lack of difference in pain and tooth numbness seen in Figures 1 and 2. One would expect that if there is no difference in pain control between anesthetics, then both groups would be expected to take similar amounts of medications. Both groups utilized the greatest amount of non-narcotic analgesics on day 0-1, with a mean total of 5 tablets. It should be appreciated that those 5 tablets could have been

taken at any time within the day 0-1 timeframe that ranged between 32-40 hours. However, since the results show that pain increased to mild and moderate levels by day 0B (the night of treatment) and remained in this pain range throughout day 3, it is possible that many patients required pain medication the night of treatment and that not all 5 tablets were taken on day 1. After day 0-1, non-narcotic drug use continued to decline throughout day 3 with patients taking a total of 3 tablets for both groups, despite their pain remaining mild to moderate. This decrease in non-narcotic analgesic use may be the result of increased utilization of narcotics over the course of the three days.

Narcotic utilization by total number of patients remained low with only 23% (11/48) of bupivacaine patients and 33% (15/46) of liposomal bupivacaine patients utilizing narcotics at least once throughout the post-treatment period. In fact, for both groups, mean number of tablets of narcotics used per patient remained less than 1 tablet each day. This shows that despite the availability of the narcotic pain medication most patients chose not to use narcotics and were able to manage mild and moderate pain levels with non-narcotic medications. However, it should be acknowledged that the mean value of less than 1 tablet per day does not represent the mean consumption for the 26 patients who utilized narcotics. For these 26 patients, the mean narcotic tablet consumption was greater than 1.

Additionally, 95 of the total 100 patients were able to adequately manage their pain through use of analgesics and return for treatment at their scheduled appointment. This means that only 5% of the 100 total patients required unscheduled post-treatment emergency visits due to intolerable pain that could not be sufficiently controlled by

analgesics. Interestingly, all of the patients who returned were part of the bupivacaine HCl treatment group. Table 15 shows that of these patients, 6% (3/50) returned day 0-1 and 4% (2/50) returned day 3. The reported VAS pain scores on the day of the emergency treatment ranged from 113 mm to 170 mm, with all but one categorized as severe pain. With VAS pain scores that were approximately double the mean pain ratings for the average patients in both groups, one can understand why these 5 patients returned for unscheduled visits.

Gallatin et al reported a slightly higher rate of unscheduled emergency visits for untreated symptomatic vital teeth. Fourteen percent (3/21) of patients in the placebo group experienced emergent pain that was great enough to warrant return for emergency debridement prior to their scheduled return appointment (73). When considering that in both studies the symptomatic vital teeth were not treated with pulpal debridement, a method known to be a reliable and predictable means of achieving patient comfort, it is surprising that more patients did not return for unscheduled emergency visits.

Ideally, we would like to compare our rate of unscheduled emergency visits to studies that performed emergency endodontic debridement for treatment of symptomatic irreversible teeth; however, no studies have reported such data. Even so, we postulate that unscheduled emergency visits would be much less frequent in patients undergoing emergency debridement than those with untreated cases, as the source of pain, the inflamed pulpal tissue, has been removed.

INJECTION PAIN

In our study, patients were administered two injections spaced 20 minutes apart, in accordance to the manufacturer's instructions, to avoid disruption of the liposomes and immediate release of bupivacaine (14, 37, 42, 43). The primary injection consisted of an infiltration for maxillary teeth and an IANB for mandibular teeth with 2% lidocaine 1:100,000 epinephrine. The goal of the first injection was to ensure patient comfort as the effects of liposomal bupivacaine could be delayed. The secondary injection consisted of an additional infiltration with 4 mL of either bupivacaine or liposomal bupivacaine in the buccal vestibule next to the tooth. After each injection, patients were asked to rate the pain experienced upon insertion of the needle, placement of the needle, and deposition of the solution on 170 mm VAS.

For the primary injection, mean pain scores for maxillary infiltrations with lidocaine for all stages of injection ranged from mild to moderate on the VAS for both groups. The mean pain scores for mandibular inferior alveolar nerve block were within the moderate range for all stages of the injection for both groups. Using categorical values, pain experienced during primary injections in both the maxilla and mandible was between mild and moderate for the majority of patients. Our results are similar to those reported by other studies conducted at The Ohio State University investigating symptomatic irreversible pulpitis (61, 81-84). In our study, patients reported lower pain scores after IANB injection than patients in a study conducted by McCartney et al (85). McCartney et al evaluated the pain associated with needle insertion, placement, and solution deposition after administration of the IANB in irreversible teeth and found that

57% to 89% of patients experienced moderate to severe pain (85). Our results demonstrated lower levels of pain with 40-62% of bupivacaine patients and 44%-52% of liposomal bupivacaine patients reporting moderate to severe pain.

Of greater importance to this study is the pain associated with the secondary injection with liposomal bupivacaine or bupivacaine HCl. We wanted to know if injection with liposomal bupivacaine caused patients more pain. Our results show that the infiltration with liposomal bupivacaine did not cause more pain (Table 17). No significant difference in pain for injection insertion, placement, and deposition was found between bupivacaine and liposomal bupivacaine groups ($p=0.2154$). The mean pain for both groups was the least for insertion and the greatest for deposition with all ratings in the mild category. These results are supported by Perry et al who found that for maxillary infiltrations, deposition was the most painful phase of injection (86). The mean pain scores for the secondary injection were lower than the mean pain scores for the primary injection. This is not believed to be the result of the injection itself being less painful. Rather, the injection was likely perceived as less painful because the injection occurred in tissue previously anesthetized by the primary injection. The already-established soft tissue numbness would help diminish the level of pain felt during the three stages of injection. The most important conclusion that can be drawn from the injection pain ratings is that infiltration with liposomal bupivacaine is no more painful than bupivacaine HCl.

SATISFACTION

At the end of the post-treatment questionnaire patients were asked to rate their overall satisfaction with treatment on a 100 mm VAS, as well as answer four questions regarding satisfaction with numbness and pain control. Patient satisfaction ratings on the VAS were categorized into four groups based on the following levels of satisfaction: not satisfied (0 mm), somewhat satisfied (>0 mm to ≤ 33 mm), moderately satisfied (≥33 mm to <66 mm), and completely satisfied (≥66 mm). In our study, patients in both groups reported no statistically significant difference in mean VAS satisfaction ratings. Overall, the mean satisfaction rating on VAS for both groups was categorized as moderately satisfied with treatment.

Sixty-one percent of bupivacaine HCl patients and 47% of liposomal bupivacaine patients were completely satisfied with treatment. The overall satisfaction with treatment in this study was much lower than other studies researching mandibular posterior irreversible pulpitis conducted at OSU, which reported that 89-94% of patients were completely satisfied with treatment (81, 82, 87). Our lower patient satisfaction is likely the result of not completing emergency root canal debridement as in studies conducted by Fullmer (87), Click (81), and Schellenberg (82). Instead, we relied on anesthetics and analgesics to control the symptoms of symptomatic irreversible pulpitis.

The lack of difference in satisfaction between bupivacaine and liposomal bupivacaine groups in our study is supported by the previously discussed meta-analysis conducted by Bergese et al. Six of ten studies analyzed included assessment of patient satisfaction of postsurgical pain relief. Of these six studies, only one study demonstrated

statistically significantly better patient satisfaction, which also happened to be the only study of those six that compared liposomal bupivacaine to a placebo. In that study, 24 hours after surgery, 95% of patients receiving liposomal bupivacaine 266 mg dose were "satisfied" or "extremely satisfied" with their postoperative pain control as opposed to only 72% of the placebo group (p=0.0007). The remainder of the other studies, which compared liposomal bupivacaine to bupivacaine HCl, showed no statistically significant between-group differences (45). Although the nature of pain in these studies (hemorrhoidectomy, breast augmentation, bunionectomy, total knee arthroplasty, or hernia repair) differs from symptomatic irreversible pulpitis, overall their findings of no difference in satisfaction are congruent with our findings.

In the present study, although there was no difference found between liposomal bupivacaine and bupivacaine HCl with regard to whether or not being numb decreased pain, satisfaction with the level of pain control achieved while numb, as well as patients' preference for feeling numbness versus pain the patients responses help us better understand their satisfaction recordings. For example, 91% of patients in both groups responded that being numb helped with their pain. Around half of each group, 42% of bupivacaine and 51% of liposomal bupivacaine patients, responded 'Yes' to feeling satisfied with the level of pain control achieved while numb. Of those who were not satisfied, between 86-89% would have liked to have been numb longer. Specifically, 96% of patients preferred feeling numb, while 4% of patients preferred feeling pain. While it may be difficult to imagine patients preferring moderate to severe pain over the sensation of numbness, this expresses how disturbing and uncomfortable the 4% of

patients found prolonged soft tissue numbness to be. Some patients reported that lip numbness interfered with talking and eating. Others reported feeling as though they had had a stroke. Interestingly, there was a statistically significant difference in satisfaction with the level of pain control achieved while numb with 98% of the bupivacaine HCl and 82% percent of the liposomal bupivacaine respondents being satisfied. This difference is interesting because 16% more patients in the bupivacaine group were satisfied with the level of pain control achieved while numb; however, our data demonstrated no statistically significant difference in reported pain levels between groups during this period. Although this cannot be substantiated by our data, it is possible that the difference was the result of the amount of free bupivacaine available immediately after injection. After a 4 mL injection with 0.5% bupivacaine 1:200,000 epinephrine, 20 mg bupivacaine is available to aid in pain control, while there is only a small amount (approximately 3%) of free bupivacaine within liposomal bupivacaine suspension, which allows for near- immediate anesthesia, while the remaining drug is released from the liposomes over time (14).

In conclusion, the use of a 4 mL dose of liposomal bupivacaine is currently not recommended for pain control in untreated symptomatic vital teeth. However, further research should be conducted to investigate the effects of increased dose and drug concentration for use in inferior alveolar nerve blocks in symptomatic vital and necrotic teeth. Liposomal bupivacaine anesthetic may have application in a multi-modal analgesic regimen for treatment of symptomatic teeth.

CHAPTER 5

SUMMARY AND CONCLUSIONS

The purpose of this double-blind, randomized controlled study was to compare liposomal bupivacaine and bupivacaine HCl for pain control in untreated symptomatic vital teeth. Medical studies have demonstrated prolonged pain relief and reduction in opioid utilization up to 72 hours postoperatively (15, 16, 40, 45, 46, 50, 51). However, there are currently no studies that evaluate pain control after treatment with liposomal bupivacaine in patients with moderate to severe pain resulting from untreated symptomatic vital teeth. It was hypothesized that the use of liposomal bupivacaine for pain control in patients with untreated symptomatic vital teeth and moderate to severe pain would result in extended pain control and reduced analgesics consumption throughout the post-treatment period.

The result of this study demonstrated no significant differences in pain control, tooth numbness, or analgesics use between groups throughout the post-treatment period. No significant difference in narcotic use was found. Only 23% of patients who received bupivacaine HCl and 33% of patients who received liposomal bupivacaine utilized narcotics. A significant difference in lip numbness was reported day 1 through day 3 in patients treated with liposomal bupivacaine. However, this did not result in significant

reduction in pain levels during that time period. Pain levels remained between mild and moderate day 0B to day 3 for both groups.

In conclusion, administration of liposomal bupivacaine in patients with untreated symptomatic vital teeth reporting moderate to severe pain did not result in significantly different pain control or analgesic utilization throughout the post-treatment period when compared to administration of bupivacaine HCl.

REFERENCES

1. Reader A, Nusstein J, Drum M. *Successful Local Anesthesia for Restorative Dentistry and Endodontics*, Quintessence Publishing Co, Hanover Park, IL., 2011.

2. Nagle D, Reader A, Beck M, Weaver J. Effect of systemic penicillin on pain in untreated irreversible pulpitis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000 90:636-40.

3. Danielsson K, Evers H, Holmlund A, Kjellman O, Nordenram A, Persso NE. Long-acting local anesthetics in oral surgery. Clinical evaluation of bupivacaine and etidocaine for mandibular nerve block. Int J Oral Maxillofac Surg 1986;15:119-26.

4. Tuffin JR, Cunliffe DR, Shaw SR. Do local analgesics injected at the time of third molar removal under general anaesthesia reduce significantly postoperative analgesic requirements? A double-blind controlled study. Br J Oral Maxillofac Surg 1989;27:27-32.

5. Bouloux GF, Punnia-Moorthy A. Bupivacaine versus lidocaine for third molar surgery: a double-blind, randomized, crossover study. J Oral Maxillofac Surg 1999;57:510-4.

6. Crout R, Koraido G, Moore P. A clinical trial of long-acting local anesthetics for periodontal surgery. Anesth Prog 1990;37:194-8.

7. Neal JA, Welch TB, Halliday RW. Analysis of the analgesic efficacy and cost-effective use of long-acting local anesthetics in outpatient third molar surgery. Oral Surg Oral Med Oral Pathol 1993;75:283-5.

8. Rosenquist JB, Nystrom E. Long-acting analgesia or long-acting local anesthetic in controlling immediate postoperative pain after lower third molar surgery. Anesth Prog 1987;34:6-9.

9. Rosenquist J, Rosenquist K, Lee P. Comparison between lidocaine and bupivacaine as local anesthetics with diflunisal for postoperative pain control after lower third molar surgery. Anesth Prog 1988;35:1-4.

10. Moore P, Dunsky J. Bupivacaine anesthesia - a clinical trial for endodontic therapy. Oral Surg Oral Med Oral Pathol 1983;55:176-9.

11. Dunsky J, Moore P. Long-acting local anesthetics: a comparison of bupivacaine and etidocaine hydrochloride in endodontics. J Endod 1984;10:457-60.

12. Linden ET, Abrams H, Matheny J, Kaplan AL, Kopczyk RA, Jasper SJ. A comparison of postoperative pain experience following periodontal surgery using two local anesthetic agents. J Periodontol 1986;57:637-42.

13. Exparel® (bupivacaine liosome extended-release injectable suspension [prescribing information]. San Diego, CA:Pacira Pharmaceuticals; 2011.

14. Formulary. Liposomal bupivacaine: along-acting local anesthetic for postsurgical analgesia. 2012;47:212-26.

15. Gorfine SR, Onel E, Patou G, Krivokapic ZV. Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: a multicenter, randomized, double-blind placebo-controlled trial. Dis Colon Rectum 2011;54:1552-9.

16. Golf M, Daniels SE, Onel E. A phase 3, randomized, placebo-contolled trial of DepoFoam bupivacaine (extended-release bupivacaine local analgesia) in bunionectomy. Adv Ther 2011;28: 776-88.

17. Bramlett KW, Jones RK, Pink M, Pink T. A single administration of depobupivacaine intraoperatively provides analgesia and reduction in use of rescue opiates compared with bupivacaine HCl in patients undergoing total knee arthroplasty. Presented at: 36th Biennial World Congress of the International College of Surgeons. December 3-6, 2008; Vienna, Austria. Poster 0218.

18. Bramlett K, Onel E, Viscusi ER, Jones K. A randomized, double-blind, dose-ranging study comparing wound infiltration of DepoFoam® bupivacaine, an extended-release liposomal bupivacaine, to bupivacaine HCl for postsurgical analgesia in total knee arthroplasty. Knee 2012;19:530-6.

19. Clinical trial no. SKY0402-C-208. A multicenter, randomized, double-blind, parallel-group, active-control, dose-ranging study to evaluate the safety, efficacy, and comparative systemic bioavailability of a single administration of SKY0402 via local infiltration for prolonged postoperative analgesia in subject undergoing total knee arthroplasty. Pacira Pharmaceuticals Inc., 2010.

20. Minkowitz H, Smoot J. Long-term safety of Exparel® (bupivacaine extended release liposome injection) reveals no impact on silicone breast implants at up to two years follow-up. Presented at: American Society of Plastic Surgeons Annual Meeting; September 24, 2011; Denver, CO.

21. Clinical trial no. SKY0402-C-210. A randomized, double-blind, active-control study to evaluate the safety and efficacy of a single local administration of SKY0402 for prolonged postoperative analgesia in subjects undergoing augmentation mammoplasty. Pacira Pharmaceuticals Inc.

22. Viscusi ER, Sinatra AS. The safety of Exparel®, a multi-vesicular liposomal extended-release bupivacaine [abstract + poster]. Anesth Analg 2011;112:S-305.

23. Malamed SF. *Handbook of Local Anesthesia, 5th ed.*, The C.V. Mosby Company. St. Louis, MO. 2004;37.

24. Skolnik A, Gan TJ. New formulations of bupivacaine for the treatment of postoperative pain: liposomal bupivacaine and SABER-Bupivacaine. Expert Opin Pharmacother 2014;15:1535-42.

25. Yi Cai Isaac Tong, Alan David Kaye, Richard D Urman. Liposomal bupivacaine and clinical outcomes. Best Practice & Research Clinical Anaesthesiolgy 2014;28:15-27.

26. Pateromichelakis S, Prokopiou AA. Local anesthesia efficacy: Discrepancies between in vitro and in vivo studies. Acta Anaesthesiol Scand 1988;32:672-5.

27. Fernandez C, Reader A, Beck FM, Nusstein J. A prospective, randomized, double-blind comparison of bupivacaine and lidocaine for inferior alveolar nerve blocks. J Endod 2005;34:1306-11.

28. Parirokh M, Yosefi MH, Nakhaee N, Manochehrifar H, Abbott PV, Reza Forghani F. Effect of bupivacaine on postoperative pain for inferior alveolar nerve block anesthesia after single-visit root canal treatment in teeth with irreversible pulpitis. J Endod 2012;38:1035-9.

29. Al-Kahtani A. Effect of long acting local anesthetic on postoperative pain in teeth with irreversible pulpitis: randomized clinical trial. Saudi Pharm J 2014;22:39-42

30. Su N, Wang H, Zhang S, Liao S, Yang S, Huang Y. Efficacy and safety of bupivacaine versus lidocaine in dental treatments: a meta-analysis of randomised controlled trials. Int Dent J 2014;64:34-45.

31. Sampaio RM, Carnaval TG, Lanfredi CB, Horliana AC, Rocha RG, Tortamano IP. Comparison of the anesthetic efficacy between bupivacaine and lidocaine in patients with irreversible pulpitis of mandibular molar. J Endod 2012;38(5):594-7.

32. Gross R, McCartney M, Reader A, Beck FM. A prospective, randomized, double-blind comparison between bupivacaine and lidocaine for maxillary infiltrations. J Endod 2008;34:121-5.

33. Meechan J, Blair G. The effect of two different local anesthetic solutions on pain experience following apicoectomy. Br Dent J 1993;175;410-13.

34. Lonner J. Role of liposomal bupivacaine in pain management after total joint arthroplasty. J Surg Orthop Adv 2014;23:37-41.

35. Chahar P, Cummings KC 3rd. Liposomal bupivacaine: a review of a new bupivacaine formulation. J Pain Res 2012;5:257-64.

36. Tong YC, Kaye AD, Urman RD. Liposomal bupivacaine and clinical outcomes. Best Pract Res Clin Anaesthesiol 2014;28:15-27.

37. Saraghi M, Hersh EV. Three newly approved analgesics: an update. Anesth Prog 2013;60:178-87.

38. Portillo J, Kamar N, Melibary S, Quevedo E, Bergese S. Safety of liposome extended-release bupivacaine for postoperative pain control. Front Pharmacol 2014;5:90.

39. Viscusi ER, Sinatra R, Onel E, Ramamoorthy SL. The safety of liposome bupivacaine, a novel local analgesic formulation. Clin J Pain 2014;30:102-10.

40. Noviasky J, Pierce DP, Whalen K, Guharoy R, Hildreth K. Bupivacaine liposomal versus bupivacaine: comparative review. Hosp Pharm 2014;49:539-43.

41. VA pharmacy benefits management services, medical advisory panel and VISN pharmacist executives. Bupivacaine liposome injectable suspension (Exparel®) national drug monograph. 2013 Jun. www.pbm.va.gov.

42. Candiotti K. Liposomal bupivacaine: an innovative nonopioid local analgesic for the management of postsurgical pain. Pharmacotherapy 2012;32:19S-26S.

43. Kharitonov V. A review of the compatibility of liposome bupivacaine with other drug products and commonly used implant materials. Postgrad Med 2014;126:129-38.

44. Smoot JD, Bergese SD, Onel E, Williams HT, Hedden W. The efficacy and safety of DepoFoam® bupivacaine in patients undergoing bilateral, cosmetic, submuscular augmentation mammaplasty: a randomized, double-blind, active-control study. Anesthet Surg J 2012;32:69-76.

45. Bergese SD, Ramamoorthy S, Patou G, Bramlett K, Gorfine S, Candiotti K. Efficacy of liposome bupivacaine, a novel formulation of bupivacaine for postsurgical analgesia. J Pain Res 2012;5:107-16.

46. Bergese SD, Onel E, Portillo J. Evaluation of DepoFoam® bupivacaine for the treatment of postsurgical pain. Pain Manag 2011;1:539-47.

47. Corah NL. Development of a dental anxiety scale. J Dent Res 1969;48:596.

48. Heft M, Parker SR. An experimental basis for revising the graphic rating scale for pain. Pain 1984;19:153-61.

49. Wells LK, Drum M, Nusstein J, Reader A, Beck M. Efficacy of ibuprofen and ibuprofen/acetaminophen on postoperative pain in symptomatic patients with a pulpal diagnosis of necrosis. J Endod 2011;37(12):1608.

50. Haas E, Onel E, Miller H, Ragupathi M, White PF. A double-blind, randomized, active-controlled study for post-hemorrhoidectomy pain management with liposome bupivacaine, a novel local analgesic formulation. Am Surg 2012;78:574-81.

51. Dasta J, Ramamoorthy S, Patou G, Sinatra R. Bupivacaine liposome injectable suspension compared with bupivacaine HCl for the reduction of opioid burden in the postsurgical setting. Curr Med Res Opin 2012;28:1609-15.

52. Kanaa MD, Whitworth JM, Corbett IP, Meechan JG. Articaine and lidocaine mandibular buccal infiltration anesthesia: a prospective randomized double-blind crossover study. J Endod 2006;32:296-8.

53. Robertson D, Nusstein J, Reader A, Beck M, McCartney M. The anesthetic efficacy of articaine in buccal infiltration of mandibular posterior teeth. J Am Dent Assoc 2007;138:1104-12

54. Jung I, Kim J, Kim E, Lee C, Lee S. An evaluation of buccal infiltrations and inferior alveolar nerve blocks in pulpal anesthesia for mandibular first molars. J Endod 2008;34:11-3.

55. Corbett IP, Kanaa MD, Whitworth JM, Meechan JG. Articaine infiltration for anesthesia of mandibular first molars. J Endod 2008;34:514-8.

56. Abdulwahab M, Boynes S, Moore P, Seifikar S, Al-Jazzaf A, Alshuraidah A, Zovko J, Close J. The efficacy of six local anesthetic formulations used for posterior mandibular buccal infiltration anesthesia. J Am Dent Assoc 2009;140:1018-24.

57. Haase A, Reader A, Nusstein J, Beck M, Drum M. Comparing anesthetic efficacy of articaine versus lidocaine as a supplemental buccal infiltration of the mandibular first molar after an inferior alveolar nerve block. J Am Dent Assoc 2008;139:1228-35.

58. Kanaa MD, Whitworth JM, Corbett IP, Meechan JG. Articaine buccal infiltration enhances the effectiveness of lidocaine inferior alveolar nerve block. Int Endod J 2009;42:238-46.

59. Haas DA, Harper DG, Saso MA, Young ER. Comparison of articaine and prilocaine anesthesia by infiltration in maxillary and mandibular arches. Anesth Prog 1990;37:230-7.

60. Haas DA, Harper DG, Saso MA, Young ER. Lack of a differential effect by Ultracaine (articaine) and Citanest (prilocaine) in infiltration anesthesia. J Can Dent Assoc 1991;57:217-23.

61. Matthews R, Drum M, Reader A, Nusstein J, Beck M. Articaine for supplemental buccal mandibular infiltration anesthesia in patients with irreversible pulpitis when the inferior alveolar nerve block fails. J Endod 2009;35:343-6.

62. Pabst L, Nusstein J, Drum M, Reader A, Beck M. The efficacy of a repeated buccal infiltration of articaine in prolonging duration of pulpal anesthesia in the mandibular first molar. Anesth Prog 2009;56:128-34.

63. Fan S, Chen W, Pan C, Huang Z, Xian M, Yang Z, Dias-Ribeiro E, Liang Y, Jiao J, Ye Y, Wen TY. Anesthetic efficacy of inferior alveolar nerve block plus buccal infiltration or periodontal ligament injections with articaine in patients with irreversible pulpitis in the mandibular first molar. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;108:89-93.

64. Aggarwal V, Jain A, Kabi D. Anesthetic efficacy of supplemental buccal and lingual infiltrations of articaine and lidocaine after an inferior alveolar nerve block in patients with irreversible pulpitis. J Endod 2009;35:925-8.

65. Nuzum FM, Drum M, Nusstein J, Reader A, Beck M. Anesthetic efficacy of articaine for combination labial plus lingual infiltrations versus labial infiltration in the mandibular lateral incisor. J Endod 2010;36:952-6.

66. Meechan JG, Jaber AA, Corbett IP, Whitworth JM. Buccal versus lingual articaine infiltration for mandibular tooth anesthesia: a randomized controlled trial. Int Endod J 2011;36:952-6.

67. Aggarwal V, Singla M, Rizvi A, Miglani S. Comparative evaluation of local infiltration of articaine, articaine plus ketorolac, and dexamethasone on anesthetic efficacy of inferior alveolar nerve block with lidocaine in patients with irreversible pulpitis. J Endod 2011;37:445-9.

68. McEntire M, Nusstein J, Drum M, Reader A, Beck M. Anesthestic efficacy of 4% articaine with 1:100,000 epinephrine versus 4% articaine with 1:200,000 epinephrine as a primary buccal infiltration in the mandibular first molar. J Endod 2011;37:450-4.

69. Martin M, Nusstein J, Drum M, Reader A, Beck M. Anesthetic Efficacy of 1.8 mL versus 3.6 mL of 4% articaine with 1:100,000 epinephrine as a primary buccal infiltration of the mandibular first molar. J Endod 2011;37:588-92.

70. Poorni S, Venishok B, Senthilkumar AD, Indira R, Ramachandran S. Anesthetic efficacy of four percent articaine for pulpal anesthesia by using inferior alveolar nerve block and buccal infiltration techniques in patients with irreversible pulpitis: A prospective randomized double-blind clinical trial. J Endod 2011;37:1603-7.

71. Dressman AS, Nusstein J, Drum M, Reader A. Anesthetic efficacy of a primary articaine infiltration and a repeat articaine infiltration in the incisive/mental nerve region of mandibular premolars: A prospective, randomized, single-blind study. J Endod 2013;39:313-8.

72. Cohen SM. Extended pain relief trial utilizing infiltration of Exparel®, a long-acting multivesicular liposome formulation of bupivacaine: a Phase IV health economic trial in adult patients undergoing open colectomy. J Pain Res 2012;5:567-72.

73. Gallatin E, Reader A, Nist R, Beck M. Pain reduction in untreated irreversible pulpitis using an intraosseous injection of Depo-Medrol. J Endod 2000;26(:633-8.

74. Langford RM, Chappell GM, Karrasch JA. A single administration of depobupivacaine intraoperatively results in prolonged detectable plasma bupivacaine and analgesia in patients undergoing inguinal hernia repair. Presented at: 62nd Postgraduate Assembly in Anesthesiology; December 12-16, 2008; New York, NY. Poster 9088.

75. Hargreaves K, Cohen S. *Pathways of the Pulp* 10th edition. St. Louis: Mosby Elsevier 2011;26-7.

76. Henry M, Hargreaves K. Peripheral mechanisms of odontogenic pain. Dent Clin North Am 2007;51:19-44.

77. Strichartz GR. Novel ideas of local anaesthetic actions on various ion channels to ameliorate postoperative pain. Brit J Anaesth 2008;101:45-7.

78. Roy M and Narahashi T. Differential properties of tetrodotoxin-sensitive and tetrodotoxin-resistant sodium channels in rat dorsal root ganglion neurons. J Neurosci 1992;12:2104-11.

79. Hargreaves KM, Keiser K. Local anesthetic failure in endodontics: mechanisms and management. Endodon Topics 2002;1:26-39.

80. Owatz CB, Khan AA, Schindler WG, Schwartz SA, Keiser K, Hargreaves KM. The incidence of mechanical allodynia in patients with irreversible pulpitis. J Endod 2007;33:552-6.

81. Click V, Drum M, Reader A, Nusstein J, Beck M. Evaluation of the Gow-Gates and Vazirani-Akinosi techniques in patients with symptomatic irreversible pulpitis: a prospective randomized study. J Endod 2015;4:16-21.

82. Schellenberg J, Drum M, Reader A, Nusstein J, Fowler S, Beck M. Effect of buffered 4% lidocaine on the success of the inferior alveolar nerve block in patients with symptomatic irreversible pulpitis: a prospective, randomized, double-blind study. J Endod 2015;41:791-6.

83. Oleson M, Drum M, Reader A, Nusstein J, Beck M. Effect of preoperative ibuprofen on the success of the inferior alveolar nerve block in patients with irreversible pulpitis. J Endod 2010;36:379-82.

84. Simpson M, Drum M, Nusstein J, Reader A, Beck M. Effect of combination of preoperative ibuprofen/acetaminophen on the success of the inferior alveolar nerve block in patients with symptomatic irreversible pulpitis. J Endod 2011;37:593-7.

85. McCartney M, Reader A, Beck M. Injection pain of the inferior alveolar nerve block in patients with irreversible pulpitis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;104:571-5.

86. Perry S, Drum M, Reader A, Nusstein J, Beck M. Effect of operator and subject gender on injection pain: a randomized double-blind study. J Endod 2015;41:141-5.

87. Fullmer S, Drum M, Reader A, Nusstein J, Beck M. Effect of preoperative acetaminophen/hydrocodone on the efficacy of the inferior alveolar nerve block in patients with symptomatic irreversible pulpitis: a prospective, randomized, double-blind, placebo-controlled study. J Endod 2014;40:1-5.

APPENDIX A

TABLES

	Bupivacaine	Liposomal	p -value
Total Subjects	50	50	
Jaw	24 Maxilla (48%) 26 Mandible (52%)	25 Maxilla (50%) 25 Mandible (50%)	0.8414^
Gender	Female 32/50 (64%) Male 18/50 (36%)	Female 26/50 (52%) Male 24/50 (48%)	0.2235^
Age (Mean +/- SD) years	34 ($\pm$ 10)	33 ($\pm$ 11)	0.6049***
Initial Pain (Mean +/- SD) mm	136 ($\pm$ 27)	135 ($\pm$ 23)	0.9294***
Corah Dental Anxiety (Median)	9	10	0.1805**
Tooth Type	43 Molars (86%) 7 Premolars (14%)	39 Molars (78%) 11 Premolars (22%)	0.2961*

Table 1. Preliminary Data for Bupivacaine and Liposomal

^ Chi-square test

*Fischer exact test

** Mann-Whitney-Wilcoxon test

*** Randomization Test

Group	Success	Count	Percent	p*
Liposomal	NO	37	79	0.1266
	YES	10	21	
Bupivacaine	NO	31	65	
	YES	17	35	

Table 2. Success (no or mild pain and no narcotic usage) Summary

*Chi-square test

**Success defined by no or mild pain and no narcotic usage

Comparison	Odds Ratio Estimate	DF	95% Confidence	Limits
Liposomal vs Bupivacaine	0.493	93	0.195	1.2462

Effect**	Num DF	Den DF	Chi-Square	F Value	Pr > ChiSq	Pr > F
Group	1	93	2.3	2.3	0.1298	0.1332

Table 3. Crude Odds Ratio

**Type III tests of fixed effects

Comparison	Odds ratio Estimate	DF	95% Confidence	Limits
Liposomal vs Bupivacaine	0.44	90	0.166	1.167
Gender Female vs Male	1.23	90	0.466	3.249
Jaw Maxilla vs Mandible	1.254	90	0.489	3.212
Tooth Type Molar vs Premolar	0.36	90	0.116	1.117

Effect**	Num DF	Den DF	Chi-Square	F Value	Pr > ChiSq	Pr > F
Group	1	90	2.8	2.8	0.0945	0.098
Gender	1	90	0.18	0.18	0.6716	0.6726
Jaw	1	90	0.23	0.23	0.6331	0.6343
Tooth Type	1	90	3.22	3.22	0.0729	0.0763

Table 4. Adjusted Odds Ratio

**Type III tests of fixed effects

Group	Period	Variable	N	Mean	Std Dev	Min	Max	p(adj)**
Bupivacaine	DAY0A	Tooth	50	87	21	0	100	1.0000
	DAY0B	Tooth	47	37	39	0	100	1.0000
	DAY1	Tooth	47	18	34	0	100	0.0545
	DAY2	Tooth	42	16	33	0	100	1.0000
	DAY3	Tooth	41	11	30	0	100	0.3830
Liposomal	DAY0A	Tooth	50	87	16	40	100	
	DAY0B	Tooth	47	42	39	0	100	
	DAY1	Tooth	47	30	33	0	100	
	DAY2	Tooth	47	19	29	0	100	
	DAY3	Tooth	47	11	24	0	100	

Table 5. Tooth numbness as Rated on 100 mm VAS

**Multiple Randomization tests and Step-down Bonferroni method of Holm adjusted among pain types

A= end of appointment

B= before bed

Group	Period	Variable	Outcome	Count	Percent	p(adj.)**
Bupivacaine	DAY0A	Tooth	No	1	2	1.0000
	DAY0A	Tooth	Yes	49	98	
	DAY0B	Tooth	No	25	52	1.0000
	DAY0B	Tooth	Yes	23	48	
	DAY1	Tooth	No	33	69	0.4750
	DAY1	Tooth	Yes	15	31	
	DAY2	Tooth	No	33	77	0.6401
	DAY2	Tooth	Yes	10	23	
	DAY3	Tooth	No	35	88	1.0000
	DAY3	Tooth	Yes	5	13	
Liposomal	DAY0A	Tooth	No	0	0	
	DAY0A	Tooth	Yes	50	100	
	DAY0B	Tooth	No	22	47	
	DAY0B	Tooth	Yes	25	53	
	DAY1	Tooth	No	25	52	
	DAY1	Tooth	Yes	23	48	
	DAY2	Tooth	No	29	63	
	DAY2	Tooth	Yes	17	37	
	DAY3	Tooth	No	39	85	
	DAY3	Tooth	Yes	7	15	

Table 6. Binary Tooth Numbness Responses

**Multiple Chi-square tests and Step-down Bonferroni method of Holm adjusted among variable types

A=end of appointment

B=before bed

Group	Period	Variable	N	Mean	Std Dev	Min	Max	p(adj)**
Bupivacaine	DAY0A	Lip	50	89	21	21	100	0.8211
	DAY0B	Lip	46	32	35	0	100	0.9546
	DAY1	Lip	48	8	19	0	81	**0.0003**
	DAY2	Lip	42	3	13	0	84	**0.0019**
	DAY3	Lip	41	3	14	0	87	**0.0414**
Liposomal	DAY0A	Lip	50	89	15	43	100	
	DAY0B	Lip	48	34	35	0	100	
	DAY1	Lip	48	25	30	0	100	
	DAY2	Lip	48	14	23	0	100	
	DAY3	Lip	48	8	18	0	75	

Table 7. Lip and Cheek Numbness as Rated on 100 mm VAS

**Multiple Randomization tests and Step-down Bonferroni method of Holm adjusted among pain types

A= end of appointment

B= before bed

Group	Period	Variable	Outcome	Count	Percent	p(adj.)**
Bupivacaine	DAY0A	Lip	No	0	0	NA
	DAY0A	Lip	Yes	50	100	
	DAY0B	Lip	No	21	45	0.6037
	DAY0B	Lip	Yes	26	55	
	DAY1	Lip	No	42	88	**0.0003**
	DAY1	Lip	Yes	6	13	
	DAY2	Lip	No	42	98	**0.0007**
	DAY2	Lip	Yes	1	2	
	DAY3	Lip	No	41	100	**0.0269**
	DAY3	Lip	Yes	0	0	
Liposomal	DAY0A	Lip	No	0	0	
	DAY0A	Lip	Yes	50	100	
	DAY0B	Lip	No	24	50	
	DAY0B	Lip	Yes	24	50	
	DAY1	Lip	No	24	50	
	DAY1	Lip	Yes	24	50	
	DAY2	Lip	No	32	68	
	DAY2	Lip	Yes	15	32	
	DAY3	Lip	No	40	85	
	DAY3	Lip	Yes	7	15	

Table 8. Binary Lip and Cheek Numbness Responses

**Multiple Chi-square tests and Step-down Bonferroni method of Holm adjusted among variable types

A=end of appointment

B=before bed

Group	Period	Variable	N	Mean	Std Dev	Min	Max	p(adj)**
Bupivacaine	DAY0A	Pain	50	8	18	0	83	0.3498
	DAY0B	Pain	47	49	41	0	141	1.0000
	DAY1	Pain	47	59	51	0	170	1.0000
	DAY2	Pain	42	49	50	0	170	1.0000
	DAY3	Pain	40	54	50	0	163	1.0000
Liposomal	DAY0A	Pain	50	16	25	0	106	
	DAY0B	Pain	48	57	48	0	156	
	DAY1	Pain	47	49	42	0	138	
	DAY2	Pain	46	58	45	0	156	
	DAY3	Pain	47	63	45	0	156	

Table 9. Pain as Rated on 170 mm VAS

**Multiple Randomization tests and Step-down Bonferroni method of Holm adjusted among pain types

A= end of appointment

B= before bed

Group	Period	Variable	Outcome	Count	Percent	p(adj.)**
Bupivacaine	DAY0A	Pain	No	48	96	1.0000
	DAY0A	Pain	Yes	2	4	
	DAY0B	Pain	No	16	33	1.0000
	DAY0B	Pain	Yes	32	67	
	DAY1	Pain	No	13	27	1.0000
	DAY1	Pain	Yes	35	73	
	DAY2	Pain	No	19	44	1.0000
	DAY2	Pain	Yes	24	56	
	DAY3	Pain	No	14	34	1.0000
	DAY3	Pain	Yes	27	66	
Liposomal	DAY0A	Pain	No	44	88	
	DAY0A	Pain	Yes	6	12	
	DAY0B	Pain	No	14	29	
	DAY0B	Pain	Yes	34	71	
	DAY1	Pain	No	16	33	
	DAY1	Pain	Yes	32	67	
	DAY2	Pain	No	16	33	
	DAY2	Pain	Yes	32	67	
	DAY3	Pain	No	12	25	
	DAY3	Pain	Yes	36	75	

Table 10. Binary Pain Responses

**Multiple Chi-square tests and Step-down Bonferroni method of Holm adjusted among variable types

A=end of appointment

B=before bed

Group	Period	Variable	N	Mean	Std Dev	Min	Max	p(adj.)**
Bupivacaine	DAY0-1	TOTAL	48	5	7	0	42	1.0000
	DAY2	TOTAL	42	4	7	0	40	1.0000
	DAY3	TOTAL	42	3	4	0	16	0.7906
Liposomal	DAY0-1	TOTAL	46	5	6	0	25	
	DAY2	TOTAL	46	4	4	0	21	
	DAY3	TOTAL	46	3	4	0	13	

Table 11. Total Non-narcotic Utilization (Number of Tablets)
*Mann-Whitney-Wilcoxon test
**Step-down Bonferroni method of Holm

Group	Period	Variable	N	Mean	Std Dev	Min	Max	P(adj.)**
Bupivacaine	DAY0-1	IBP	48	3	5	0	24	1.0000
		ACT	48	2	3	0	18	1.0000
	DAY2	IBP	42	2	5	0	24	1.0000
		ACT	42	2	4	0	16	1.0000
	DAY3	IBP	42	2	3	0	16	1.0000
		ACT	42	1	2	0	6	1.0000
Liposomal	DAY0-1	IBP	46	2	2	0	9	
		ACT	46	3	4	0	16	
	DAY2	IBP	46	2	2	0	8	
		ACT	46	2	3	0	14	
	DAY3	IBP	46	2	2	0	10	
		ACT	46	1	3	0	13	

Table 12. Acetaminophen and Ibuprofen Utilization (Number of Tablets)
*Mann-Whitney-Wilcoxon test
**Step-down Bonferroni method of Holm
IBP=Ibuprofen
ACT=Acetaminophen

Group	N	Used	Count	Percent
Bupivacaine	48	Yes	11/48	23
		No	37/48	77
Liposomal	46	Yes	15/46	33
		No	31/46	67

Table 13. Narcotic Utilization

Group	Period	Variable	N	Mean	Std Dev	Min	Max	p(adj.)**
Bupivacaine	DAY0-1	NARC	48	0.4	1	0	5	1.0000
	DAY2	NARC	42	0.3	1	0	5	0.3817
	DAY3	NARC	42	0.4	1	0	6	0.6189
Liposomal	DAY0-1	NARC	46	0.5	1	0	4	
	DAY2	NARC	46	0.7	1	0	5	
	DAY3	NARC	46	1	2	0	11	

Table 14. Narcotic Utilization (Number of Tablets)
*Mann-Whitney-Wilcoxon test
**Step-down Bonferroni method of Holm
NARC= Hydrocodone/acetaminophen 5mg/325mg

Group	Period	Unscheduled Visit
Bupivacaine	DAY0-1	3/50 (6%)
	DAY2	0
	DAY3	2/50 (4%)
Liposomal	DAY0-1	0
	DAY2	0
	DAY3	0

Table 15. Unscheduled Post-treatment Emergency Visits

Group	Jaw	Type	N Obs	N	Mean	Std Dev	Min	Max
Bupivacaine	MAX	INS	24	24	51	38	0	139
		PLC	24	24	57	37	0	140
		DEP	24	24	50	35	0	116
	MND	INS	26	26	76	44	0	170
		PLC	26	26	82	51	0	170
		DEP	26	26	64	48	0	170
Liposomal	MAX	INS	25	25	51	39	0	125
		PLC	25	25	56	45	0	139
		DEP	25	25	55	39	0	136
	MND	INS	25	25	58	39	0	140
		PLC	25	25	62	37	0	139
		DEP	25	25	70	40	0	150

Table 16. Primary Injection Pain as Rated on 170 mm VAS

* Randomization test

** Step-down Bonferroni method of Holm

***Maxillary Buccal Infiltration or Mandibular IANB

INS= Needle Insertion

PLC=Needle Placement

DEP=Solution Deposition

Group	Type	N Obs	N	Mean	Std Dev	Min	Max	p(adj)**
Bupivacaine	INS	50	49	21	33	0	113	0.2154
	PLC	50	49	26	37	0	137	0.2154
	DEP	50	49	34	45	0	170	0.2154
Liposomal	INS	50	48	34	38	0	118	
	PLC	50	48	40	43	22	140	
	DEP	50	48	46	44	0	140	

Table 17. Secondary Injection Pain as Rated on 170 mm VAS

* Randomization test

** Step-down Bonferroni method of Holm

*** Maxillary or Mandibular Buccal Infiltration

INS= Needle Insertion

PLC=Needle Placement

DEP=Solution Deposition

Group	Jaw	Stage	N	None (0 mm)	Mild (>0 mm, <54 mm)	Moderate (>54 mm, <114 mm)	Severe (>114 mm)
Bupivacaine	MAX	INS	24	1/24 (4%)	14/24 (58%)	7/24 (29%)	2/24 (8%)
		PLC	24	1/24 (4%)	12/24 (50%)	10/24 (42%)	1/24 (4%)
		DEP	24	3/24 (13%)	12/24 (50%)	8/24 (33%)	1/24 (4%)
	MND	INS	26	1/26 (4%)	11/26 (42%)	9/26 (35%)	5/26 (19%)
		PLC	26	3/26 (12%)	7/26 (27%)	8/26 (31%)	8/26 (31%)
		DEP	26	2/26 (8%)	12/26 (46%)	7/26 (27%)	5/26 (19%)
Liposomal	MAX	INS	25	4/25 (16%)	11/25 (44%)	8/25 (32%)	2/25 (8%)
		PLC	25	4/25 (16%)	10/25 (40%)	6/25 (24%)	5/25 (20%)
		DEP	25	3/25 (12%)	9/25 (36%)	11/25 (44%)	2/25 (8%)
	MND	INS	25	1/25 (4%)	13/25 (52%)	9/25 (36%)	2/25 (8%)
		PLC	25	2/25 (8%)	10/25 (40%)	11/25 (44%)	2/25 (8%)
		DEP	25	1/25 (4%)	11/25 (44%)	10/25 (40%)	3/25 (12%)

Table 18. Primary Injection Pain by Stage Using Categorical Values of the 170 mm VAS

*** Maxillary Infiltration or Mandibular IANB
INS= Needle Insertion
PLC=Needle Placement
DEP=Solution Deposition

Group	Stage	N	None (0mm)	Mild (>0 mm, ≤54 mm)	Moderate (>54 mm, <114 mm)	Severe (≥114 mm)
Bupivacaine	INS	49	21/49 (43%)	20/49 (41%)	8/49 (16%)	0/49 (0%)
	PLC	49	21/49 (43%)	17/49 (38%)	9/49 (18%)	2/49 (4%)
	DEP	49	15/49 (31%)	20/49 (48%)	10/49 (20%)	4/49 (8%)
Liposomal	INS	48	13/48 (10%)	23/48 (48%)	11/48 (34%)	1/48 (8%)
	PLC	48	12/48 (12%)	19/48 (40%)	15/48 (34%)	2/48 (4%)
	DEP	48	8/48 (17%)	21/48 (44%)	16/48 (33%)	3/48 (6%)

Table 19. Secondary Injection Pain by Stage Using Categorical Values of the 170 mm VAS

*** Maxillary or Mandibular Buccal Infiltration
INS= Needle Insertion
PLC=Needle Placement
DEP=Solution Deposition

Variable	Group	N	Mean	Std Dev	Median	Min	Max	p*
Satisfaction	Bupivacaine	44	60	34	67	0	100	0.9770
	Liposomal	45	59	31	63	0	100	

Table 20. Satisfaction with Procedure as Rated on 100 mm VAS
*Mann-Whitney-Wilcoxon test

Group	N	Satisfaction	Count	Percent
Bupivacaine	44	Not Satisfied (0mm)	5	11
		Somewhat Satisfied (>0mm to ≤ 33mm)	8	18
		Moderately Satisfied (≥33mm to <66mm)	4	9
		Completely Satisfied (≥66mm)	27	61
Liposomal	45	Not Satisfied (0mm)	3	7
		Somewhat Satisfied (>0mm to ≤ 33mm)	11	24
		Moderately Satisfied (≥33mm to <66mm)	10	22
		Completely Satisfied (≥66mm)	21	47

Table 21. Percent Satisfaction by Satisfaction Categories

Group	Question	Outcome	Count	Percent	p**
Bupivacaine	1	Missing	6	.	1.0000
	1	No	4	9	
	1	Yes	40	91	
	2	Missing	6	.	**0.0298**
	2	No	1	2	
	2	Yes	43	98	
	3A	Missing	5	.	0.5264
	3A	No	26	58	
	3A	Yes	19	42	
	3B	Missing	23	.	1.0000
	3B	Longer	24	89	
	3B	Shorter	3	11	
	4	Missing	5	.	1.0000
	4	Numb	43	96	
	4	Pain	2	4	
Liposomal	1	Missing	6	.	
	1	No	4	9	
	1	Yes	40	91	
	2	Missing	6	.	
	2	No	8	18	
	2	Yes	36	82	
	3A	Missing	5	.	
	3A	No	22	49	
	3A	Yes	23	51	
	3B	Missing	29	.	
	3B	Longer	18	86	
	3B	Shorter	3	14	
	4	Missing	5	.	
	4	Numb	43	96	
	4	Pain	2	4	

Table 22. Post-injection Questionnaire

**Fisher exact test

1. Did being numb help with your pain?

2. Were you satisfied with the level of pain control achieved while numb?

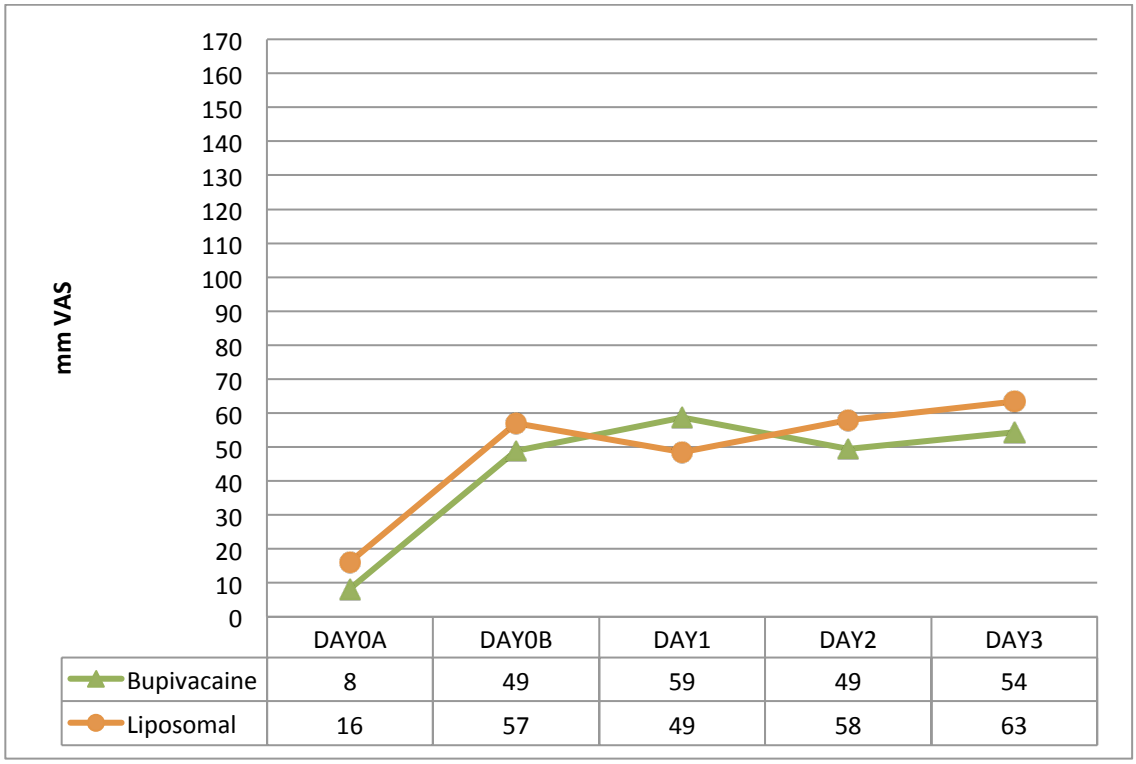
3A. Were you satisfied with the length of time that you were numb?

3B. If no, would you rather have been numb a longer time / shorter time.

4. Would you rather be numb or feel pain?

APPENDIX B

FIGURES



	DAY0A	DAY0B	DAY1	DAY2	DAY3
Bupivacaine	8	49	59	49	54
Liposomal	16	57	49	58	63

Figure 1. Pain by Day (mean in mm on 170 mm VAS)

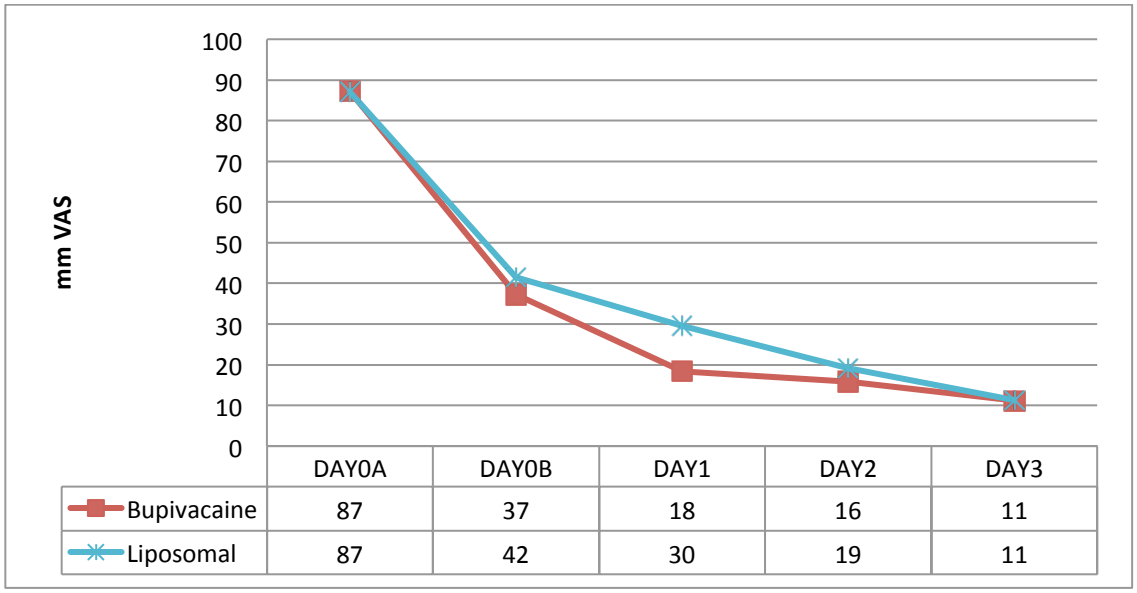


Figure 2. Tooth Numbness by Day (mean in mm on 100 mm VAS)

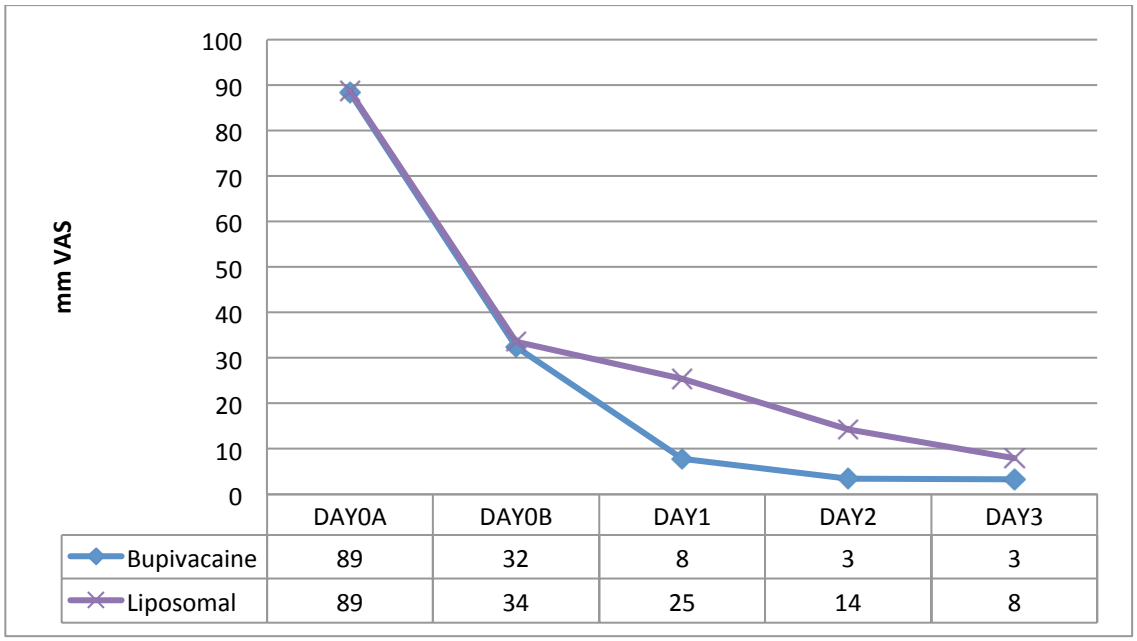


Figure 3. Lip and Cheek Numbness by Day (mean in mm on 100 mm VAS)

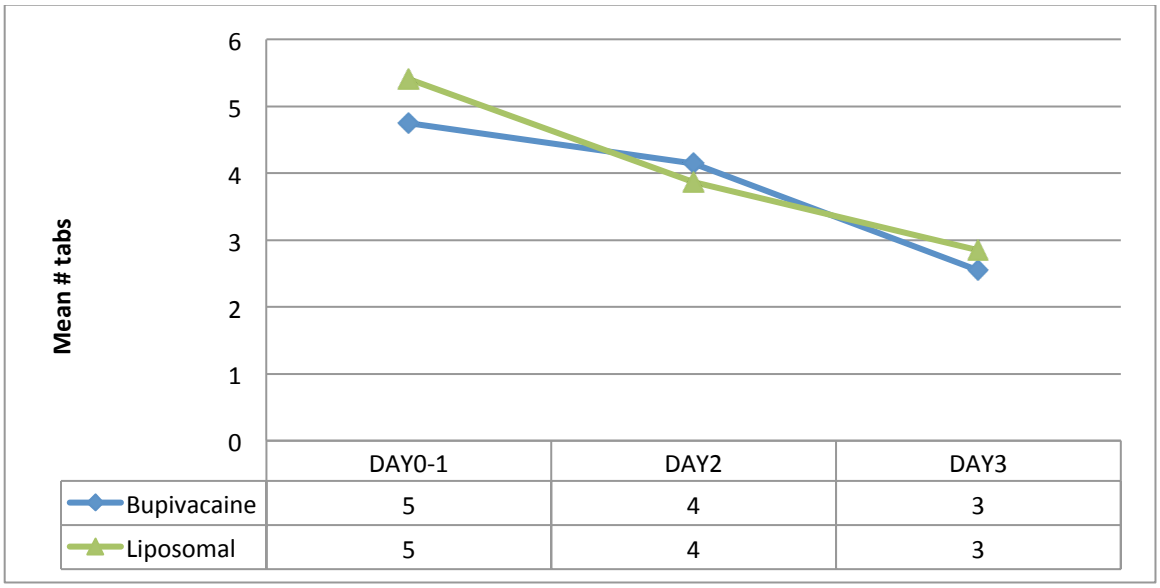
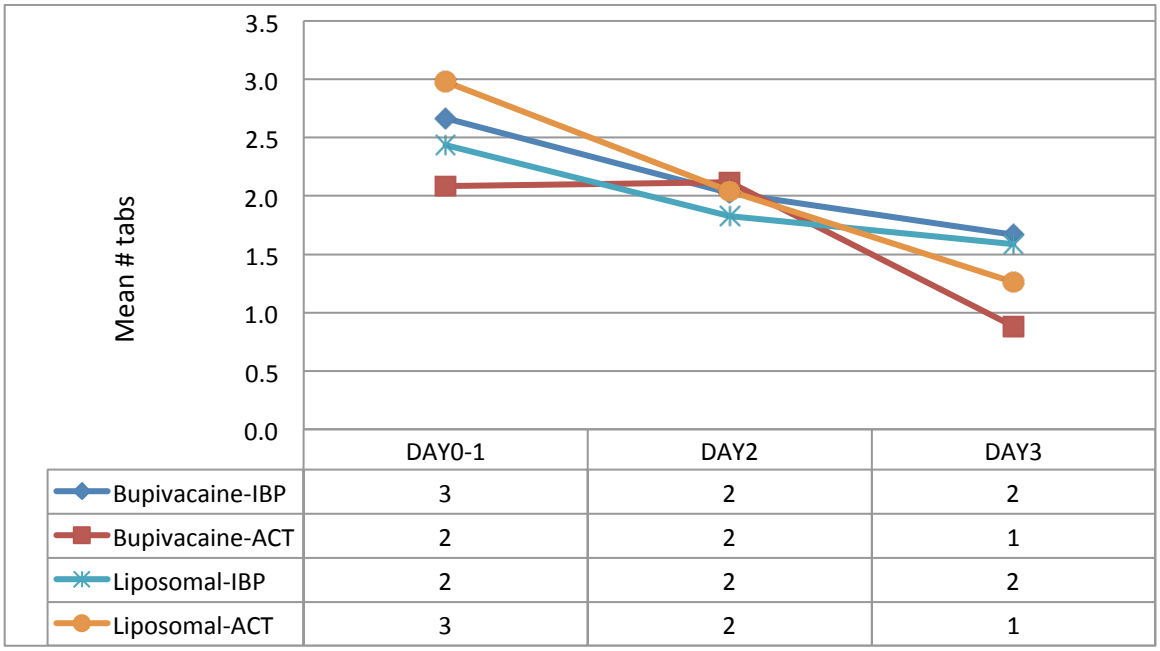


Figure 4. Total Non-narcotic Utilization by Day (mean number of tablets)



	DAY0-1	DAY2	DAY3
Bupivacaine-IBP	3	2	2
Bupivacaine-ACT	2	2	1
Liposomal-IBP	2	2	2
Liposomal-ACT	3	2	1

Figure 5. Ibuprofen and Acetaminophen Utilization by Day (mean number of tablets)

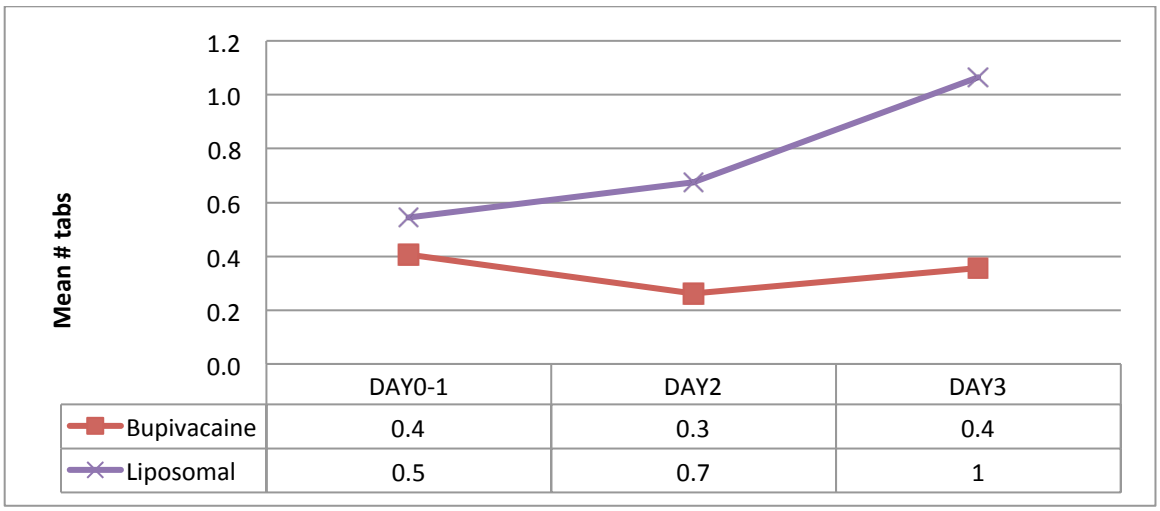


Figure 6. Narcotic Utilization by Day (mean number of tablets)

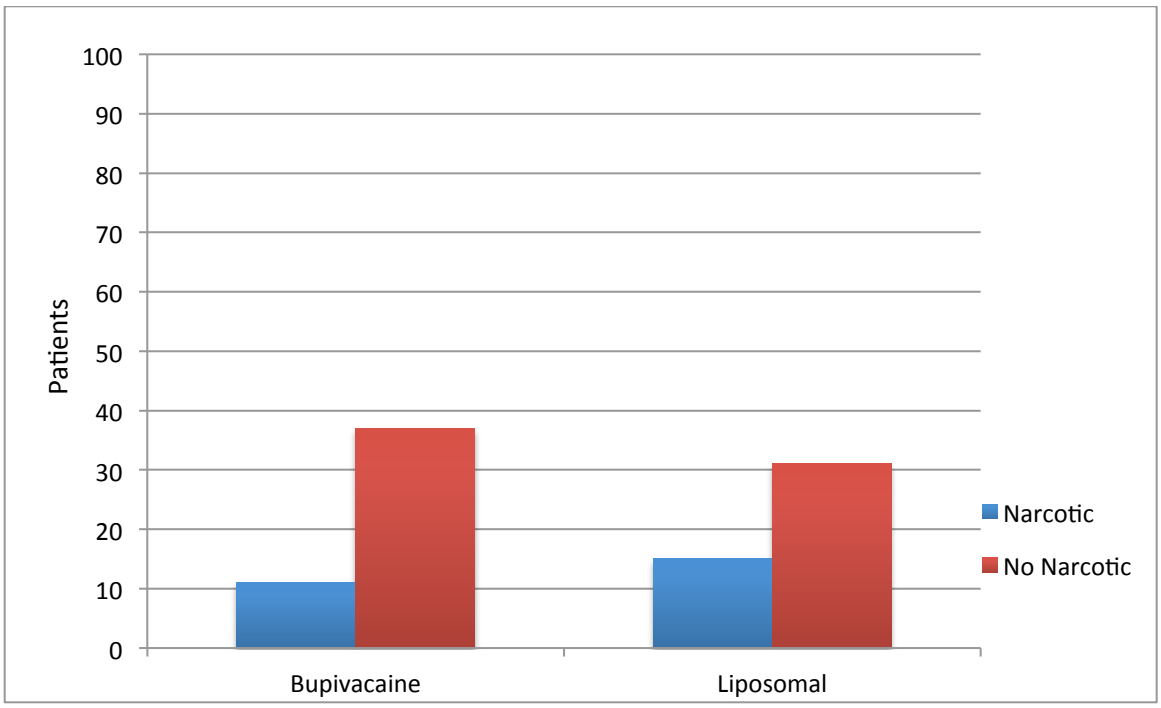


Figure 7. Narcotic Utilization by Group

APPENDIX C

CONSENT FORM

The Ohio State University Consent to Participate in Research

Study Title:	**A comparison of liposomal bupivacaine and bupivacaine for pain control in untreated symptomatic vital teeth**
Principal Investigator:	**Dr. Melissa Drum**
Sponsor:	Not applicable

- **This is a consent form for research participation.** It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate.
- **Your participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The Ohio State University. If you are a student or employee at Ohio State, your decision will not affect your grades or employment status.
- **You may or may not benefit as a result of participating in this study.** Also, as explained below, your participation may result in unintended or harmful effects for you that may be minor or may be serious depending on the nature of the research.
- **You will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.** If you decide to participate, you will be asked to sign this form and will receive a copy of the form. You are being asked to consider participating in this study for the reasons explained below.

1. Why is this study being done?

The purpose of this study is to compare the effect of liposomal bupivacaine (a long acting numbing solution) to bupivacaine (a long acting numbing solution) for pain control in patients with untreated painful teeth.

2. How many people will take part in this study?

One hundred people (100) will take part in this study.

3. What will happen if I take part in this study?

You have a tooth, which is hurting (painful), and you are aware that it needs a root canal. If you decide to participate in this study, you will be required to complete a medical history questionnaire. Numbing solution will then be administered in a routine manner to make your tooth numb. At the end of today's appointment, either a long acting local anesthetic (it is called Exparel®and is a numbing solution) or a long acting anesthetic (it is called Marcaine and is a numbing solution) will be administered in a routine manner, after which you will rate the pain of injection and rate the level of numbness and pain that you feel. Neither you nor the doctor will know which anesthetic solution you receive. Both the liposomal bupivacaine (Exparel®, Pacira Pharmaceuticals,San Diego, CA) and regular bupivacaine (Marcaine, Cook-Waite, Atlanta, Ga) you receive have been approved by the Food and Drug Administration (FDA) for dental and medical use. The purpose of this study is to see if the long acting numbing solution (Exparel®, liposomal bupivacaine) prolongs numbness and decreases pain associated with your tooth when compared to the long acting numbing solution (Marcaine, bupivacaine).

If you are a female and are pregnant or nursing, you will not be able to participate. If you are a woman able to have children, you will be required to take a urine pregnancy test before participation. The study requires one appointment but you will need at least one additional appointment to perform the root canal if you elect to save your tooth.

You will be asked to rate the pain you are having prior to any treatment. You will be asked to complete a questionnaire regarding your level of anxiety. The tooth causing your pain will first be tested to insure an accurate diagnosis. It will first be tested with a cold cotton pellet chilled with an ice spray. Your tooth may hurt for a few moments after being tested with the cold. The cold pellet will be removed immediately after you feel the sensation in your tooth. The cold test is used routinely.

In order to numb your tooth, an injection (shot) will be given in the tissue that surrounds your tooth. You will be asked to rate the amount of pain you feel when the injection (shot) is being given. You will do this by marking your pain with a pen on a line graph.

Following the injection (shot) of numbing solution the doctor will begin asking you every 5 minutes for 20 minutes whether you are experiencing pain, lip or cheek numbness, and tooth numbness. At 20 minutes if your lip or cheek is not numb, you will not be able to continue with the study. Alternative treatment will be provided. An additional injection (shot) of numbing solution may be given, if necessary, to help reduce your pain. If you are numb, no root canal treatment will be started today.

At the end of your appointment, you will be given a return appointment 4-7 days later to start root canal treatment, as well as medications and a questionnaire to take home. You

will be asked to keep a diary to record your pain level after the injection (shot) and the amount and type of pain medication taken over the 3 days following your appointment. If the ibuprofen/acetaminophen does not control your pain, a stronger pain medication may be prescribed. Should you experience significant pain, not relieved by the pain medication before the fourth to seventh day appointment, you will be seen immediately and root canal treatment will be rendered at that time.

Your participation or non-participation will have no effect on whether you will receive emergency root canal treatment. You will be responsible for the emergency root canal and tooth restoration fee.

4. How long will I be in the study?

You will have one appointment, which will last approximately 45 minutes. You will be asked to keep a diary to record your pain level after the injection (shot) and the amount and type of pain medication taken over the 3 days following your appointment. You will be scheduled for the root canal treatment 4-7 days later.

5. Can I stop being in the study?

You may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. Your decision will not affect your future relationship with The Ohio State University.

6. What risks, side effects or discomforts can I expect from being in the study?

You may have an allergic reaction (rash, difficulty breathing) to ibuprofen, which is very rare, upset stomach, nausea, heartburn, diarrhea, gastric bleeding, and increased bleeding. You may have an allergic reaction (rash, difficulty breathing) to acetaminophen, which is very rare, upset stomach, nausea and liver trouble. You may have pain associated with the numbing solution or soreness at the site of the injections (shots) for approximately two days after the numbness wears off. Where you receive the injection (shot), you may have swelling (hematoma-a collection of blood in your mouth) or a bruise may develop. You may experience a feeling of anxiety, lightheadedness or fainting, and or a temporary increase in your heart rate. Your toothache may stay the same or worsen during the study. The tingling sensation and/or slight discomfort (pain) produced by the cold ice spray may be uncomfortable to you. You may have an allergic reaction to the numbing solution (itching or hives, very rare), or have an unexpected infection (rare) which could result in permanent nerve damage. You may have soreness of your gum tissue for a few days or a possible altered sensation of your lip or tongue that may last up to a few weeks. Your tooth may feel sore to bite on for a few days.

If you are a woman able to have children, you will be questioned regarding pregnancy or suspected pregnancy and will not be allowed to participate if pregnant, suspect a pregnancy, trying to become pregnant, or nursing. Additionally, you will be required to take a urine pregnancy test before you can start this study. The reason for excluding pregnant or potentially pregnant women is an attempt to minimize this population in the study because the potential risks to the fetus and nursing baby are unknown.

7. What benefits can I expect from being in the study?

You will not directly benefit from this study other than possible pain reduction or numbness.

8. What other choices do I have if I do not take part in the study?

You may have the emergency root canal procedure completed without participating in the study. You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled.

9. Will my study-related information be kept confidential?

Efforts will be made to keep your study-related information confidential. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

Also, your records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- The sponsor supporting the study, their agents or study monitors; and
- Your insurance company (if charges are billed to insurance).

If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic, or physician's office records. Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information.

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

You may also be asked to sign a separate Health Insurance Portability and Accountability Act (HIPAA) research authorization form if the study involves the use of your protected health information.

10. What are the costs of taking part in this study?

Costs such as parking and future treatment will not be reimbursed in this study. Should you request the strong pain medication, you will be responsible for the cost incurred.

11. Will I be paid for taking part in this study?

You will receive up to $100 to participate in this study. If you complete the first visit, you will receive $50. You will receive an additional $50 upon completion and return of the 3-day diary and return of all unused study medications. By law, payments to subjects are considered taxable income**.**

12. What happens if I am injured because I took part in this study?

If you suffer an injury from participating in this study, you should notify the researcher or study doctor immediately, who will determine if you should obtain medical treatment at The Ohio State University Medical Center.

The cost for this treatment will be billed to you or your medical or hospital insurance. The Ohio State University has no funds set aside for the payment of health care expenses for this study.

13. What are my rights if I take part in this study?

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a participant in this study.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

An Institutional Review Board responsible for human subjects research at The Ohio State University reviewed this research project and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of participants in research.

14. Who can answer my questions about the study?

For questions, concerns, or complaints about the study you may contact Dr. Melissa Drum, Dr. Sara Fowler or Dr. Kristy Bultema at 614 – 292-5399

For questions about your rights as a participant in this study or to discuss other study related concerns or complaints with someone who is not part of the research team, you may contact Ms. Sandra Meadows in the Office of Responsible Research Practices at 1-800-678-6251.

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact Dr. Melissa Drum, Dr. Sara Fowler or Dr. Kristy Bultema at 614 – 292-5399.

Signing the consent form

I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this form**.**

Printed name of subject	**Signature of subject**
	AM/PM
	Date and time
Printed name of person authorized to consent for subject (when applicable)	**Signature of person authorized to consent for subject (when applicable)**

		AM/PM
Relationship to the subject	**Date and time**	

Investigator/Research Staff

I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

Printed name of person obtaining consent	**Signature of person obtaining consent**	
		AM/PM
	Date and time	

Witness(es) - *May be left blank if not required by the IRB*

Printed name of witness	**Signature of witness**	
		AM/PM
	Date and time	
Printed name of witness	**Signature of witness**	
		AM/PM
	Date and time	

APPENDIX D

PRIVACY FORM

THE OHIO STATE UNIVERSITY
AUTHORIZATION TO USE
PERSONAL HEALTH INFORMATION IN RESEARCH

Title of the Study: A comparison of liposomal bupivacaine and bupivacaine for pain control in untreated symptomatic vital teeth

Protocol Number: 2013H0418

Principal Investigator: Melissa Drum DDS, MS

Subject Name_____

Before researchers use or share any health information about you as part of this study, The Ohio State University is required to obtain your authorization. This helps explain to you how this information will be used or shared with others involved in the study.

- The Ohio State University and its hospitals, clinics, health-care providers, and researchers are required to protect the privacy of your health information.
- You should have received a Notice of Privacy Practices when you received health care services here. If not, let us know and a copy will be given to you. Please carefully review this information. Ask if you have any questions or do not understand any parts of this notice.
- If you agree to take part in this study your health information will be used and shared with others involved in this study. Also, any new health information about you that comes from tests or other parts of this study will be shared with those involved in this study.
- Health information about you that will be used or shared with others involved in this study may include your research record and any health care records at The Ohio State University. For example, this may include your medical records, x-rays, or laboratory results. Psychotherapy notes in your health records (if any) will not, however, be shared or used. Use of these notes requires a separate, signed authorization.

Please read the information carefully before signing this form. Please ask if you have any questions about this authorization, the university's Notice of Privacy Practices or the study before signing this form.

Those Who May Use, Share, and Receive Your Information as Part of This Study

- Researchers and staff at The Ohio State University will use, share, and receive your personal health information for this research study. Authorized Ohio State staff not involved in the study may be aware that you are participating in a research study and have access to your information. If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic, or physician's office records.

Initials/Date: _____

- Those who oversee the study will have access to your information, including the following:
    - Members and staff of The Ohio State University's Institutional Review Boards, including the Western Institutional Review Board
    - The Ohio State University Office of Responsible Research Practices
    - University data safety monitoring committees
    - The Ohio State University Office of Research.

- Your health information may also be shared with federal and state agencies that have oversight of the study or to whom access is required under the law. These may include the following:
    - Food and Drug Administration
    - Office for Human Research Protections
    - National Institutes of Health
    - Ohio Department of Job and Family Services.

- These researchers, companies and/or organization(s) outside of The Ohio State University may also use, share and receive your health information in connection with this study:
    - NONE

The information that is shared with those listed above may no longer be protected by federal privacy rules.

Authorization Period

This authorization will not expire unless you change your mind and revoke it in writing. There is no set date at which your information will be destroyed or no longer used. This is because the information used and created during the study may be analyzed for many years, and it is not possible to know when this will be completed.

Initials/Date_____

Signing the Authorization

- You have the right to refuse to sign this authorization. Your health care outside of the study, payment for your health care, and your health care benefits will not be affected if you choose not to sign this form.

- You will not be able to take part in this study and will not receive any study treatments if you do not sign this form.
- If you sign this authorization, you may change your mind at any time. Researchers may continue to use information collected up until the time that you formally changed your mind. If you change your mind, your authorization must be revoked in writing. To revoke your authorization, please write to: *Dr. Melissa Drum at the College of Dentistry, 305 w 12th avenue, the Ohio State University, Columbus, Ohio 43218 or Dr. Fonda Robinson at the College of Dentistry, 305 w 12th avenue, the Ohio State University, Columbus, Ohio 43218.*
- Signing this authorization also means that you will not be able to see or copy your study-related information until the study is completed. This includes any portion of your medical records that describes study treatment.

Contacts for Questions

- If you have any questions relating to your privacy rights, please contact: *Dr. Fonda Robinson at the College of Dentistry, 305 w 12th avenue, the Ohio State University, Columbus, Ohio 43218. Phone:(614)292-6983.*
- If you have any questions relating to the research, please contact: *Dr. Melissa Drum at the College of Dentistry, 305 W. 12th Ave., The Ohio State University, Columbus, OH 43210. Phone:(614)292-3596.*

Signature

I have read (or someone has read to me) this form and have been able to ask questions. All of my questions about this form have been answered to my satisfaction. By signing below, I permit *Dr. Melissa Drum* and the others listed on this form to use and share my personal health information for this study. I will be given a copy of this signed form.

Signature_____
_____
(Subject or Legally Authorized Representative)

Print Name _____ Date_____ Time _____ AM/PM

_____
(If legal representative, also print relationship to subject)

APPENDIX E

CORAH DENTAL ANXIETY SCALE

Code#:_____

Pre-Injection Questionnaire

PLEASE ANSWER THE FOLLOWING QUESTIONS BY CIRCLING THE ANSWER THAT BEST DESCRIBES HOW YOU FEEL.

1. If you had to go to the dentist tomorrow, how would you feel about it?
a) I would look forward to it as a reasonably enjoyable experience.
b) I wouldn't care one way or the other.
c) I would be a little uneasy about it.
d) I would be afraid that it would be unpleasant and painful.
e) I would be very afraid of what the dentist might do.

2. When you are waiting in the dentist's office for you turn in the chair, how do you feel?
a) Relaxed.
b) A little uneasy.
c) Tense.
d) Anxious.
e) So anxious that I sometimes break in a sweat or almost feel physically sick.

3. When you are in the dentist's chair waiting while she/he gets her/his drill ready to begin working on your teeth, how do you feel?
a) Relaxed.
b) A little uneasy.
c) Tense.
d) Anxious.
e) So anxious that I sometimes break in a sweat or almost feel physically sick.

4. You are in the dentist's chair to have your teeth cleaned. While you are waiting and the dentist is getting out the instruments, which she/he will use to scrape your teeth around your gums, how do you feel?
a) Relaxed.
b) A little uneasy.
c) Tense.
d) Anxious.
e) So anxious that I sometimes break in a sweat or almost feel physically sick.

APPENDIX F

INITIAL PAIN VISUAL ANALOG SCALE

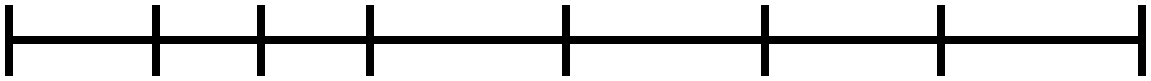
(Note: VAS not drawn to scale)

Date: _____ Code #: _____

Tooth:_____

Initial Pain Rating

1. Please mark a vertical line " | " on the line below to rank the level of pain you are feeling today.



APPENDIX G

PRIMARY ANESTHETIC INJECTION VISUAL ANALOG SCALE

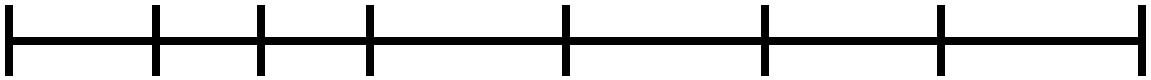
(Note: VAS not drawn to scale)

Date: _____ Code #: _____

Injection Pain Rating-Lidocaine

Needle Insertion

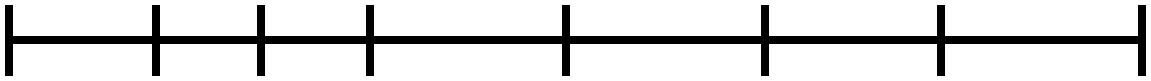
2. Please mark a vertical line " | " on the line below to rank the level of pain felt during needle insertion.



None Faint Weak Mild Moderate Strong Intense Maximum Possible

Needle Placement

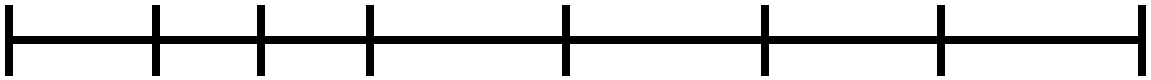
3. Please mark a vertical line " | " on the line below to rank the level of pain felt during needle placement.



None Faint Weak Mild Moderate Strong Intense Maximum Possible

Solution Deposition

4. Please mark a vertical line " | " on the line below to rank the level of pain felt during solution deposition.



None Faint Weak Mild Moderate Strong Intense Maximum Possible

APPENDIX H

SECONDARY ANESTHETIC INJECTION VISUAL ANALOG SCALE

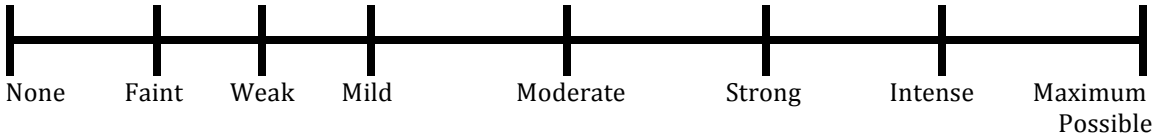
(Note: VAS not drawn to scale)

Date: _____ Code #: _____

Injection Pain Rating-STUDY DRUG

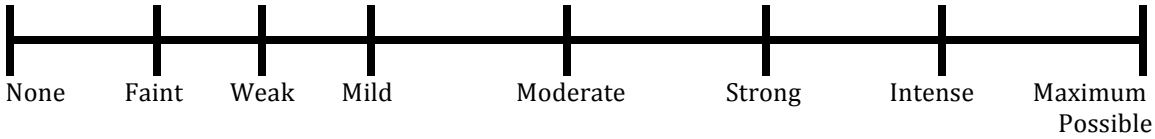
Needle Insertion

5. Please mark a vertical line " | " on the line below to rank the level of pain felt during needle insertion.



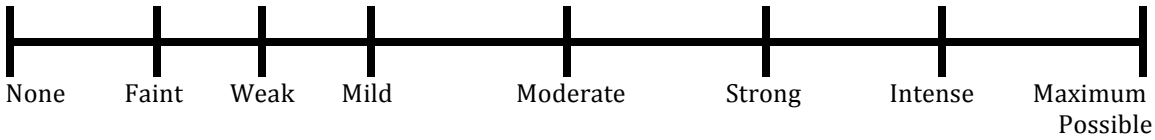
Needle Placement

6. Please mark a vertical line " | " on the line below to rank the level of pain felt during needle placement.



Solution Deposition

7. Please mark a vertical line " | " on the line below to rank the level of pain felt during solution deposition.



APPENDIX I

POST-INJECTION PAIN AND NUMBNESS RATING VISUAL ANALOG SCALE AND BINARY RESPONSE

(Note: VAS not drawn to scale)

Date: _____ Code #: _____

Post-injection Pain and Numbness Rating

Time elapsed since injection: _____ minutes

Is your **lip or cheek** numb? **Yes / No**

8. Please mark a vertical line " | " on the line below to rank the level numbness.

Not Numb |——————————————————————| **Completely Numb**

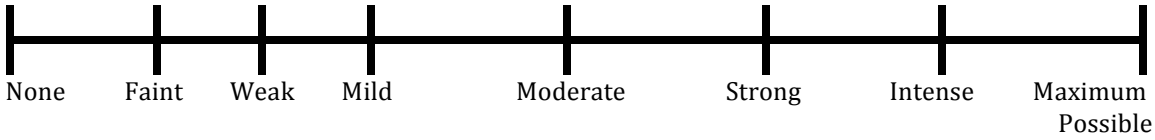
Is your **tooth** numb? **Yes / No**

9. Please mark a vertical line " | " on the line below to rank the level numbness.

Not Numb |——————————————————————| **Completely Numb**

Are you feeling pain? **Yes / No**

10. Please mark a vertical line " | " on the line below to rank the level of pain.



APPENDIX J

POST-TREATMENT SURVEY
(Note: VAS not drawn to scale)

Code #_____ Tooth #_____

Date:_____

DAY 0 (day of appointment)

If your numbness has worn off, please record the time _____am/pm

Before bed, please complete the following.

Time:_____

A. Is your **lip or cheek** still numb? **Yes / No**

Please mark a vertical line "|" on the line below to rank the level of **lip or cheek** numbness.

Not Numb |_____| **Completely Numb**

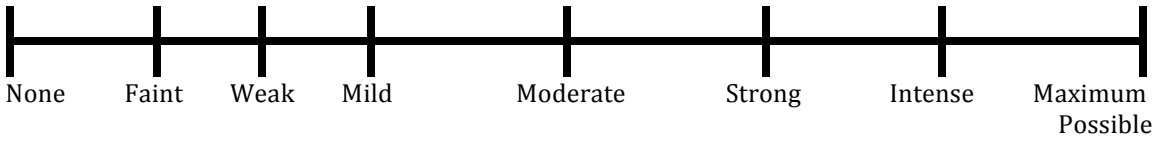
B. Is your **tooth** still numb? **Yes / No**

Please mark a vertical line "|" on the line below to rank the level of **tooth** numbness.

Not Numb |_____| **Completely Numb**

C. Do you have any **pain**? **Yes / No**

Place mark a vertical line "|" on the line below to rank the level of pain



If **Yes**, please record the time of day when the pain began.

Time:_____

DAY 1 (day after appointment)

Date:_____

When you wake up in the morning, please complete the following.

Time:_____

A. Is your **lip or cheek** still numb? **Yes / No**

Please mark a vertical line "|" on the line below to rank the level of **lip or cheek** numbness.

Not Numb |_____| **Completely Numb**

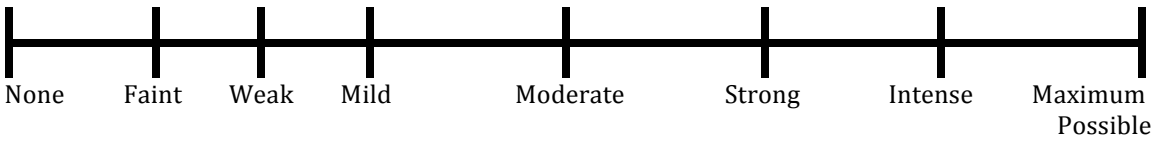
B. Is your **tooth** still numb? **Yes / No**

Please mark a vertical line "|" on the line below to rank the level of **tooth** numbness.

Not Numb |_____| **Completely Numb**

C. Do you have any **pain**? **Yes / No**

Place mark a vertical line "|"on the line below to rank the level of pain



If **Yes**, please record the time of day when the pain began.

Time:_____

D. Have you taken any pain medication since your treatment? **Yes / No**

If yes, please complete the following table indicating the time and number of tablets since your treatment.

Time	Number of Ibuprofen (Yellow)	Number of Acetaminophen (White)	Number of escape medication (if needed)
: am pm			
: am pm			
: am pm			
: am pm			
: am pm			
: am pm			
: am pm			
: am pm			

When you took medication what happened to your pain?

_____

_____

_____

DAY 2

Date:_____

When you wake up in the morning, please complete the following.

Time:_____

A. Is your **lip or cheek** still numb? **Yes / No**

Please mark a vertical line "|" on the line below to rank the level of **lip or cheek** numbness.

Not Numb |_____| **Completely Numb**

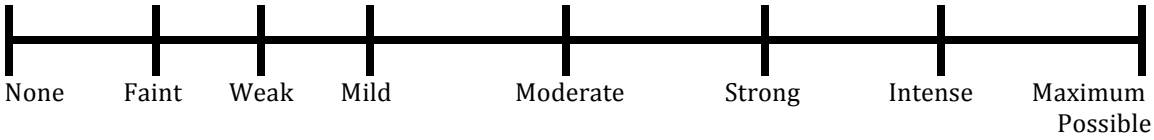
B. Is your **tooth** still numb? **Yes / No**

Please mark a vertical line "|" on the line below to rank the level of **tooth** numbness.

Not Numb |_____| **Completely Numb**

C. Do you have any **pain**? **Yes / No**

Place mark a vertical line "|" on the line below to rank the level of pain



If **Yes**, please record the time of day when the pain began.

Time:_____

D. Have you taken any pain medication in the past 24 hours? **Yes / No**

If yes, please complete the following table indicating the time and number of tablets taken.

Time	Number of Ibuprofen (yellow)	Number of Acetaminophen (white)	Number of escape medication (if needed)
: am pm			
: am pm			
: am pm			
: am pm			
: am pm			
: am pm			
: am pm			
: am pm			

When you took medication what happened to your pain?

_____
_____
_____

DAY 3

Date:_____

When you wake up in the morning, please complete the following.

Time:_____

A. Is your **lip or cheek** still numb? **Yes / No**

Please mark a vertical line "|" on the line below to rank the level of **lip or cheek** numbness.

Not Numb |_____| **Completely Numb**

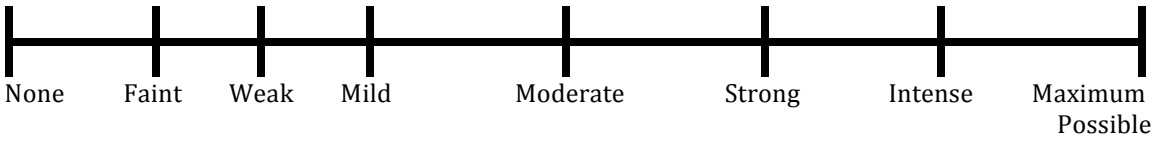
B. Is your **tooth** still numb? **Yes / No**

Please mark a vertical line "|" on the line below to rank the level of **tooth** numbness.

Not Numb |_____| **Completely Numb**

C. Do you have any **pain**? **Yes / No**

Place mark a vertical line "|" on the line below to rank the level of pain



If **Yes**, please record the time of day when the pain began. Time:_____

D. Have you taken any pain medication in the past 24 hours? **Yes / No**

If yes, please complete the following table indicating the time and number of tablets taken.

Time	Number of Ibuprofen (yellow)	Number of Acetaminophen (white)	Number of escape medication (if needed)
: am pm			
: am pm			
: am pm			
: am pm			
: am pm			
: am pm			
: am pm			
: am pm			

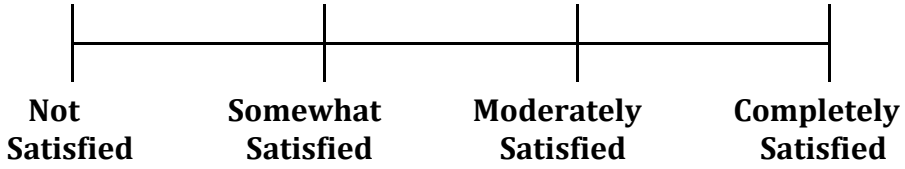
When you took medication what happened to your pain?

_____
_____
_____

Date: _____ Code #: _____

Satisfaction Rating

Mark a vertical line " | " on the point on the scale line that best describes your satisfaction with this treatment (numbing).



Did being numb help with your pain? **Yes / No**

Were you satisfied with the level of pain control achieved while numb? **Yes / No**

Were you satisfied with the length of time that you were numb? **Yes / No**

If **no**, would you rather have been numb a **longer time / shorter time** (please circle)

Would you rather be numb or feel pain? **Numb / Pain**

What did you like about this treatment?

_____
_____
_____
_____
_____

What did you dislike about this treatment?

_____
_____
_____
_____
_____