THE EFFECT OF PREOPERATIVE ACETAMINOPHEN/HYDROCODONE ON THE EFFICACY OF THE INFERIOR ALVEOLAR NERVE BLOCK IN PATIENTS WITH SYMPTOMATIC IRREVERSIBLE PULPITIS

A Thesis

Presented in Partial Fulfillment of the Requirements for

the Degree of Master of Science in the

Graduate School of The Ohio State University

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ABSTRACT

The inferior alveolar nerve block (IANB) is frequently used as a mandibular injection technique for achieving local anesthesia for endodontic treatment. Successful anesthesia, however, is not always achieved with the IANB. Studies have suggested that preoperative medications may increase the ability of clinicians to achieve profound pulpal anesthesia in conjunction with local anesthesia techniques. Acetaminophen/hydrocodone combination medications have been shown to effectively manage pain in a variety of dental pain models. The purpose of this prospective, randomized, double-blind, placebo-controlled study was to determine the effect of the administration of acetaminophen/hydrocodone on the efficacy of the IANB in patients with symptomatic irreversible pulpitis. One hundred emergency patients diagnosed with symptomatic irreversible pulpitis of a mandibular posterior tooth randomly received (in a double-blind manner) either 10 mg hydrocodone and 1000 mg acetaminophen (divided into four capsules) or an identical placebo 60 minutes before the administration of a conventional IANB. Fifteen minutes after administration of the IANB, profound lip numbness was confirmed, and endodontic access was initiated. Determination of success was, no or mild pain (≤54 mm on a 170 mm visual analog scale) on access or instrumentation. The success rate for the IANB was 32% with the acetaminophen/hydrocodone group and 28% with the placebo group, with no significant difference (p = 0.66) between the groups. For
mandibular posterior teeth, a preoperative dose of 10/1000 mg (hydrocodone/acetaminophen) did not result in a statistically significant increase of the success rate of the IAN block in patients with symptomatic irreversible pulpitis.
DEDICATION

To my supportive, patient, and loving family. To my wife Brittney who works twice as hard as I do, and who takes care of me like her fourth child. To my unconditionally loving kids, “Princess Isabelle”, “Maximus Aurelius”, and “Katey-bug”.
ACKNOWLEDGMENTS

To Dr. Drum: Thank you for working so hard at everything you do. I’ve never known someone that has taught me so much and has equally as much, made me laugh. I look up to you so much…when I’m sitting down…on the floor.

To Dr. Reader: You are the reason I’m in endodontics. I don’t say that lightly. The more I learned about you while in dental school, the more I knew that I wouldn’t settle for training under anyone else. Thank you so much for taking a chance on me.

To Dr. Nusstein: We are so lucky to have someone like you. Thank you for always being so kind and complimentary, even when I know I don’t deserve it. I can’t say enough how much I appreciate your passion for endodontics and for instilling that passion in me. Thank you.

To Dr. Beck: I hope you realize you’re worth more than your weight in gold. All residents have sat around many times thanking our lucky stars that you are as smart as you are. You make all of our live easier. Thank you.
To my fellow residents, Mark Conard, Matt Balasco, and Lisa Leone Poweski: What a ride huh?!? It was a blast wasn’t it! So many great memories, and more to come. Thank you for your friendships. I’ll always consider each of you a great friend.
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CHAPTER 1

INTRODUCTION

The inferior alveolar nerve block (IANB) is used in endodontics to achieve local anesthesia of mandibular teeth. Although this technique seems to be the best available injection for mandibular anesthesia, success has been shown to be from 51% in first molars to 10% in central incisors in patients with normal healthy dental pulp (1-16). With this poor rate of success, it is important to explore ways to improve the IANB.

To further complicate the ability of the IANB to successfully anesthetize mandibular teeth, teeth with unhealthy, inflamed pulp tissue can be even more difficult to anesthetize. These teeth are diagnosed with symptomatic irreversible pulpitis. The success rate for the IANB in mandibular teeth in this condition has been shown to be 23% to 64.2% (17-20).

Reader and co-authors suggest multiple explanations why profound pulpal anesthesia does not always occur even when soft tissue anesthesia is provided (16). A theory has been suggested that involves lowered pH of inflamed tissue which reduces the amount of the base form of anesthetic that is available to penetrate the nerve membrane.
This theory, however, does not explain the failure of the IANB on a mandibular tooth in which the anesthetic solution is deposited in a location in where there is not inflammation (16).

Another possible explanation for the failure is nerves often arise from inflamed tissue that may alter the resting potentials and may decrease their excitability thresholds (16). Some sodium channels, termed tetrodotoxin-resistant (TTX-r), have been shown to be resistant to local anesthetics. It is also possible that there is increased expression of sodium channels in the pulps of teeth diagnosed with symptomatic irreversible pulpitis (16). Also, the lower pain thresholds of anxious patients may be a factor in the failure of local anesthesia (16).

Pulpitis in human dentition can be described as a diseased state of teeth caused by any insult that disrupts the healthy pulp. This pathology can cause intermittent or spontaneous pain. Teeth in this state can respond differently to stimuli that would be considered normal. This is referred to as hypersensitivity or allodynia (21). An extremely cold stimulus can be very helpful in the diagnosis of pulpitis. Pressure, heat, and especially cold sensations can be exaggerated and or prolonged. When pulpal disease has progressed to a state in that the body’s normal immune response is unable to repair the damage from this disease, a diagnosis of irreversible pulpitis is given. (21). The presence of pulpitis can be of significance when administering an IANB. Lack of success of the IANB can be due to possible heightened or hypersensitivity of the tooth (22).

Pain sensory and pain perception are very complex. To add to this complexity is the anxiety, or even fear, of the dentist. Vika and co-authors found that nearly 17% of
dental patients showed high anxiety for their last dental appointment (23). Van Wijk and co-authors reported that patients who were anxious reported more pain than did those patients who were not anxious (24). Furthermore, not only has it been shown that these anxious patients report more pain, but they also have less tolerance for pain (25). Carter and co-authors (25) found that patients who were subjected to negative emotions showed lower pain tolerance. As pain is multifaceted, so should be the approach to manage pain.

Many studies have been performed with the goal to increase success rates of the IANB such as increasing the volume of anesthetic solution (5,6,11,12,16,26,74), increasing epinephrine concentrations (2,27), adding hyaluronidase to the anesthetic solution (7), adding carbonation to the anesthetic solution (28), using dyphenhydramine as an anesthetic solution (29-31), or combining meperidine and lidocaine (32). Interestingly, none of these studies were able to show significant increases in the success rate of the IANB.

The use of preoperative analgesics to increase the success rate of the IANB has been recently investigated. Oleson and co-authors (33) studied the effect of preoperative ibuprofen on the success of the IANB in patients with symptomatic irreversible pulpitis. One-hundred emergency patients with moderate-to-severe pain were studied. Eight hundred mg of ibuprofen or a placebo drug was administered. After 45 minutes, a conventional IANB was given using 3.6 mL of 2% lidocaine with 1:100,000 epinephrine. After 15 minutes, profound lip numbness was verified and endodontic access was initiated. Success was defined as the patient feeling no or mild pain during treatment verified with a 170 mm VAS. They found the success rate for the experimental ibuprofen
group was 41%. The success rate for the placebo group was 35%. There was no significant difference between the two groups (33).

Simpson and co-authors (34) studied the effect of preoperative acetaminophen/ibuprofen on the success of the IANB in patients with symptomatic irreversible pulpitis. This study included 100 emergency patients in moderate-to-severe pain. Either a combination of 800 mg of ibuprofen and 1000 mg of acetaminophen or a placebo drug was given. After 45 minutes an IANB was given using 3.6 mL of 2% lidocaine with 1:100,000 epinephrine and treatment was initiated (after profound lip numbness was verified). The authors defined success as no or mild pain upon access and instrumentation of the tooth. Their results showed a success rate of 32% with the ibuprofen/acetaminophen group, and 24% success rate for the placebo group. This did not demonstrate a significant difference (34).

Ianiro and co-authors (35) studied the effect of preoperative acetaminophen or a combination of acetaminophen and ibuprofen on the success of IANB for teeth with symptomatic irreversible pulpitis. They randomly assigned 40 patients to one of three groups. One group was given 1000 mg of acetaminophen. Another group was given a combination of 600 mg ibuprofen and 1000 mg of acetaminophen. The last group was given a placebo drug. After waiting 30 minutes, an IANB was administered using 3.6 mL of 2% lidocaine with 1:100,000 epinephrine. After 15 more minutes, a cold test was done on the tooth. If there was cold sensitivity, the IANB was counted as a failure. If there was no cold sensitivity, endodontic therapy was initiated. If pain was felt during access, the IANB was deemed a failure and supplemental anesthesia was given. If access and
subsequent treatment were rendered without pain, the IANB was recorded as a success. The authors demonstrated an overall success rate of 60% for all three groups combined. The success rate for acetaminophen was 71.4%. The success rate for the combination acetaminophen/ibuprofen group was 75.9%. The placebo group success rate was 46.2%. There were no significant differences between groups.

Aggarwal and co-authors (36) evaluated the effect of the preoperative oral medications ibuprofen and ketorolac on anesthetic efficacy of the IANB with lidocaine in patients with symptomatic irreversible pulpitis. Sixty-nine adults who were actively in pain were randomly assigned to 1 of 3 groups and received either ibuprofen, ketorolac, or a placebo. They waited one hour and administered 1.8 mL of 2% lidocaine with 1:200,000 epinephrine as an IANB. Endodontic therapy was initiated after 15 minutes following the IANB. Success was defined as none or mild pain using a Heft-Parker visual analog scale upon access of the tooth. The placebo group had a 29% success rate. Premedication with ibuprofen yielded a 27% success rate, and premedication with ketorolac had a 39% success rate. They found these percentages were statistically not significant (36).

Modaresi and co-authors (37) compared ibuprofen, acetaminophen-codeine, and placebo premedication therapy on the depth of anesthesia during treatment of teeth with symptomatic irreversible pulpitis. Sixty patients participated in their study and randomly received either 200 mg ibuprofen, 300 mg acetaminophen and 20 mg codeine, or a placebo. The patients were administered an IANB using 1.8 mL of 2% lidocaine with 1:80,000 epinephrine 60 minutes after administering the oral premedication. A baseline
sensitivity level was assessed using an electric pulp tester (EPT) before administration of medication, following administration of medication, and following administration of the IANB. Data were analyzed comparing sensitivity levels at each of these periods. To measure these sensitivity levels the investigators used an index called “tooth sensitivity level” (TSL). Tooth sensitivity level = 1/pulp tester scale. The index ranges between 1 to nearly 0. A TSL of 1 means that the tooth is responsive to EPT at a low stimulation, while 0 means that there is no response to EPT. They observed significantly lower TSLs after intervention with acetaminophen/codeine and ibuprofen groups. These differences were more significant in the ibuprofen group, noting a significant difference between the ibuprofen group and acetaminophen/codeine group. They concluded that ibuprofen (if not contraindicated) is superior for achieving “deep anesthesia” compared to acetaminophen/codeine and placebo when given 1 hour before local anesthesia in patients diagnosed with symptomatic irreversible pulpitis in mandibular teeth (37). However, TSL levels were not confirmed by accessing the teeth and therefore are not clinically meaningful.

Parirokh and co-authors (38) studied the success of the IANB in mandibular first or second molars diagnosed with asymptomatic irreversible pulpitis following preoperative administration of ibuprofen or indomethacin. One-hundred and fifty patients participated in the randomized, double-blind study. They were separated into three groups; placebo, 600 mg ibuprofen, and 75 mg indomethacin. The mandibular molar qualified if it presented with normal radiographic appearance and an exaggerated painful response to cold. They found success rates of the IANB were 32% for placebo,
78% for ibuprofen, and 62% for indomethacin. They concluded that preoperative administration of ibuprofen and indomethacin significantly increased the success of the IANB in mandibular molars diagnosed with asymptomatic irreversible pulpitis (38).

Li and co-authors (39) performed a systematic review and meta-analysis based on randomized controlled trials using preoperative oral nonsteroidal anti-inflammatory drugs (NSAIDs) for the success of the IANB. A total of 137 citations were identified by electronic and hand searching numerous scientific journal data banks. Using specific inclusion and exclusion criteria the articles were narrowed down to seven articles that met their desired quality, (33,34,35,36,37,38,40). Meta-analysis was performed and their conclusion was there is evidence that pre-emptive oral NSAIDs may have some good effects and are safe for increasing the success rate of IANB (39).

Few studies have been done demonstrating the use of narcotic combination medications for dental local anesthetic success. Investigation is needed concerning their efficacy when used with the IANB clinically. Acetaminophen/hydrocodone may address the problem of poor success rates with IANB.

To date, studies have provided some insight into the efficacy of acetaminophen/opioid combinations when used to control varying types and models of pain. Miner and co-authors (41) studied acetaminophen, ibuprofen, acetaminophen/hydrocodone, and placebo for the relief of pain from a standard painful stimulus. Twenty-five subjects received 1000 mg of acetaminophen, 800 mg of ibuprofen, a combination of 650 mg of acetaminophen with 10 mg of hydrocodone, or placebo (800 mg of lactose) in a randomized order over four separate occasions each 1
week apart. Prior to receiving the drug on each study day, the subject was asked to place their hand in a bath of 0°C water for 45 seconds. Subjects completed a 100-mm visual analog scale (VAS) representing perceived pain during the exposure. The cold water exposure and VAS were repeated 1 hour after receiving the study drug. The mean decrease in VAS values after receiving the study drug for acetaminophen was 10.2%, for ibuprofen -6.6% (negative meaning lack of effect), for acetaminophen/hydrocodone 9.5%, and for placebo -6.9% (also showing lack of effect). Acetaminophen and the acetaminophen/hydrocodone combination resulted in a similar decrease in pain. Conversely, ibuprofen and placebo had a similar lack of effect.

Roberts and co-authors (42) compared oxycodone and hydrocodone for the treatment of acute pain associated with fractures in emergency department patients. Fractures included facial, trunk, upper extremity, and lower extremity fractures. This study included emergency department patients over the age of 12 with fractures. Patients randomly received either oxycodone (5 mg orally) with acetaminophen, or hydrocodone (5 mg orally) with acetaminophen. No indication of a placebo group was made. The following information was recorded; verbal pain scores ranging from 0 to 10 with “0” defined as “no pain” and “10” defined as “worst pain imaginable” (done at baseline, 30 and 60 minutes after drug administration); vital signs at baseline, 30 and 60 minutes; and adverse side effects. Sixty-seven subjects completed the emergency department study period. Thirty-five patients received oxycodone and thirty-two received hydrocodone. There was no significant difference between the two groups in age, weight, gender, ethnicity, diagnosis, baseline pain scores, or vital signs. Patients in both groups had pain
relief (measured on the same 1-10 scale) from baseline to 30 minutes (oxycodone mean change 3.7; hydrocodone mean change 2.5) and from baseline to 60 minutes (oxycodone mean change 4.4; hydrocodone mean change 3.0). They found no difference in pain between the patients treated with oxycodone and hydrocodone at either time period. Data suggested that both oxycodone and hydrocodone are similarly effective in the first hour of treatment for emergency department patients with acute fractures.

Rodriguez and co-authors (43) studied the management of chronic cancer pain with codeine/acetaminophen and hydrocodone/acetaminophen. Their study included adult outpatients with cancer who had chronic moderate-to-severe cancer-related pain. Patients randomly were assigned to receive 1 tablet of codeine/acetaminophen (C/A) 30/500 mg or hydrocodone/acetaminophen (H/A) 5/500 mg orally every 4 hours for 23 days. In both groups, if pain intensity was rated as >3 cm on a 10-cm VAS at week 1 or 2, the dosage was doubled. The primary endpoint was the proportion of patients who achieved pain relief defined as a score of >1 on a 5-stage verbal rating scale (VRS) (0 = none; 1 = a little; 2 = some; 3 = a lot; and 4 = complete). The secondary endpoint was the proportion of patients in whom pain was decreased (Visual Analog Scale score ≤3 cm). Of the patients given C/A, 58% responded to the initial dose of 150/2500 mg/day, and 8% of the patients responded to the double dosage; and 34% did not experience any pain relief. In patients given H/A, pain was reported at none or mild in 56% of patients at the starting dose of 25/2500 mg/day; 15% of the patients responded to the double dosage; the remaining 29% of patients did not experience relief. They found no significant differences between the two groups (43).
Ziccardi and co-authors (44) compared the efficacy and safety of single-dose acetaminophen with codeine (acetaminophen 600 mg/codeine 60 mg) to hydrocodone with ibuprofen (ibuprofen 400 mg/hydrocodone 15 mg), and placebo in patients with acute postoperative pain after third molar extractions. One hundred twenty-five patients participated in the study. A stopwatch was used to measure the time of first perceptible pain relief and meaningful pain relief. Meaningful pain relief was recorded by having “the patient stop the stopwatch when they first begin to feel any pain-relieving feeling of the drug, that is, when they first felt a little relief” (44). Verbal descriptors were used to record pain intensity and pain relief scores at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, and 8 hours after dosing. They found both experimental treatment groups were significantly superior to placebo for all analgesic measures. The ibuprofen/hydrocodone group was also better than the acetaminophen/codeine group from 2 through 8 hours after dosing. The duration of analgesia was significantly longer for ibuprofen/hydrocodone (median, 5.5 hours) compared with acetaminophen/codeine (median, 3.03 hours) and placebo (median, 1.00 hours). Ibuprofen/hydrocodone was significantly better than the other 2 groups concerning the mean global evaluation of effectiveness (44).

Rosenthal and co-authors (45) studied the efficacy and safety of tramadol/acetaminophen (T/APAP), hydrocodone/acetaminophen (HC/APAP), and placebo after extraction of at least 2 impacted third molars. Two-hundred patients were randomly given one or two T/APAP tablets (37.5mg/325mg), 1 HC/APAP (10mg/650mg), or placebo. Measurements were made for hourly pain relief (PAR), pain intensity difference (PID), and combined PAR and PID (PRID) at 30 minutes and each
successive hour for 8 hours. Onset of pain relief for T/APAP 37.5mg/ 325mg was 33.3 minutes, T/APA 75mg/ 650mg was 34.0 minutes, and pain relief with HC/APAP was seen at 25.4 minutes. Other measurements were summary pain intensity and pain relief scores (total pain relief [TOTPAR], sum of pain intensity [SPID], and sum of pain relief and pain intensity differences [SPRID]). These were measured for 0 to 4 hours, 4 to 8 hours, and 0 to 8 hours. T/APAP 75/650 mg and HC/APAP were statistically superior to placebo when measuring TOTPAR, SPID, and SPRID, as well as on hourly PAR, PID, and PRID over 6 hours. All active treatment was statistically superior to placebo in terms of onset of pain relief, duration of pain relief, and patients’ overall assessment of medication. Dose response was also significant with T/APAP (75/650 mg > 37.5/325 mg > placebo) concerning TOTPAR, SPID, and SPRID (45).

Newman and co-authors (46) investigated the efficacy and tolerability of oxycodone 5 mg/ibuprofen 400 mg compared with oxycodone 5 mg/acetaminophen 325 mg and hydrocodone 7.5 mg/acetaminophen 500 mg or placebo in patients with moderate-to-severe postoperative pain. Two-hundred forty-nine patients who experienced moderate-to-severe pain after surgical removal of at least 2 ipsilateral impacted third molars participated in this study. The primary measures were total pain relief through 6 hours after dosing (TOTPAR6), sum of pain intensity differences through 6 hours (SPID6), and adverse events. Secondary efficacy measures included SPID 3 and TOTPAR3, peak pain relief, peak pain intensity difference, time to onset of pain relief, time to use of rescue medication, proportion of patients reporting pain half gone, and the patient’s global evaluation of the medication. Data indicated that oxycodone 5
mg/ibuprofen 400 mg provided significantly greater analgesia compared with oxycodone 5 mg/acetaminophen 325 mg, hydrocodone 7.5 mg/acetaminophen 500 mg, and placebo. Oxycodone 5 mg/ibuprofen 400 mg was significantly more effective compared with all other treatment on all secondary end points, with the exception of the time to onset of analgesia in which there was no difference. Time of onset was found to be 30.4 minutes for oxycodone 5 mg/ibuprofen 400 mg, 28.2 minutes for oxycodone 5 mg/acetaminophen 325 mg, and 41.1 minutes for hydrocodone 7.5 mg/acetaminophen 500 mg. SPID6 values also differed significantly when comparing oxycodone 5 mg/ibuprofen 400 mg to the other groups suggesting it may have a superior ability to suppress pain.

It has been questioned if pain medication could affect the results of pulp testing. Kardelis and co-authors (47) studied the effects of narcotic pain reliever on pulp testing in women. Fifteen women, with healthy, uninflamed tooth pulp were randomly given an oral dose of 10 mg hydrocodone/1000 mg acetaminophen or placebo. At baseline (before administration of drug), and after 2, 4, and 8 hours, sensitivity thresholds were evaluated for each subject using 4 tests: electric pulp tester applied on exposed root; electric pulp tester on adjacent mucosa; increasing probe pressure on adjacent mucosa; and decreasing cold probe on the exposed root. The electric pulp testing was done on the exposed root of each tested tooth. The electric testing of the mucosa was done near the mucogingival junction adjacent to the corresponding test tooth. In both electric tests, the patients were instructed to raise a hand the moment they felt any type of sensation. The cold tests were performed using a thermal couple which allowed slow decreases in temperature defined temperatures. The temperature was lowered by 2.5°C per time frame from 25°C and
placed on the exposed root of the test tooth. The patients were instructed to raise a hand the moment moderate pain was experienced. Their data indicated that there was no statistically significant difference between the experimental drug and placebo at any time point or for any of the 4 tests. They concluded that oral systemic administration of 10 mg hydrocodone/1000 mg acetaminophen has little impact on sensitivity of healthy pulp or mucosa in women as measured by these commonly used tests (47).

Carnes and co-authors (48) investigated the changes in pain threshold determined by electric pulp testing after administration of one of the following medications: 100 mg meperidine, 220 mg naproxen sodium, 1000 mg acetaminophen, or placebo. Eighty patients who presented with moderate-to-severe odontogenic pain participated. An explanation was not given as to how pain was determined. Electric pulp test readings were taken at baseline, and then each patient was allowed to wait for 45 minutes to allow for drug absorption. The patients were then re-tested using EPT. Their results showed that among the 4 possible treatments, acetaminophen was the only drug that demonstrated a statistically significant difference pain threshold change from test 1 to test 2. However, even this change was so slight that the investigators concluded that clinically there is no difference in pain threshold for patients who are administered these drugs preoperatively as measured with EPT (48).

Other studies have looked at whether cold-induced pain, as is often used for dental diagnoses, would be affected by the administration of acetaminophen. Foss and co-authors (49) used a cold-pressor test to study the dose-related effects of acetaminophen on cold-induced pain. Eighteen healthy adult patients participated. Administration of
doses of acetaminophen (325, 650, 1000 mg) or placebo was given at 4 different sessions per subject. Each session was separated by at least 48 hours. Each subject received each possible drug once. At the beginning of each session one of the described doses or placebo were administered randomly. The cold-pressor test was initiated 110 minutes after administration of the experimental drug. The cold-pressor test involved submerging the patients’ forearm in ice water for 180 seconds. Pain levels were recorded at 30, 70, 110, and 170 seconds after the immersion. The authors observed statistically significant differences of both dose and time (pain and bothersome ratings decreased with increasing drug dose and increased over time). However, in a pair-wise comparison, only the highest dose of acetaminophen (1000 mg) (as compared to placebo) reached statistical significance.

Research has been done on gender differences in analgesia for endodontic pain. Ryan and co-authors (50) performed a clinical trial of 43 patients who were randomly given 600 mg ibuprofen, placebo, or pentazocine 50 mg/0.5 mg naloxone immediately after endodontic treatment. Their emphasis was on analgesic differences between the sexes. Both necrotic and irreversible pulpitis cases were included. Pain was measured using a 100 mm visual analog scale at 5 time periods following endodontic treatment: 0, 6, 12, 18, and 24 hours. In all medication groups women had lower pain scores than men, however this was not statistically significant. There was a statistically significant difference found within the pentazocine/naloxone group where men had statistically higher post-operative pain levels than women. Their data suggest that there may be a
correlation between gender and analgesic efficacy of pentazocine/naloxone with regard to postoperative endodontic pain.

Acetaminophen is the only aniline derivative currently in clinical use. Aniline is an organic compound that consists of a phenyl group and an amine group. It is used extensively used as a precursor for making industrial chemicals, mainly polyurethane. Acetaminophen has analgesic and antipyretic activity that are comparable to aspirin (51).

The mechanism of action appears to be the inhibition of prostaglandin synthesis. However, the spectrum of cyclooxygenase (COX) enzymes that are targeted may differ than those of other COX inhibitors. It is also believed that central nervous system (CNS) COX enzymes are more affected by acetaminophen than are enzymes located peripherally (51). There are other proposed mechanisms of action of acetaminophen that include the activation of spinal serotonergic pathways and inhibition of nitric oxide synthase. When compared to aspirin, acetaminophen is a very weak anti-inflammatory agent. The effect of acetaminophen on inflammation is limited due to its inhibition in the presence of peroxides from leukocytes in inflamed tissues (51).

When compared to aspirin, acetaminophen has little effect on specific organs or systems. It has little effect on the respiratory and cardiovascular systems. It does not inhibit platelet aggregation, cause occult bleeding or gastric irritation, affect uric acid excretion, nor does it have as many drug interactions as aspirin. However, acetaminophen’s potency and efficacy as an antipyretic is similar to aspirin. When overdosed, the liver is most affected, followed by possible renal toxicity. Analgesic neuropathy is also possible with long-term use, but the risk is low (51).
Acetaminophen is normally ingested orally in capsules or tablets. It is well absorbed in the small intestine. After oral administration, peak plasma concentrations are attained within 10-60 minutes. Following oral administration of a single 500 mg conventional tablet, average plasma concentrations of 2.1 mg/mL, occur at 6 hours. Following administration, only small amounts of the drug are detectable in plasma after 8 hours (52). It is found to distribute well through all body fluids and tissues, and pass freely through the placenta. The main site of biotransformation is the liver. It has a half-life of about 2 to 4 hours. Acetaminophen is broken down first by reaction with a cytochrome p450 enzyme, forming the highly toxic intermediate N-acetyl-p-benzoquinoneimine. By the addition of glutathione in the liver, a nontoxic product is formed. In the case of overdose, the accumulation of N-acetyl-p-benzoquinoneimine can cause serious, irreversible harm to the liver. The drug is eliminated by glomerular filtration and active proximal tubular secretion in the kidney (51).

Other drugs such as aspirin and NSAIDs are much more efficacious and therapeutic for inflammatory conditions. Acetaminophen is normally reserved for mild to moderate analgesia. Acetaminophen is usually the drug of choice in patients that have contraindications to the use of aspirin and NSAIDs. It is the antipyretic drug of choice in teenagers and children because it is not associated with the development of Reye’s syndrome. It has been customary in the past for doctors to prescribe 650 mg doses. This is changing as acetaminophen has shown a positive dose-effect curve for analgesia up to 1000 mg. Aspirin has recently endured some negative publicity that has primarily linked its use to increased risk of internal bleeding. Due to this negative publicity with aspirin, a
trend toward the substitution for acetaminophen has become popular for the treatment of postoperative dental pain (51).

Acetaminophen has proven to be a relatively safe drug. The adverse side effects seem to be isolated to situations of acute or chronic overdose. When compared to NSAIDs, at therapeutic doses, acetaminophen does not demonstrate side effects related to nausea, platelet inhibition, nor does it prolong prothrombin time. Allergies to acetaminophen are reported very rarely and generally manifest as skin eruptions. Acetaminophen does not interfere with the quality or quantity of white blood cells (51).

Acute overdose has become a problem due to the sharp increase in the use of the drug. It is commonly used in suicide attempts because of its availability in large quantities. The therapeutic index of acetaminophen is high. It is estimated that 6 grams or more of the drug must be ingested in a relatively short amount of time for hepatotoxicity to occur. Severe hepatotoxicity in children under 10 years old has become common from miscalculations on dosage of the drug given to the child (51). The correlation of damage to the liver is directly related to the amount of drug ingested. Patients with preexisting liver disease are especially susceptible to damage. Acetaminophen overdose resulting in severe hepatotoxicity can be fatal, however there is satisfactory treatment for acetaminophen overdose if initiated in time (51).

Acetaminophen products contain labels concerning potential adverse interactions between it and alcohol. Chronic alcohol use and acetaminophen overdose are both linked to liver damage. The theoretic interaction involves a molecule called CYP2E1 that is highly induced with alcohol consumption. More CYP2E1 would be available to promote
acetaminophen conversion to a molecule called NAPQI, a highly reactive metabolite which normally is inactivated by glutathione. In alcoholics glutathione is depleted, thus there is nothing to inactivate the NAPQI. The NAPQI accumulates in the liver resulting in cellular injury (51).

There has been some recent controversy concerning the public health problem of liver injury due to the use of acetaminophen in both over-the-counter and prescription products. It has been demonstrated that acetaminophen-induced acute liver failure far exceeds other causes of acute liver failure in the United States (53). In June of 2009 a meeting was held involving the Drug Safety and Risk Management Advisory Committee, the Anesthetic and Life Support Drug Advisory Committee, and the Nonprescription Drug Advisory Committee. The FDA recognized that acetaminophen containing products are used extensively enough to increase the number of liver injury cases making it a public health concern (54). The U.S. Food and Drug Administration now asks manufacturers of products that contain acetaminophen to limit the amount of acetaminophen to no more than 325 milligrams (mg) in each tablet or capsule (55-58). Manufacturers will have three years to limit this amount in their prescription drug products (56,58). Manufacturers are now required by the FDA to update labels of all prescription combination acetaminophen products to warn of the potential risk for severe liver injury (55,56,58). Recently, Abbott Laboratories presented a reformulation and discontinuation announcement regarding current formulations of Vicodin. The following boxed warning was issued; “Hepatotoxicity: acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the
cases of liver injury are associated with the use of acetaminophen at doses that exceed 4000 milligrams per day, and often involve more than one acetaminophen-containing product” (59-62).

Hydrocodone is a phenanthrene opioid that is similar in structure to codeine and morphine. It is primarily used as an oral analgesic. It is also used as an antitussive. Hydrocodone/acetaminophen combinations are the most prescribed analgesics in the United States. These are considered a Schedule III narcotic by the U.S. Drug Enforcement Administration (51). Hydrocodone, when prescribed alone, is considered a Schedule II narcotic (63).

There are three main opioid receptors: mu (μ), kappa (κ), and delta (δ), although up to seventeen have been reported. Each receptor is distributed differently throughout the CNS and peripheral nervous system. The μ receptor is the site used for pure opioid agonists such as morphine. When these agonists bind to these sites, analgesia is the result. This analgesia has been the most thoroughly studied among the many effects of opioids. Opioids acting at opioid receptors in spinal and supraspinal sites can produce clinically effective analgesia. The understanding that opioids work in the CNS came first, followed by documentation of direct peripheral analgesic actions of opioids (51).

Three main mechanisms will be discussed here. First, peripheral receptors in skin, muscles, joints, and viscera respond to pain stimuli. These stimuli can be influenced at the site where they first synapse in the spinal, or medullary dorsal horn. The modulation of sensory stimuli relies on the binding of opioid receptors in the midbrain. This binding in the midbrain ultimately leads to the release of the neurotransmitters serotonin and
norepinephrine which inhibit those pain stimuli coming from the skin, muscles, joints, and viscera. This is called the descending pain inhibitory system (51).

Secondly, opioids like hydrocodone can modulate pain by acting at opioid receptors in the brain that are not associated with the descending pain inhibitory system. Opioids bind to specific receptors in the nervous system and other tissues. This binding occurs at binding sites that involve the primary classes of opioid receptors, μ, κ, δ (mu, kappa, and delta). The action of opioids at these sites influences the emotional reaction to and interpretation of the pain stimulus (51).

Lastly, opioid agonists can act at receptors located on the terminals of specialized nerve fibers that connect the CNS and peripheral nervous systems. This type of action is seen when opioids are directly administered into, for example, a joint or intrathecal space (51).

When hydrocodone is given systemically, such as in this study, the opioids have access to all potential sites of action. With all of these mechanisms working together, there is likely a synergistic effect resulting in increased potency, and consequently, less toxicity. Hydrocodone toxicity, however, is not of clinical concern when the drug is administered properly at a single and therapeutic dose (51).

Hydrocodone affects the CNS with a combination of stimulation and depression. The CNS effects include analgesia, drowsiness, euphoria, dysphoria, respiratory depression, suppression of cough reflex, pupillary constriction, suppression and or enhancement of pituitary hormones, and initial stimulation in the medulla depressing
vomiting. A significant feature of opioid analgesics is that they are more effective against continuous, dull, aching pain than sharp, intermittent pain (51).

The analgesia hydrocodone provides is only symptomatic relief without alleviating the source of the pain. The therapeutic dose of 10 mg/70 kg of body weight is used for moderate-to-severe pain (51).

The peripheral pharmacologic effects of hydrocodone are mainly on smooth muscle tone that can have both therapeutic and toxic implications. It also affects gastrointestinal activity by reducing glandular secretions and by promoting absorption of fluid from the gastrointestinal tract. The peripheral analgesic effect of opioids has recently become more significant. Much of this effect is associated with opioid receptors located on the terminals of nociceptors. With tissue insult, opioid receptors increase in number. This up-regulation of opioid receptors can be taken advantage of by introducing exogenous opioid agonists that can then bind to these receptors producing analgesia at the very site of tissue insult (51).

Most opioids, including hydrocodone, are much more effective when given parenterally rather than orally in the same doses. The decrease in effect after oral administration is caused by the first pass metabolism through the liver. Opioids in general are primarily eliminated from the body via the kidney. Only small amounts of free drug are found in the urine. Other small amounts may appear in the bile, and eventually a small amount is excreted in the feces. The drug is normally about 90% excreted from the body after the first 24 hours following administration. This fact demonstrates that opioids generally do not accumulate in tissues (51).
Opioids are the most efficacious analgesic drugs known. It is significant to this study that opioids, when administered at therapeutic doses, not only produce analgesia, but also drowsiness and tranquilization (51). With this effect, opioids have an application not only for pain relief but for sleep induction provided that pain or coughing is the cause of sleeplessness. Opioids are often given to supplement benzodiazepines or other sedatives to facilitate moderate sedation, or with increasing doses, induce deep sedation or general anesthesia (51).

Opiate users very commonly report constipation. Although usually mild, this side-effect can turn serious if left unchecked. Allergic reactions may manifest as signs of rash, wheezing, difficulty breathing, closing of the throat, hives or swelling of the lips, face, tongue or throat. Additional commonly reported side-effects include: headache, mood changes, dry mouth, ringing in the ears, trouble sleeping, nausea, vomiting, upset stomach and blurred vision. When hydrocodone is combined with acetaminophen, caution must be used to avoid overdose. These symptoms may manifest as extreme drowsiness, fainting, nausea, sweating, muscle weakness, small pupils, vomiting, dark urine, jaundice, confusion, cold and clammy skin, weak pulse, depressed heart rate, coma, blue lips and shallow breathing (64).

Acetaminophen/hydrocodone is usually found in tablet form, produced and marketed under the trade names Vicodin, Vicodin ES, Vicodin HP, Anexas, Anolor DH5, Bancap HC, Zydome, Dolacet, Lorcet, Lortab, and Norco, as well as generic brands. Hydrocodone bitartrate and acetaminophen tablets for oral administration are available in a variety of strengths as follows: (hydrocodone bitartrate/acetaminophen) 2.5 mg/500mg,
5 mg/500 mg, 7.5 mg/325 mg, 7.5 mg/500 mg, 7.5 mg/650 mg, 7.5 mg/750 mg, 10 mg/325 mg, 10 mg/500 mg, 10 mg/650 mg, 10 mg/660 mg, 10 mg/750 mg. Recently added is the new formulation of 5 mg/300 mg. This is due to concerns of hepatotoxicity. In addition, each tablet contains the following inactive ingredients: anhydrous lactose, croscarmellose sodium, crospovidone, magnesium stearate, microcrystalline cellulose, povidone, starch and stearic acid; except the 7.5 mg/325 mg, 10 mg/325 mg and 7 mg/500 mg tablets do not contain anhydrous lactose. The 7.5 mg/325 mg tablets include FD&C Yellow #6 Aluminum Lake; the 7.5 mg/650 mg tablets include FD&C Red #40 Aluminum Lake; the 10 mg/325 mg and 10 mg/750 mg tablets include D&C Yellow #10 Aluminum Lake; the 10 mg/500 mg tablets include FD&C Blue #2 Aluminum Lake; and the 10 mg/650 mg tablets include FD&C Blue #1 Aluminum Lake and D&C Yellow #10 Aluminum Lake (65).

The beneficial theory of using a combination of drugs is that these medications alleviate pain using different mechanisms. By employing more than one mechanism of action, pain will, theoretically, be controlled on more than one level. Also, it is believed by some that the adverse side-effects of each medication are reduced by using reduced dosages, while still benefiting from similar analgesic effects (66).

The usual dental dosage in children and adults \( \geq 50 \text{ kg} \) is 5-10 mg of hydrocodone 4 times per day; the dosage of acetaminophen should be limited to \( \leq 4 \text{ grams per day} \) and possibly less in patients with hepatic impairment or ethanol use (67). Severity of the pain and patient tolerance should dictate adjustments in dosage. Normally, when opiate
analgesics are administered in combination with nonopiate analgesics, the opiate dosage may be limited by the nonopiate component, in this case acetaminophen (52).

Following oral administration, peak plasma concentrations of acetaminophen are attained within 10-60 minutes. Hydrocodone generally has an onset of 15-30 minutes and has a peak plasma concentrations, on average, at 1 hour (68).

To avoid serious side effects the combination of hydrocodone/acetaminophen should be taken only as prescribed by a doctor. Taking hydrocodone/acetaminophen with alcohol can cause a potentially serious slowing of breathing. Other narcotics, allergy medication and sleeping pills can also magnify drowsiness when combined with hydrocodone/acetaminophen (64).

It was hypothesized in the present study that administering acetaminophen and hydrocodone preoperatively to patients experiencing active, moderate-to-severe pain would increase the success rate of the inferior alveolar nerve block due to the multi-site and multi-action qualities of their mechanisms of action.
CHAPTER 2

MATERIALS AND METHODS

Approval for this study was given by The Ohio State University Human Subjects Review Committee. One-hundred patients participated in this study. Emergency walk-in patients from The Ohio State College of Dentistry were selected upon consenting and meeting qualifications. The patients were at least 18 years old. The patients did not have any health contraindications to dental treatment (ASA classification of I or II). This was verified through a written health history form and follow-up questions.

The patients were actively experiencing moderate to severe pain with a diagnosis of symptomatic irreversible pulpitis of a posterior mandibular tooth, and had prolonged response to pulp testing with Endo-Ice ® (1,1,1,2 tetrafluoroethane, Hygenic Corp., Akron Ohio). The level of pain (moderate/severe) was verified using a 170 mm visual analog scale (VAS) (69). This scale measured no pain, mild, moderate, and severe pain. No pain measured 0 mm, mild pain measured greater than 0 mm and less than or equal to
54 mm, moderate pain measured greater than 54 mm and less than 114 mm, and severe pain measured equal to or greater than 114 mm.

The patient was excluded from the study if they had allergies or any other contraindications to acetaminophen/hydrocodone, were ASA III or IV, were pregnant (which was verified with urine pregnancy test from Osom Genzyme Corp, San Diego, CA to eligible females), lactating, were not capable of giving proper consent, were experiencing only mild pain (verified with VAS), or had taken pain medication in the last 6 hours. Patients with no response to cold testing, periradicular pathosis (other than a widened periodontal ligament), or no vital coronal pulp tissue upon access were excluded from the study. If the patient met all inclusion criteria, the study was described in detail, and consent was obtained. The patients were then asked to sign a HIPAA form, followed by the completion of Corah’s Dental Anxiety Scale (70,71). The patients were then asked the last time they ate or drank anything. This was then recorded.

Patients were randomly assigned to the hydrocodone/acetaminophen or placebo group. Fifty patients received four opaque, purple, “soft-shelled”, oral capsules containing 10 mg hydrocodone powder, 1000 mg acetaminophen powder, and Riboflavin USP (as a colorimetric indicator to ensure complete mixing of the active pharmaceutical ingredients). The other fifty patients received four identical placebo capsules. The placebo capsules contained Avicel PH-105 microcrystalline cellulose NF powder. All capsules were compounded by a registered compounding pharmacist (Anthony J. Buchta R. MBA; Central Ohio Compounding Pharmacy LLC, Columbus, OH). The capsules were placed in orange, semi-transparent, 6 dram medication containers with a random
six-digit number printed on the label on the outside of the container. The containers were assigned a six-digit number by the compounding pharmacist that was then assigned randomly to a corresponding patient. These six-digit numbers were generated by Dr. Melissa Drum and given only to the compounding pharmacist. The designation of these numbers was kept unknown to the investigator, blinding both the patient and the investigator to the medication being utilized.

Immediately before the administration of capsules, the patient’s tooth was ice tested with Endo-Ice ® using a loose cotton pellet placed on the buccal surface of the tooth. An ice test, with a corresponding VAS for pain was marked and this procedure was repeated every ten minutes until minute 60, resulting in seven ice tests total. At each of these seven tests, the patient’s reaction to the ice was recorded with a numerical value of 0, 1, or 2 as determined by the calibrated tester.

Sixty minutes after the capsules were ingested, topical anesthetic (20% benzocaine, Patterson Dental Supply, Inc., St. Paul, MN) was placed at the inferior alveolar nerve block injection site for 60 seconds using a cotton tip applicator. One inferior alveolar nerve block was then administered using 1.8 mL 2% lidocaine with 1:100,000 epinephrine (Xylocaine, AstraZeneca LP, Dentsply, York, PA) with a 27-gauge 1½-inch needle (Monoject; Tyco Healthcare Group LP, Mansfield, MA). Following initial needle penetration (insertion), the needle was advanced to the target site (placement). After gentle contact with bone, the needle was withdrawn 1 mm, aspiration was performed and the anesthetic solution was deposited over a 1-minute time period (deposition). Pain levels were assessed with a 170 mm VAS for needle insertion, needle
placement, and solution deposition (69). Each of these tested phases were assigned a numerical number of 1, 2, or 3. Before the injection was administered, the patient was informed of these three phases of the injection. They were asked to, in their mind, assess the pain felt when the tester verbalized 1, 2, and 3. When the injection was complete, the patient was asked to rate these three phases for pain on three corresponding VAS’s.

The patient was questioned every minute for 15 minutes, following the IANB, if his/her lip was numb. If profound lip numbness was not recorded at 15 minutes, the block was considered missed and the patient was given another injection of 1.8 mL 2% lidocaine with 1:100,000 epinephrine. This occurred 9 times out of 100 patients. All 9 patients then achieved lip numbness within the additional 15 minutes.

At 15 minutes (or 30 minutes in the 9 cases described above) post-injection, the tooth was isolated with a rubber dam and endodontic access was performed. Patients were instructed to definitively rate any pain felt during the endodontic procedure. The patient was instructed to raise their hand if pain was felt. If pain was felt, treatment was immediately stopped and the patient rated their discomfort using the Heft-Parker VAS. The extent of access achieved when the patient felt pain was recorded as either within dentin, entering the pulp chamber, or initial file placement. The success of the IANB was defined as the ability to access and instrument the tooth without pain (VAS score of zero) or mild pain (VAS rating less than or equal to 54 mm).

If the patient felt no pain or mild pain, treatment continued. If the patient experienced moderate or severe pain (VAS rating greater than 54 mm), the rubber dam was removed and a buccal infiltration of 1.8 mL of 4% articaine with 1:100,000.
epinephrine (Septocaine, Septodont, New Castle, DE) was injected over 1 minute directly buccal to the tooth requiring emergency treatment. Anesthetic was deposited at the approximate level of the root apices. The patient was again shown the VAS and marked it corresponding to pain involved with the buccal infiltration. The patient was asked to rate their pain upon initial needle penetration (insertion), needle advancement (placement), and deposition of anesthetic solution over a 1-minute time period.

After waiting 5 minutes to allow sufficient time for proper anesthesia (72) the rubber dam was replaced and endodontic access was continued. If the patient felt no pain or mild pain, treatment continued. If the patient felt moderate-to-severe pain (VAS rating equal or greater than 54 mm), the treatment was again stopped. The extent of access achieved when the patient felt pain was again recorded as within dentin, entering the pulp chamber, or initial file placement. The success of the buccal infiltration was defined as the ability to access and instrument the tooth without pain (VAS score of zero) or mild pain (VAS rating less than or equal to 54 mm).

If the buccal infiltration was unsuccessful, the rubber dam was removed and an intraosseous injection using 1.8 mL 2% lidocaine with 1:100,000 epinephrine was administered as described in previous studies (73). This was done using the Stabident® intraosseous anesthetic delivery system (Fairfax Dental Inc., 2937 SW 27 Ave, Suite 102, Miami, FL 33133). The rubber dam was replaced and treatment continued. If moderate to severe pain was felt again (VAS rating greater than 54 mm), the intraosseous injection was repeated. If moderate to severe pain was felt yet again (VAS rating equal to or
greater than 55 mm), intrapulpal injections were administered using 2% lidocaine with 1:100,000 epinephrine.

Root canals were then prepared with hand and rotary instrumentation, using K-type hand files. Oral post-operative instructions were given when treatment was completed. Pain management prescriptions were given as indicated. The patient was asked to mark a vertical line at the point on a scale line that best described their satisfaction with the entire treatment procedure (0 to 100 mm). The patient was instructed to leave the satisfaction form on the counter in the operatory. This form was not collected by the operator to minimize any potential influence the operator may have had on the rating. Another VAS was then marked (0-170 mm) asking the patient if they remember pain during treatment, and if yes, what was the greatest amount of pain felt. The patient was then reappointed for completion of root canal therapy at a later date or referred for extraction of the tooth as appropriate. The patient then received $75.00 cash for their participation.

All results were collected and statistically analyzed. Comparisons between the acetaminophen/hydrocodone and placebo groups for age and initial pain were analyzed using the randomization test. The patient’s Corah Dental Anxiety Scales were analyzed using the Mann-Whitney-Wilcoxon Test. Comparisons of tooth types between the two groups were analyzed using the Fisher Exact Test. Gender, food intake, and whether or not patients experienced acetaminophen/hydrocodone related symptoms were analyzed using the Chi-Square Test. Preoperative pain using ice stimulation was analyzed by the ANOVA and Tukey Test. The success rates of the IANB and buccal infiltration injections
were analyzed by the Chi-Square Test, and the success rate of the intraosseous injection was analyzed by the Fisher Exact Test. The pain of the IANB and buccal infiltration injections were analyzed using ANOVA. Patient post-treatment satisfaction ratings were analyzed using the Randomization Test.

With a two-sided alpha risk of 0.05 and assuming a success rate of 24% (12), a sample size of 50 subjects per group was required to detect a difference of ±30 percentage points in anesthetic success with a power >0.88. Comparisons were considered significant if p<0.05.
CHAPTER 3

RESULTS

One-hundred (50 in each group) patients participated in this study (Table 1). In the placebo group, the mean age of the participating patient was 35.7 ± 12.7 years with a maximum age of 61 and a minimum age of 18. In the acetaminophen/hydrocodone group, (Acet/Hydro used throughout tables) the mean age of the participating patient was 35.0 ± 11.7 years with a maximum age of 67 and a minimum age of 20. There was no statistically significant difference between the two groups. To qualify for participation, the patient needed to be experiencing moderate-to-severe pain, at the time of the appointment, as assessed on a 170 mm Heft-Parker Visual Analog Scale. The initial mean pain experienced by patients in the placebo group was 125.1 ± 24.0 mm, and the mean pain experienced by patients in the acetaminophen/hydrocodone group was 125.1 ± 23.7 mm. There was no statistically significant difference between the two groups.

Table 2 illustrates the anxiety of each patient as assessed by Corah’s Dental Anxiety Scale. A score was given between 4 and 20, with a higher number indicating
more anxiety. The median anxiety score for patients in the placebo group was 10, and the median anxiety score for patients in the acetaminophen/hydrocodone group was 11. There was no statistically significant difference between the two groups.

Table 3 analyzes the tooth type, gender, whether the patient had eaten within 6 hours of treatment (Food), and if the patient was experiencing symptoms related to the consumption of the study drug (Symptoms). These symptoms included descriptions of deepened relaxation, sleepiness, feelings of euphoria, or nausea. The majority of studied teeth for both groups were molars, as there were only 6 premolars studied in the placebo group, and 7 premolars studied in the acetaminophen/hydrocodone group. There was no statistically significant difference between the two groups for tooth type. Of the 50 participants in the placebo group, 27 were male and 23 were female. Of the 50 participants in the acetaminophen/hydrocodone group, 19 were male and 31 were female. There was no statistically significant difference between the two groups for gender. Of the 50 participants in the placebo group, 22 had not eaten and 28 had eaten within 6 hours. Of the 50 participants in the acetaminophen/hydrocodone group, 20 had not eaten and 30 had eaten with 6 hours. There was no statistical difference between the two groups for food intake. There was, however, a statistically significant difference in patients who demonstrated acetaminophen/hydrocodone related symptoms. Data related to symptoms was not collected until the 19th participant. Of the 50 participants in the placebo group, 45 were assessed using this criterion. Of these 45, 15 demonstrated symptoms and 30 did not. Of the 50 participants in the acetaminophen/hydrocodone group, 37 were assessed using this criterion. Of these 37, 28 demonstrated symptoms and 9 did not.
Table 4 and Figure 1 show the results of pain upon cold stimulation with Endo-Ice® using a loose cotton pellet placed on the buccal surface of the tooth. If the buccal surface was not intact due to breakage or decay, the lingual surface was tested. Pain to cold was assessed using a 170 mm VAS starting with initial pain which was recorded as time 0. Assessments were continued at 10 minute intervals for 1 hour before anesthesia was administered. In both groups, mean pain decreased with each time period. There was no statistically significant difference between the two groups for any of the studied time periods.

Table 5 demonstrates a subjective evaluation of the patients’ reaction to the same cold stimulation as described in Table 4. The patient’s reaction to the cold was recorded with a numerical value of 0, 1, or 2 as determined by the calibrated tester. Zero represented no reaction by the patient. One represented a reaction by the patient involving body and or verbal language demonstrating mild-to-moderate pain. Two represented a reaction by the patient involving dramatic body and or verbal language demonstrating severe pain. In the placebo group, two instances were recorded where no reaction was found. These were at minutes 10 and 20. In the acetaminophen/hydrocodone group 5 instances were recorded where no reaction was found. These recordings of “0” or “no reaction” were at minute 40 (1), minute 50 (3), and minute 60 (1). For both groups, there was a decrease in the frequency of “2” reactions for each subsequent test period.

Table 6 and Figure 2 illustrate the pulpal anesthetic success rates of the IANB, infiltration injection, and intraosseous injection. The IANB was successful in 14 of 50 patients in the placebo group (28%), and 16 of 50 in the acetaminophen/hydrocodone
group (32%). One-hundred percent of these patients had successful IANB’s defined as profound lip numbness. For this study, success was defined as the ability to access and instrument the tooth without pain (VAS score of zero) or mild pain (VAS rating less than or equal to 54 mm) for all three injections. Following the IANB, 36 placebo patients and 34 acetaminophen/hydrocodone patients required additional anesthesia using a buccal infiltration of 4% articaine with 1:100,000 epinephrine. This proved successful in 15 of the 36 placebo patients (41%), and 17 of the 34 acetaminophen/hydrocodone patients (50%). Following the buccal infiltration, 21 placebo patients and 17 acetaminophen/hydrocodone patients required additional anesthesia using an intraosseous technique with 2% lidocaine with 1:100,000 epinephrine. This proved successful in 16 of the 21 placebo patients (76%), and 12 of the 17 acetaminophen/hydrocodone patients (70%). A second intraosseous injection was administered to each of the participants whose first intraosseous injection was not successful. There was no instance in which a second intraosseous injection given resulted in pulpal anesthetic success. Five placebo patients and five acetaminophen/hydrocodone patients required intrapulpal injections which all resulted in pulpal anesthetic success. There was no instance in which the patient could not finish the study for any reason. There were no statistically significant differences for any of the 3 types of anesthesia.

Tables 7, 8, and 9 analyze the success of the IANB, buccal infiltration, and intraosseous injections, respectively, by tooth type.

Table 7 illustrates that for the placebo group, 32% of 1st molars, 29% of second molars, 50% of 3rd molars, and 0% of premolars were successfully anesthetized using
only the IANB. It also shows that for the acetaminophen/hydrocodone group, 38% of 1\textsuperscript{st} molars, 24% of second molars, no 3\textsuperscript{rd} molars were tested, and 29% of premolars were successfully anesthetized using only the IANB.

Table 8 shows that for the placebo group, 37% of 1\textsuperscript{st} molars, 50% of second molars, 0% of 3\textsuperscript{rd} molars, and 50% of premolars were successfully anesthetized using an articaine infiltration after failure of the IANB. It also shows that for the acetaminophen/hydrocodone group, 31% of 1\textsuperscript{st} molars, 62% of second molars, no 3\textsuperscript{rd} molars were tested, and 80% of premolars were successfully anesthetized using an articaine infiltration after failure of the IANB.

Table 9 illustrates that for the placebo group, 67% of 1\textsuperscript{st} molars, 80% of second molars, 100% of 3\textsuperscript{rd} molars, and 100% of premolars were successfully anesthetized using an intraosseous injection after failure of the IANB and buccal infiltration with articaine. It also shows that for the acetaminophen/hydrocodone group, 82% of 1\textsuperscript{st} molars, 40% of second molars, no 3\textsuperscript{rd} molars were tested, and 100% of premolars were successfully anesthetized using an intraosseous injection after failure of the IANB and buccal infiltration with articaine.

Table 10 shows the treatment stage in which moderate-to-severe pain was felt (i.e. point of failure). The majority of anesthetic failures were found to be in dentin for both the IANB and buccal infiltration. When the intraosseous injection failed, it occurred only once in the dentin for both the placebo and acetaminophen/hydrocodone patients. Four failures with the intraosseous technique were found in both the placebo and
acetaminophen/hydrocodone groups, when the operator had entered the pulp chamber or was filing the root canal system.

Table 11 also demonstrates the location of anesthetic failure for each injection as well as the severity of pain felt by the patient when anesthetic failure occurred. Generally less pain was experienced when failure occurred as the operator was instrumenting the canals.

Table 12 and Figure 3 illustrate the pain of injection for the IANB for all 3 stages of the injection. Table 13 illustrates the pain of injection for the buccal infiltration injection. No significant differences were found at any of the 3 stages of the injections when comparing the placebo group and acetaminophen/hydrocodone group for both the IANB and buccal infiltration.

Table 14 and Figure 4 illustrate the significant difference found when studying the patient satisfaction of the placebo group versus the acetaminophen/hydrocodone group. Scaling from 0 to 100, with 100 being completely satisfied and 0 being not satisfied, the mean satisfaction of the placebo group was $88.7 \pm 17.9$ mm and the mean satisfaction for the acetaminophen/hydrocodone group was $94.7 \pm 10.6$ mm. The maximum rating for both groups was 100. The minimum rating for the placebo group was 24 while the minimum rating for the acetaminophen/hydrocodone group was 67. All 50 participants in the acetaminophen/hydrocodone group were either moderately or completely satisfied. Forty-six participants in the placebo group were either moderately or completely satisfied, while three were somewhat satisfied. Only one was not satisfied.
CHAPTER 4

DISCUSSION

The purpose of this prospective, randomized, double-blind, placebo-controlled study was to determine the effect of the administration of acetaminophen/hydrocodone on the efficacy of the IANB in patients with symptomatic irreversible pulpitis. Table 6 and Figure 2 illustrate the pulpal anesthetic success rates of the IANB, infiltration injection, and intraosseous injection. The IANB was successful in 14 of 50 patients in the placebo group (28%), and 16 of 50 in the acetaminophen/hydrocodone group (32%). One-hundred percent of these patients had successful blocks as defined by profound lip numbness. Nine of the 100 patients required an additional cartridge (1.8 mL) of anesthetic to achieve lip numbness. Four of these patients were in the acetaminophen/hydrocodone group, while five were in the placebo group. In these nine cases, access of the tooth was delayed. It is important to note that an additional amount of anesthetic has been shown to have little increased, if any effect (6). Also, it is unlikely the additional amount of time the patient waited with the medication in their system would
have an effect, since the delay was minimal. Also, these cases occurred naturally occurring evenly between the experimental and placebo groups (4 in experimental and 5 in placebo). Even if these discussed factors played any type of significance, this even distribution would nullify any effect in our results.

For this study, success was defined as the ability to access and instrument the tooth without pain (VAS score of zero) or mild pain (VAS rating less than or equal to 54 mm) for all three injections. Following the IANB, 36 placebo patients and 34 acetaminophen/hydrocodone patients required additional anesthesia using a buccal infiltration of one cartridge of 4% articaine with 1:100,000 epinephrine. This proved successful in 15 of the 36 placebo patients (41%), and 17 of the 34 acetaminophen/hydrocodone patients (50%). Following the buccal infiltration, 21 placebo patients and 17 acetaminophen/hydrocodone patients required additional anesthesia using an intraosseous technique with 1.8 mL of 2% lidocaine with 1:100,000 epinephrine. This proved successful in 16 of the 21 placebo patients (76%), and 12 of the 17 acetaminophen/hydrocodone patients (70%). A second intraosseous injection was administered to each of the participants whose first intraosseous injection was not successful. There was no instance in which a second intraosseous injection resulted in pulpal anesthetic success. Five placebo patients and five acetaminophen/hydrocodone patients required intrapulpal injections which all resulted in pulpal anesthetic success. There was no instance in which the patient could not finish the study for any reason. There were no statistically significant differences between the placebo and treatment group for any of the 3 types of anesthesia. It is difficult, however, to come to accurate
conclusions with the buccal infiltration and intraosseous injections as the sample sizes are smaller than those of the IANB groups.

Similar to the present study, previous studies have been performed with the goal to increase success rates of the IANB such as increasing the volume of anesthetic solution (5, 6, 11, 12, 26, 74), increasing epinephrine concentrations (2, 17), adding hyaluronidase to the anesthetic solution (7), adding carbonation to the anesthetic solution (28), using dyphenhydramine as an anesthetic solution (29-31), adding a buccal infiltration of 1.8 mL of 4% articaine with 1:100,000 epinephrine (101), or combining meperidine and lidocaine (32). Interestingly, none of these studies were able to show significant increases in the success rate of the IANB. The results of these studies were similar to those of the present study (Table 6 and Figure 2).

The use of preoperative analgesics to increase the success rate of the IANB was recently investigated. Oleson and co-authors (33) studied the effect of preoperative ibuprofen on the success of the IANB in patients with symptomatic irreversible pulpitis. One-hundred emergency patients in moderate to severe pain were chosen. Eight hundred mg of ibuprofen or an identical placebo drug was administered. After 45 minutes, a conventional IANB was given using 3.6 mL of 2% lidocaine with 1:100,000 epinephrine. After 15 minutes, profound lip numbness was verified and access was initiated. Success was defined as the patient feeling no or mild pain verified with a 170 mm VAS. They found the success rate for the experimental ibuprofen group was 41%. The success rate for the placebo group was 35%. There was no significant difference between the two groups (33). Oleson’s success rates were slightly higher than the success rates of the
IANB of the present study (Table 6). Oleson’s findings support the findings of the present study, in that preoperative medication does not significantly increase the success rate of the IANB in patients with symptomatic irreversible pulpitis in a mandibular posterior tooth.

Simpson and co-authors (34) studied the effect of preoperative acetaminophen/ibuprofen on the success of the IANB in patients with symptomatic irreversible pulpitis. This study included 100 emergency patients in moderate-to-severe pain. Either a combination of 800 mg of ibuprofen and 1000 mg of acetaminophen or a placebo drug was given. After 45 minutes an IANB was given 3.6 mL of 2% lidocaine with 1:100,000 epinephrine and treatment was initiated after profound lip numbness was verified (after 15 minutes). They defined success as no or mild pain upon access and instrumentation of the tooth. Their results showed a success rate of 32% with the ibuprofen/acetaminophen group, and 24% success rate for the placebo group. This did not demonstrate a significant difference (34). Simpson’s success rate for the experimental drug group was identical to the success rate of the experimental group of the present study. Acetaminophen combinations were used in both studies, with the difference being the addition of 800 mg of ibuprofen for Simpson’s study, and 10 mg of hydrocodone for the present study. The data suggests that the respective different drugs had a similar lack of efficacy.

Ianiro and co-authors (35) studied the effect of preoperative acetaminophen and a combination of acetaminophen and ibuprofen on the success of IANB for teeth with symptomatic irreversible pulpitis. They randomly assigned 40 patients to one of three
groups. One group (n = 14) was given 1000 mg of acetaminophen. Another group (n = 13) was given a combination of 600 mg ibuprofen and 1000 mg of acetaminophen. The last group (n = 13) was given a placebo drug. After waiting 30 minutes, an IANB was administered using 3.6 mL of 2% lidocaine with 1:100,000 epinephrine. After 15 more minutes, a cold test was done on the tooth. If there was cold sensitivity, it was counted as a failure. If there was no cold sensitivity, therapy was initiated. If pain was felt during access, the IANB was deemed a failure and supplemental anesthesia was given. If access and subsequent treatment were rendered without pain, the IANB was recorded as a success. They demonstrated an overall success rate of 60% for all three groups combined. The success rate for acetaminophen was 71.4%. The success rate for the combination acetaminophen/ibuprofen group was 75.9%. The placebo group success rate was 46.2%. There were no significant differences between groups (35). Ianiro’s success rates are higher than those of the present study. This may be due to the relatively small number of participating patients in their study. The power of the study was greatly reduced when there were 40 patients who were divided into three groups.

Aggarwal and co-authors (36) evaluated the effect of the preoperative oral medications ibuprofen and ketorolac on anesthetic efficacy of the IANB with lidocaine in patients with symptomatic irreversible pulpitis. Seventy-two adults who were actively in pain were randomly assigned to 1 of 3 groups of 24 patients each to receive either 300 mg ibuprofen, 10 mg ketorolac, or a placebo. They waited one hour after administration of the drug and then gave 1.8 mL 2% lidocaine with 1:200,000 epinephrine as an IANB. Endodontic therapy was initiated 15 minutes following the IANB. Success was
determined as no or mild pain using a Heft-Parker visual analog scale upon access of the tooth. The placebo group had a 29% success rate. Premedication with ibuprofen yielded a 27% success rate, and premedication with ketorolac group had a 39% success rate. They found these percentages statistically not significantly different (36). These findings support the results of the present study. This is expected as Aggarwal’s materials and methods are very similar in that the preoperative medication was given 1 hour to reach sufficient plasma levels, and treatment began 15 minutes after administration of the IANB.

Modaresi and co-authors (37) compared ibuprofen, acetaminophen-codeine, and placebo premedication therapy on the depth of anesthesia during treatment of teeth with symptomatic irreversible pulpitis. Sixty patients divided into three groups of 20 patients participated in their study and randomly received either 200 mg ibuprofen, 300 mg acetaminophen and 20 mg codeine, or a placebo. The patients received an IANB using 1.8 mL of 2% lidocaine with 1:80,000 epinephrine 60 minutes after administration of the drug. A baseline sensitivity level was assessed using EPT before administration of medication, following administration of medication, and following administration of the IANB. Data were analyzed comparing sensitivity levels at each of these periods. To measure these sensitivity levels the investigators used an index called “tooth sensitivity level” (TSL). Tooth sensitivity level = 1/pulp tester scale. In other words, the TSL is the inverse of the EPT reading. The index ranges between 1 to nearly 0. A TSL of 1 means that the tooth is responsive to EPT at a low stimulation, while 0 means that there is no response to EPT. They observed significantly lower TSLs after intervention with
acetaminophen/codeine and ibuprofen groups. These differences were more significant in the ibuprofen group, noting a significant difference between the ibuprofen group and acetaminophen/codeine group. They concluded that ibuprofen (if not contraindicated) is superior for achieving “deep anesthesia” to acetaminophen/codeine and placebo when given 1 hour before local anesthesia in patients diagnosed with symptomatic irreversible pulpitis in mandibular teeth (37). Moderasi and co-authors did not clinically assess the IANB through endodontic access or treatment of any kind. As endodontic access and treatment was used in the present study, correlations to Moderasi’s results appear to be of little value. Although TSL’s may have its own significance, it is possible that TSL’s do not accurately determine pulpal anesthesia. In the present study, endodontic access and treatment was used to determine success of the IANB as that is what is done clinically.

Parirokh and co-authors (38) studied the success of the IANB in mandibular first or second molars diagnosed with irreversible pulpitis following preoperative administration of ibuprofen or indomethacin. One-hundred and fifty patients participated in the randomized, double-blind study. They were separated into three groups of 50 patients each; placebo, 600 mg ibuprofen, and 75 mg indomethacin. A mandibular molar qualified if it presented with normal radiographic appearance and an exaggerated painful response to cold. There was no inclusion criterion of the patient being in active pain at the time of the study. They found success rates of the IANB in each group was 32% for placebo, 78% for ibuprofen, and 62% for indomethacin. They concluded that preoperative administration of ibuprofen and indomethacin significantly increased the success of the IANB in mandibular molars diagnosed with irreversible pulpitis (38). The
results of the present study are very similar to Parirokh’s findings when comparing the placebo groups. However, Parirokh reports much higher success for both of their experimental groups. It is possible that patients who participated in Parirokh’s study were not experiencing pain at the time of treatment (asymptomatic irreversible pulpitis), as this was not in their inclusion criteria. It has been shown that teeth that are actively experiencing pain, diagnosed with symptomatic irreversible pulpitis are more difficult to achieve profound pulpal anesthesia (20,100,101).

The earlier discussed studies (Oleson et al., Simpson et al., Ianiro et al., Aggarwal et al., Moderasi et al., Parirokh et al.) each used an anti-inflammatory agent. However, none of the studies took advantage of the strength of an opioid, and combined it with an anti-inflammatory agent. One should note that the present study did not address inflammation by using ibuprofen, or a similar agent. It may be of interest for future studies to combine the action and strength of an opioid analgesic with the anti-inflammatory effects of ibuprofen.

Li and co-authors (39) performed a systematic review and meta-analysis based on randomized controlled trials using preoperative oral nonsteroidal anti-inflammatory drugs for the success of the IANB. A total of 137 citations were identified by electronic and hand searching numerous scientific journal data banks. The electronic sources of their information were Medline (via OVID, 1948 to July 2011), Cochrane Central Register of Controlled Trials (CENTRAL, Issue 2, 2011), EMBASE (via OVID, 1984 to July 2011), Chinese BioMedical Literature Database (1978 to July 2011), China National Knowledge Infrastructure (1994 to July 2011), and WHO International Clinical Trials Registry
Platform. Using specific inclusion and exclusion criteria, the articles were narrowed down to seven articles that met their desired quality. The chosen articles were authored by Oleson et al., Simpson et al., Ianiro et al., Aggarwal et al., Moderasi et al., Parirokh et al., and Prasanna et al. (33,34,35,36,37,38,40). The inclusion criteria were, “pre-emptive randomized control trials or quasirandomized controlled trials exploring the effect and safety of NSAIDS for acute pulpitis. At least one mandibular posterior tooth of the participants was diagnosed as having acute pulpitis that needed endodontic access under IANB without limitation in participants’ sex, age, race, or socioeconomic status. The diagnostic criteria for acute pulpitis was an active response to an electronic pulp test or spontaneous pain. The intervention group received pre-operative, single-dose oral-administrated NSAIDs compared to a placebo in the control group. Outcome variables included pain intensity (PI) (detected by visual analog scale [VAS]), success rate of the anesthesia (SRA) (if supplemental anesthesia was used, IANB should be the initial anesthesia and SRA only stands for the success rate of the initial anesthesia), tooth sensitivity level (TSL), and adverse events (AEs)” (39). The exclusion criteria were: “review articles, cohort studies, and other types of studies, participants with periapical pathoses and who were hypersensitive to NSAIDs, pregnant, lactating, not reliable, and not able to return for follow-up, participants with a regular intake of NSAIDS or undergoing any other treatment for pulpitis, repetitive publication (only the well-described one was included)” (39). Meta-analysis was performed with Review Manager 5.1. Risk of bias was assessed using a Cochrane Collaboration’s tool for, with 6 of the 7 studies showing “low” bias and the Moderasi (37) study bias being “unclear”. Five of the
seven studies compared ibuprofen with a placebo, their results showed that the pooled outcome demonstrated that the ibuprofen group had 1.63 times the successful rate of the placebo, with statistical significance. When they combined all the data in a meta-analysis with 273 participants, they again found a significant difference between the experimental and placebo groups for the success rates of the IANB. Their conclusion was there is evidence that pre-emptive oral NSAIDs may have some good effects and are safe for increasing the success rate of the IANB (39). These findings differ from those of the present study. This could be explained by various sources of bias in the review process. The authors admit that bias could not be avoided completely. One possible confounding factor is that these studies were done in various parts of the world. Three studies were done in the USA, two in Iran, and two in India. These countries have different cultures, ideologies, and populations. Important to note, not all of the studies had an inclusion criterion of patients presenting with active pain. It is also evident that not all of the studies measured outcome in the same way. The study by Moderasi et al., for example, determined outcome by measuring tooth sensitivity levels, which possibly do not correlate directly with other studies that measured success rates of anesthesia by performing actual treatment. The review also stated that the number of participants in each study was small which lessened statistical power. The authors admit that because of these biases, the overall conclusions are limited and future studies are called for to help reach a stable outcome. It is possible that these conclusions are insignificant since only seven studies were analyzed, each of them with their own unique study design and variables.
It is interesting to note that Oleson et al., Simpson, et al., and Ianiro et al. each used 3.6 mL of anesthetic for their IANB. In the present study, we gave only 1.8 mL for the initial injection. This, however, has been shown to be of little importance as Nusstein et al. (6) demonstrated that increasing the amount of anesthetic from 1.8 mL to 3.6 mL does not significantly increase the success of the IANB.

It has been discussed that preoperative medication has in some cases seemed to increase the success rates of the IANB (35,37,38), while others have demonstrated no significant increase in the success rate (33,34,36). Possible explanations have also been provided that may, at least in part, explain these differences. Oleson et al. (33) noted that although preoperative ibuprofen inhibited prostaglandin production, the previous damage that had been done along with the action of other inflammatory mediators may explain the high rate of anesthetic failure. Simpson et al. (34) believed that a combination of ibuprofen and acetaminophen could be more beneficial than the ibuprofen alone as used by Oleson et al. This proved to be unsuccessful. The investigators in the present study proposed that the combination of two well-known analgesic agents (acetaminophen/hydrocodone) may prove enough to increase the low success rate for the IANB. The present investigators proposed that a hydrocodone/acetaminophen combination may prove beneficial. The most commonly used form of this medication (Vicodin) was chosen. It is possible that the lack of effect found in the present study correlates with Oleson’s findings. Even if the acetaminophen/hydrocodone combination suppresses pain through multiple mechanisms, this was not enough to overcome the
effects of the prostaglandin production, and previous damage, as well as the action of other inflammatory mediators.

The combination drug acetaminophen/hydrocodone was chosen for the present study in part for its proven analgesic effects. Studies have provided insight into the efficacy of acetaminophen/opioid combinations when used to control varying types of pain as well as different study models of pain. Miner and co-authors (41) studied acetaminophen, ibuprofen, acetaminophen/hydrocodone, and placebo for the relief of pain from a standard painful stimulus. Twenty-five subjects received 1000 mg of acetaminophen, 800 mg of ibuprofen, the combination of 650 mg of acetaminophen with 10 mg of hydrocodone, or placebo (800 mg of lactose) in a randomized order over four separate occasions each 1 week apart. Prior to receiving the drug on each study day, the subject was asked to place their hand in a bath of 0°C water for 45 seconds. Subjects completed a 100-mm visual analog scale (VAS) representing perceived pain during the exposure. The cold water exposure and VAS were repeated 1 hour after receiving the study drug. The mean decrease in VAS after receiving the study drug for acetaminophen was 10.2%, for ibuprofen -6.6% (negative meaning lack of effect), for acetaminophen/hydrocodone 9.5%, and for placebo -6.9% (also showing lack of effect). Acetaminophen and the acetaminophen/hydrocodone combination resulted in a similar decrease in pain. Conversely, ibuprofen and placebo had a similar lack of effect. Their findings demonstrate the analgesic efficacy of acetaminophen alone, as well as acetaminophen/hydrocodone in combination. Although this pain model is different than dental pain when performing root canal therapy, these data suggest pain management
using acetaminophen/hydrocodone may also be of benefit to the dental patient. Their data also suggests that measuring pain 1 hour after administration of medication is reasonable, as was done in the present study.

Roberts and co-authors (42) compared oxycodone and hydrocodone for the treatment of acute pain associated with fractures in emergency department patients. This study included emergency department patients over the age of 12 with fractures. Fractures included facial, trunk, upper extremity, and lower extremity fractures. Patients randomly received either oxycodone (5 mg orally) with acetaminophen (325 mg), or hydrocodone (5 mg orally) with acetaminophen (325 mg). There was no placebo group. The following information was recorded; verbal pain scores ranging from 0 to 10 with “0” defined as “no pain” and “10” defined as “worst pain imaginable” (done at baseline, 30 and 60 minutes); vital signs at baseline, 30 and 60 minutes; and adverse side effects. Sixty-seven subjects completed the emergency department study period. Thirty-five patients received oxycodone and thirty-two received hydrocodone. There was no significant difference between the two groups in age, weight, gender, ethnicity, diagnosis, baseline pain scores, or vital signs. Patients in both groups had pain relief (measured on the same 1-10 scale) from baseline to 30 minutes (oxycodone mean change 3.7; hydrocodone mean change 2.5) and from baseline to 60 minutes (oxycodone mean change 4.4; hydrocodone mean change 3.0). They found no difference in pain between the patients treated with oxycodone and hydrocodone at either time period. Data suggested that both oxycodone and hydrocodone are similarly effective in the first hour of treatment for emergency department patients with acute fractures (42). It is difficult to
assess the efficacy of these two drugs when no comparison to a placebo was made. The present study’s use of hydrocodone instead of oxycodone is supported by this data as there was no statistically significant difference between the two drugs. However, this may need to be studied further in the symptomatic irreversible pulpitis pain model and in an adult population.

Rodriguez and co-authors (43) studied the management of chronic cancer pain with codeine/acetaminophen and hydrocodone/acetaminophen. Their study included adult outpatients with cancer who had chronic moderate to severe cancer-related pain. Patients randomly were assigned to receive 1 tablet of codeine/acetaminophen (C/A) 30/500 mg or 1 tablet of hydrocodone/acetaminophen (H/A) 5/500 mg orally every 4 hours for 23 days. In both groups, if pain intensity was rated as >3 cm on a 10-cm VAS at week 1 or 2, the dosage was doubled to 2 tablets of 30/500 (C/A) or 2 tablets of 5/500 (H/A) given on the same schedule. The primary endpoint was the proportion of patients who achieved pain relief defined as a score of >1 on a 5-stage verbal rating scale (VRS) (0 = none; 1 = a little; 2 = some; 3 = a lot; and 4 = complete). The secondary endpoint was the proportion of patients in whom pain was decreased (Visual Analog Scale score ≤3 cm). Of the patients given C/A, 58% responded to the initial dose of 150/2500 mg/day, and 8% of the patients responded to the double dosage; and 34% did not experience any pain relief. In patients given H/A, pain was reported at none or mild in 56% of patients at the starting dose of 1 tablet of 5/500 mg; 15% of the patients did not respond to the initial dose, but did respond to the double dosage; the remaining 29% of patients did not experience relief. They found no significant differences between the two groups (43). The
dosage that was chosen in the present study was a single dose of 10 mg hydrocodone and 1,000 mg acetaminophen. The pain model investigated in Rodriguez’s study was a chronic issue related to pain in cancer patients. The present model differs in that the pain studied was an acute inflammatory pain in dental patients with a tooth diagnosed with symptomatic irreversible pulpitis. Although a cancer pain model is not the same as a dental pain model, Rodriguez’s findings are of interest as 15% more patients experienced relief when this dosage (10 mg hydrocodone/1,000 mg acetaminophen) was given as opposed to half this dosage. Overall efficacy is difficult to assess in Rodriguez’s study as no placebo was used. Their findings, however, support the present study’s dosage of 10 mg hydrocodone and 1,000 mg acetaminophen.

Ziccardi and co-authors (44) compared the efficacy and safety of single-dose acetaminophen with codeine (acetaminophen 600 mg/codeine 60 mg) to hydrocodone with ibuprofen (ibuprofen 400 mg/hydrocodone 15 mg), and placebo in patients with acute postoperative pain after third molar extractions. One hundred twenty-five patients participated in the study. A stopwatch was used to measure the time of first perceptible pain relief and meaningful pain relief. Meaningful pain relief was recorded by having “the patient stop the stopwatch when they first begin to feel any pain-relieving feeling of the drug, that is, when they first felt a little relief” (44). Verbal descriptors were used to record pain intensity and pain relief scores at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, and 8 hours after dosing. They found both experimental treatment groups were significantly superior to placebo for all analgesic measures. The ibuprofen/hydrocodone group was also better than the acetaminophen/codeine group from 2 through 8 hours after dosing. The duration
of analgesia was significantly longer for ibuprofen/hydrocodone (median, 5.5 hours compared with acetaminophen/codeine median, 3.03 hours) and placebo (median, 1.00 hours). Ibuprofen/hydrocodone was significantly better than the other 2 groups concerning the evaluation of effectiveness (44). Ziccardi’s study, as well as the present study addressed acute pain. These models differ, however, as Ziccardi and co-authors assessed the efficacy of these drugs postoperatively, whereas the present study assessed efficacy of preoperative administration of medication, while measuring pain intraoperatively. Ziccardi’s findings of hydrocodone being more efficacious than codeine supports the use of hydrocodone in the present study. It is also important to note that the combination with ibuprofen was more efficacious than that of the acetaminophen. This fact supports the idea for future investigations using a hydrocodone/ibuprofen combination.

Rosenthal and co-authors (45) studied the efficacy and safety of tramadol/acetaminophen (T/APAP), hydrocodone/acetaminophen (HC/APAP), and placebo after extraction of at least 2 impacted third molars. Two-hundred patients were randomly given one or two T/APAP tablets (37.5 mg/325 mg), 1 HC/APAP (10 mg/650 mg), or placebo. Measurements were made for hourly pain relief (PAR), pain intensity difference (PID), and combined PAR and PID (PRID) at 30 minutes and each successive hour for 8 hours. Onset of pain relief for T/APAP 37.5 mg/325 mg was 33.3 minutes, T/APAP 75 mg/650 mg was 34.0 minutes, and pain relief with HC/APAP was seen at 25.4 minutes. Other measurements were summary pain intensity and pain relief scores (total pain relief [TOTPAR], sum of pain intensity [SPID], and sum of pain relief and

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pain intensity differences [SPRID]). These were measured for 0 to 4 hours, 4 to 8 hours, and 0 to 8 hours. Tramadol/acetaminophen 75/650 mg and HC/APAP were statistically superior to placebo when measuring TOTPAR, SPID, and SPRID, as well as on hourly PAR, PID, and PRID over 6 hours. All active treatment was statistically superior to placebo in terms of onset of pain relief, duration of pain relief, and patients’ overall assessment of medication. Dose response was also significant with T/APAP (75/650 mg > 37.5/325 mg > placebo) concerning TOTPAR, SPID, and SPRID (45). Rosenthal and co-authors demonstrated pain relief with HC/APAP after 25.4 minutes which supports the present study design of waiting 60 minutes to start treatment after dosage. According to Rosenthal’s findings, this amount of time appears ample. Rosenthal’s findings also support the use of HC/APAP in an acute pain model. It is possible Rosenthal found significant pain relief due to the model in which the study was done. They, as well as Ziccardi (44) assessed the efficacy of these drugs postoperatively, whereas the present study assessed preoperative efficacy in a patient with active inflammation.

Newman and co-authors (46) investigated the efficacy and tolerability of oxycodone 5 mg/ibuprofen 400 mg compared with oxycodone 5 mg/acetaminophen 325 mg and hydrocodone 7.5 mg/acetaminophen 500 mg in patients with moderate-to-severe postoperative pain. Two-hundred forty-nine patients who experienced moderate-to-severe pain after surgical removal of at least 2 ipsilateral impacted third molars participated in this study. Patients were randomly given either oxycodone 5 mg/ibuprofen 400 mg, oxycodone 5 mg/acetaminophen 325 mg, hydrocodone 7.5 mg/acetaminophen 500 mg, or placebo. The primary measures were total pain relief through 6 hours after dosing
(TOTPAR6), sum of pain intensity differences through 6 hours (SPID6), and adverse events. Secondary efficacy measures included SPID3 and TOTPAR3, peak pain relief, peak pain intensity difference, time to onset of pain relief, time to use of rescue medication, proportion of patients reporting pain half gone, and the patient’s global evaluation of the medication. Data indicated that oxycodone 5 mg/ibuprofen 400 mg provided significantly greater analgesia compared with oxycodone 5 mg/acetaminophen 325 mg, hydrocodone 7.5 mg/acetaminophen 500 mg, and placebo. Oxycodone 5 mg/ibuprofen 400 mg was significantly more effective compared with all other treatment on all secondary end points, with the exception of the time to onset of analgesia in which there was no difference. Time of onset was found to be 30.4 minutes for oxycodone 5 mg/ibuprofen 400 mg, 28.2 minutes for oxycodone 5 mg/acetaminophen 325 mg, and 41.1 minutes for hydrocodone 7.5 mg/acetaminophen 500 mg. SPID6 values also differed significantly when comparing oxycodone 5 mg/ibuprofen 400 mg to the other groups suggesting it may have a superior ability to suppress pain. Newman and co-authors found the time to onset of the hydrocodone/acetaminophen group to be 41.1 minutes. This supports the present study as treatment was initiated 60 minutes following dosage. Newman used a lower dosage of hydrocodone/acetaminophen than the present study. It is possible that hydrocodone/acetaminophen may have been as efficacious as the ibuprofen/hydrocodone had the dosage been increased to the dosage of the present study (10 mg hydrocodone/1,000 mg acetaminophen). The oxycodone/ibuprofen may have performed better than the other drugs in Newman’s study due to the anti-inflammatory properties of ibuprofen. These findings may indicate further investigation using
oxycodone/ibuprofen in the present study model, as inflammation is believed to play a large part in the pain related to a tooth diagnosed with symptomatic irreversible pulpitis. Newman’s study, however, differs from the present study model, but similar to Ziccardi et al. (44) and Rosenthal et al. (45), as they assessed the efficacy of these drugs postoperatively, whereas the present study assessed preoperative efficacy in a patient with active inflammation.

It has been generally accepted that as age increases, pain threshold increases as well. Harkins and co-authors (93), however, questioned the generality of this idea. They studied the pain threshold for electrical stimulation of healthy, unfilled teeth in young and elderly women. Twenty women in the age range of 20 to 81 were divided into two groups determined by their age. The “young group” consisted of women of a mean age of 22.3 years, and the “elder group” consisted of women of a mean of 70.3 years. Teeth were stimulated at a level determined by each individual’s threshold value. Two levels of electrical stimulation were used. The low level was 1 µA above threshold, and the high level was set at 3 µA above threshold. Their results showed that the difference of determined threshold for the two groups differed by only 1 µA, which was not significant. Their data suggest that sensory threshold for noxious electrical stimulation may not increase with age. In the present study, the mean age of the patients in the placebo group was 35.7 years with a maximum of 61 and minimum of 18 (Table 1). The mean age of patients in the acetaminophen/hydrocodone group was 35.0 years with a maximum of 67 and minimum of 20. There was no statistically significant difference
between the two groups in terms of age, thus the potential of age influencing the amount of pain felt between groups was minimized (Table 1).

A possible confounding element of the present study is the initial pain the patient was experiencing when presenting for the study. Logically the patients must have been experiencing a wide range of initial pain. If patients in either the placebo or experimental group were experiencing, on average, greater pain than the other group, the data would have been skewed accordingly.

“We did not expect to see a significant difference in initial pain between the medication and placebo groups, due to the fact that we controlled the experimental patient population via the inclusion criteria and all subjects had a clinical diagnosis of mandibular posterior irreversible pulpitis with moderate-to-severe pain.” (33)

“The presence or absence of initial pain does; however, seem to have an effect on IAN block success and failure rates. Dunbar et al. (10) studied IAN block success in healthy asymptomatic first molars. Anesthetic block success was defined as achieving an 80 reading on an EPT within 15 minutes and keeping this reading for 60 minutes. The IAN block success was 42%. Anesthetic failure, defined as never achieving two 80 readings during the 60 min, was 32% with the IAN block. There are many other studies on IAN block failure in asymptomatic patients that support Dunbar’s results (10). According to Mikesell et al. (13), Steinkruger et al. (15), and Nusstein et al. (6), the inferior alveolar nerve block will fail (no two consecutive 80 readings) from 2% to 9% in the second molar, from 17% to 21% in the first molar and from 10% to 11% in the first premolar. Judging from these studies, the lowest failure rate will occur in the second
molar, followed by the first premolar and finally the first molar. A possible reason for the higher success rate in the second molar may relate to the central core theory because the innervation to the second molar is in the outer core of the nerve bundle. Hence, the concentration of anesthetic solution would be high in the outer core.” (101)

“Matthews et al. (101) evaluated the anesthetic efficacy of the supplemental infiltration injection of 4% articaine with 1:100,000 epinephrine in mandibular posterior teeth diagnosed with irreversible pulpitis when the conventional IAN block failed. Anesthetic success of the IAN block was determined based upon the patient stopping the operator at any time during treatment and recording access pain as greater than mild (VAS >54 mm). Twenty-seven out of fifty-five (33%) patients had anesthetic success. Matthews et al. (35) reported initial pain ratings similar to that of the current study, which were all moderate-to-severe.” (34)

“When studying irreversible pulpitis patients, Claffey et al. (19) found an initial pain rating of 95.6 +/-31.3 mm in the lidocaine group and an initial mean pain intensity rating of 96.4 +/-32.0 mm in the articaine group. The success rate for the inferior alveolar nerve block using articaine was 24% and for the lidocaine solution success was 23%. Kennedy et al. (102) found an initial pain rating of 115.1 +/-37.8 mm and 107.1 +/- 33.9 mm in the two study groups they utilized.” (101) “Oleson et al. (33) observed initial pain ratings of 126.39 +/-19.7 mm and 130.1 +/-20.2 mm in their two study groups. The success rate they found for the IAN block anesthetizing posterior mandibular teeth with a diagnosis of irreversible pulpitis was 41% after premedication with ibuprofen and 35% for the placebo group. The populations in these studies (19, 101, 102) and in the current
study were referred from the emergency clinic or individual clinics of The Ohio State University College of Dentistry or were referred from private practitioners outside of the university. Though the reporting of pain is always subjective, it is likely that the current study had a similar patient pool in terms of initial pain as the other studies (19, 101, 102) with the mean pain ratings being classified as moderate-to-severe in intensity.” (34)

In the present study, both groups had patients that were experiencing a mean of 125.1 mm of pain as indicated by the VAS (Table 1 and Figure 1). As both groups were statistically experiencing similar levels of pain, we were able to minimize the skewing of data in terms of initial pain felt by the patients.

Pain sensory, perception, and application is very complex. To add to this complexity is the anxiety, or even fear, of the dentist. Vika and co-authors found that nearly 17% of dental patients showed high anxiety for their last dental appointment (23). Van Wijk and co-authors showed that patients who were anxious reported more pain than did those patients who were not anxious (24). Furthermore, not only has it been shown that these anxious patients report more pain, but they also have less tolerance for pain (26).

As suggested in the above studies, it appears that anxiety can play a role in the often difficult nature of pain management in the dental patient. Thus, it is important to note the wide range in anxiety found in patients of the present study (Table 2). Of the placebo group, 32% had low levels of anxiety, 46% had moderate anxiety, 8% had high anxiety, and 14% had severe anxiety. Of the acetaminophen/hydrocodone group, 30% had low anxiety, 32% had moderate anxiety, 12% had high anxiety, and 26% had severe
anxiety. There was no statistically significant difference between the two groups (P = 0.2073). Patients were asked to complete Corah’s Dental Anxiety Scale (70,71). This is a four item, multiple choice questionnaire describing four different dental situations. The patient was able to answer the question “A” thru “E” with “A” yielding 1 point and “E” yielding five points. The values are then summed to yield a total of 4-20 points with four describing a relaxed patient, and 20 indicating a very anxious patient (70,71). In the present study, there was no significant difference between the placebo group and the acetaminophen/hydrocodone group regarding the anxiety level of the patient (P = 0.2073), thus we were able to minimize the possible influence that anxiety may play in the reporting of pain by each group.

It has been suggested that food intake prior to administration of oral medications may alter the absorption rate of the medication. Divoll and co-authors (94) administered 650 mg of acetaminophen on five separate occasions, to 24 healthy volunteers. Five modes of administration were used: intravenous acetaminophen by 5-minute infusion; oral acetaminophen as two 325 mg tablets in the fasting state; oral acetaminophen 650 mg as an elixir preparation in the fasting state; tablets with food; and elixir with food. Plasma concentrations of acetaminophen were measured for up to 12 hours after dosing. They found that in each of the four oral dosing modes there was a significant difference between the young and elderly groups with respect to peak plasma concentrations (P < 0.001), time to peak plasma concentration (P < 0.001), and systemic availability (P < 0.01). It is important to note, however, that no significant difference was found in peak acetaminophen plasma concentration or time of peak concentration as a function of age.
Interestingly, they found that food seems to slow the rate of absorption of both of the oral preparations. However, when either of the oral preparations were administered with food, they found no statistically significant difference in regard to absolute systemic availability (94). In the present study, 56% of patients in the placebo group, and 60% of patients in the acetaminophen/hydrocodone group ate food at most 6 hours before participating in the study (Table 3). There was no statistically significant difference between the two groups, thus we were able to minimize any confounding factors such as rate of absorption, time to peak plasma concentration, or systemic availability between the two groups.

Moeller and co-authors (95) also demonstrated a lack of effect regarding food intake prior to administration of oral medication. They performed a single-dose, double-blind, placebo-controlled study on the time to onset of analgesia and analgesic efficacy of 1000 mg acetaminophen. The study population consisted of patients in dental pain after extraction of one mandibular third molar. With a population of 242 patients, their results demonstrated a median time to onset of analgesia of 45 minutes and median time to pain relief of 60 minutes. There was no control of the number of patients who had fasted or had eaten when medication was given. Considering the findings of Moeller’s study, it may be suggested that the present study allowed enough time (60 minutes) for the onset of analgesia considering 56.0% of the placebo group and 60.0% of the acetaminophen/hydrocodone group had eaten food within 6 hours of oral dosing while 44% of the placebo group and 40% of the acetaminophen/hydrocodone group had not eaten within 6 hours of oral dosing (Table 3). Again, there was no statistically significant
difference between the two groups, thus we were able to minimize these confounding factors.

Research has been done on gender differences in analgesia for endodontic pain. Ryan and co-authors (50) performed a clinical trial of 43 patients who were randomly given 600 mg ibuprofen, placebo, or pentazocine 50 mg/0.5 mg naloxone immediately after endodontic treatment. Their emphasis was on analgesic differences between the sexes. Both necrotic and irreversible pulpitis cases were included. Pain was measured using a 100 mm visual analog scale at 5 time periods following endodontic treatment; 0, 6, 12, 18, and 24 hours. In all medication groups, women had lower pain scores than men. However, this was not significant. There was a statistically significant difference found within the pentazocine/naloxone group in that men had statistically higher post-operative pain levels than women. Their data suggest that there may be a correlation between gender and analgesic efficacy of pentazocine/naloxone in regards to post-operative endodontic pain (50).

Gear and co-authors (96) showed a difference between males and females who were given pentazocine, butorphanol, and nalbuphrine after the extraction of impacted third molars. Females had lower pain scores in response to butorphanol compared with morphine at 60 minutes, while men had lower pain scores in response to morphine when compared to butorphanol (96).

Miller and co-authors (98) studied sex difference in the analgesic response to mu versus kappa opioids in the management of acute moderate to severe pain in emergency department patients. Patients included those with acute uncomplicated fractures,
dislocations, severe sprains, or other isolated injuries. A comparison was done between the prototypical mu-receptor agonist, morphine sulfate, and the prototypical kappa agonist, butorphanol. A total of ninety-four patients were in the study, with 49 (52%) males and 45 (48%) females. The data showed at 60 minutes, females had significantly lower visual analog scores with butorphanol compared with morphine (P = 0.046). At 60 minutes, they reported a trend for a difference, but not a significant difference in response of males versus females to morphine, with females responding with higher VAS scores than males (P = 0.06) (98).

These studies indicate a possible correlation of gender and pain perception and/or efficacy of certain medications in the management of pain. It is important to note that in the present study, there was no statistically significant difference with regard to gender of participants (Table 3). The placebo group had 27 males and 23 females, and the acetaminophen/hydrocodone group had 19 males and 31 females (P = 0.1085). Therefore, gender is less likely to play a role in the results when there is no significant difference between groups.

An important consideration when evaluating the success of the IANB is if there is a difference of success between tooth types. Oleson and co-authors (33) studied the administration of preoperative ibuprofen on the efficacy of the IANB in patients with irreversible pulpitis. Their success rates for the IANB were 29-36% for the 1st molars, 21-25% for the 2nd molars, and 54-60% for the premolars (33). Simpson et al. showed success rates of 17-35% for 1st molars, 33-37% for 2nd molars, and 14-25% for premolars (34). Stanley et al. showed success rates of 26-50% for 1st molars, 24-45% for 2nd molars,
and 44-56% for premolars (100). Considering these varying success rates between tooth type, it is important to note the present study had 6 premolars in the placebo group, and 7 premolars in the experimental group and 44 molars in the placebo group and 43 molars in the experimental group (Table 3). There was no statistically significant difference.

Minimizing the difference of tooth type between groups was very important in the present study. If one group or the other had, for example, been performed solely on premolars, and the other group consisted of only second molars, it is likely that there would have been a significant difference in success rates of the IANB regardless of other factors.

Table 7 illustrates that for the placebo group, 32% of 1st molars, 29% of second molars, 50% of 3rd molars, and 0% of premolars were successfully anesthetized using only the IANB. It also shows that for the acetaminophen/hydrocodone group, 38% of 1st molars, 24% of second molars, no 3rd molars were tested, and 29% of premolars were successfully anesthetized using only the IANB. Note the poor rate of success with premolars. This again illustrates the importance of having an even distribution of tooth type between the placebo and treatment groups which the present study had.

Table 8 shows that for the placebo group, 37% of 1st molars, 50% of second molars, 0% of 3rd molars, and 50% of premolars were successfully anesthetized using an articaine infiltration after failure of the IANB. It also shows that for the acetaminophen/hydrocodone group, 31% of 1st molars, 62% of second molars, no 3rd molars were tested, and 80% of premolars were successfully anesthetized using an articaine infiltration after failure of the IANB. When analyzing the success rates of the
teeth that received the buccal infiltration, it is important to note the relatively small number of teeth analyzed. The 0% success rate for the 3\textsuperscript{rd} molars in the placebo group, for example, had only 1 tooth analyzed. Thus, the 1 tooth failed resulting in a success rate of 0%. It is interesting to note the increased success of premolars when using the buccal infiltration. The placebo group went from 0% to 50% success and the treatment group went from 29% to 80% success.

Table 9 illustrates that for the placebo group, 67% of 1\textsuperscript{st} molars, 80% of second molars, 100% of 3\textsuperscript{rd} molars, and 100% of premolars were successfully anesthetized using an intraosseous injection after failure of the IANB and buccal infiltration with articaine. It also shows that for the acetaminophen/hydrocodone group, 82% of 1\textsuperscript{st} molars, 40% of second molars, no 3\textsuperscript{rd} molars were tested, and 100% of premolars were successfully anesthetized using an intraosseous injection after failure of the IANB and buccal infiltration with articaine. The intraosseous injection proved to be very successful for all tooth types. These findings correlate well with previous studies.

“Pearce (103) completed a study in which a supplemental intraosseous injection was administered when an IAN block failed. Results showed that the intraosseous (I/O) injection was effective 90% of the time. Parente et al. (104) conducted a study that evaluated the efficacy of a supplemental intraosseous injection of 2% lidocaine with 1:100,000 epinephrine in maxillary and mandibular teeth diagnosed with irreversible pulpitis. They reported a success rate of 88%.

Reisman et al. (73) evaluated success of repeated intraosseous injections with 3% mepivacaine in mandibular teeth with irreversible pulpitis. They found that the initial I/O
injection resulted in 80% success and a repeat I/O injection of 3% mepivacaine raised the success rate to 98%.

Nusstein et al. (6) evaluated the efficacy of the X-tip™ intraosseous system in mandibular teeth with irreversible pulpitis. After failure of the IAN block, and supplemental intraosseous injection with 2% lidocaine was administered via the X-tip™ system. They found the intraosseous injection with the X-tip™ system to be 82% successful overall.

Oleson et al. (33) studied the effect of 800 mg ibuprofen versus placebo given 45 minutes prior to initiation of root canal therapy in patients diagnosed with symptomatic irreversible pulpitis. After failure of an IAN block with 2% lidocaine with 1:100,000 epinephrine and a supplemental buccal infiltration of 4% articaine with 1:100,000 epinephrine, patients were given an intraosseous injection with 2% lidocaine with 1:100,000 epinephrine. The results showed an 88% success rate in the ibuprofen group versus 94% for placebo, a difference that was not statistically significant.

Simpson et al. (34) conducted a similar study researching the effect of 800 mg of ibuprofen and 1000 mg of acetaminophen given together (versus a placebo) 45 minutes before initiation of root canal therapy in patients diagnosed with symptomatic irreversible pulpitis. The results showed no significant difference in the success of supplemental intraosseous injections of 2% lidocaine with 1:100,000 epinephrine given after failure of the IAN block and a supplemental buccal infiltration of 4% articaine with 1:100,000 epinephrine (ibuprofen/acetaminophen: 86%, placebo: 79%).” (100)
It has been questioned if pain medication could affect the results of pulp testing. Kardelis and co-authors (47) studied the effects of narcotic pain reliever on pulp testing in women. Fifteen women, with healthy, uninflamed tooth pulp were randomly given an oral dose of 10 mg hydrocodone/1000 mg acetaminophen or placebo. At baseline (before administration of drug), and after 2, 4, and 8 hours, sensitivity thresholds were evaluated for each subject using 4 tests: electric pulp tester applied on exposed root; electric pulp tester on adjacent mucosa; increasing probe pressure on adjacent mucosa; and decreasing cold probe on the exposed root. The electric pulp testing was done on the exposed root of each tested tooth. The electric testing of the mucosa was done near the mucogingival junction adjacent to the corresponding test tooth. In both electric tests, the patients were instructed to raise a hand the moment they felt any type of sensation. The cold tests were performed using a thermal coupler which allows slow decreases in temperature. The temperature was lowered by 2.5°C at a time from 25°C and placed on the exposed root of the test tooth. The patients were instructed to raise a hand the moment moderate pain was experienced. Their data indicated that there were no statistically significant differences between the experimental drug and placebo at any time point or for any of the 4 tests. They concluded that oral systemic administration of 10 mg hydrocodone/1000 mg acetaminophen has little impact on sensitivity of healthy pulp or mucosa in women as measured by these commonly used tests (47). It is of note that this study had a relatively low number of participants, and it was performed with women only. This pain model differs than that of the present study, as the present study involved actively inflamed, symptomatic, irreversible pulpitis cases. In the present study, the same dosage of the
same medication was used. The present study demonstrated a gradual decrease in mean VAS scores upon cold testing after administration of medications for both the experimental and placebo groups (Table 4 and Figure 1). There was no statistically significant difference between the two groups, and pain did decrease in both groups. Kardelis’s findings support what was reported in the present study. It is possible that the gradual decrease in pain in both groups was due to gradual reduction in anxiety of the patient. As the patient was able to rest between cold tests (administered every 10 minutes) the patients generally demonstrated a calmer demeanor. This decrease in anxiety level may have been due to meeting and liking their operator. It was also common for patients to show less dramatic reactions as time elapsed (Table 5). It was interesting to note a complete lack of sensation on two occasions in the placebo group, and seven occasions in the acetaminophen/hydrocodone group. The two instances in the placebo group occurred at 20 and 30 minutes after administration of the placebo drug. In the treatment group, each of the 7 reports of no pain occurred at minute 40 or later. One possible explanation for these occurrences later on may be that the patient, with each passing 10 minute period was feeling relief that treatment time was closer, and that they would soon be out of pain. It is also possible that the instances that occurred in the placebo group may have been due to the patient’s ability to “over-ride” the pain sensation. This may have been a conscious decision of the patient. This may have been done as the patient did not want to, in their mind, “upset” the operator. These possibilities may also, at least partially, explain these findings in the placebo group. These occurrences in the experimental group, however, may be attributed to something more.
One possible explanation deals with the mechanisms of action of hydrocodone. Two mechanisms will be discussed here. First, peripheral receptors in skin, muscles, joints, and viscera respond to pain stimuli. In this case, receptors in the dental pulp are responding as pain to ice stimulation. These stimuli can be influenced at the site where they first synapse in the spinal, or medullary dorsal horn. This modulation of sensory stimuli relies on the binding of opioid receptors in the midbrain. This binding in the midbrain ultimately leads to the release of the neurotransmitters serotonin and norepinephrine which inhibit those pain stimuli coming from the skin, muscles, joints, viscera, and dental pulp. This is called the descending pain inhibitory system (51).

Perception of pain for these few patients may have been modulated at any of these places along this pathway. Secondly, opioids like hydrocodone can modulate pain by acting at opioid receptors in the brain that are not associated with the descending pain inhibitory system. Opioids bind to specific receptors in the nervous system and other tissues. This binding occurs at binding sites that involve the primary classes of opioid receptors, \( \mu, \kappa, \delta \) (mu, kappa, and delta). The action of opioids at these sites influences the emotional reaction to and interpretation of the pain stimulus (51). These few patients possibly may have been emotionally effected by the hydrocodone to the point of not experiencing the pain altogether. Either one or a combination of these two mechanisms may have, in these few instances, modulated the perceived pain of the patient so that pain was completely undetected. This explanation is less likely because we see this report of no pain to ice in only a few of the experimental group, and we also saw this report in the placebo group. It should also be noted that pain is subject to interpretation of the
individual who is feeling the pain. Pain that is experienced by some may be quite
tolerable, while the same stimulus may be intolerable to others. This phenomenon may
also contribute to the reporting of pain by patients in the present study. It is also
important to consider what is known as the “placebo-effect” (99) which describes a
phenomenon in which a patient may appear to receive benefits, or symptoms that
normally correlate with the receiving of an actual treatment. In the present study, 15 of
the 45 patients who were part of the placebo group, reported having symptoms of the
treatment drug (Table 3). As the “symptom” criterion was not added until later in the
present study, it is unclear if the one patient in the placebo group who reported having no
response to the cold test was experiencing a “placebo effect” or not as this patient was
one that we did not record this criterion. It is possible, however, that the described patient
experienced a “placebo effect” to a degree that pain from the ice test was no longer
experienced by the patient.

Another study was done to investigate if pain medication could affect the results
of pulp testing. Carnes and co-authors (48) investigated the changes in pain threshold
determined by electric pulp testing after administration of one of the following
medications: 100 mg meperidine, 220 mg naproxen sodium, 1000 mg acetaminophen, or
placebo. Eighty patients who presented with moderate to severe odontogenic pain
participated. An explanation was not given as to how pain was determined. Electric pulp
test readings were taken at baseline, and then each patient was allowed to wait in the
waiting room for 45 minutes to allow for drug absorption. The patients were then re-
tested using EPT. Their results showed that among the 4 possible treatments,
acetaminophen was the only drug that demonstrated a statistically significant difference for pain threshold change from test 1 to test 2. However, even this change was so slight that the investigators concluded that clinically there is likely no difference in pain threshold for patients who are administered these drugs preoperatively as measured with EPT (48). It is of note that 1000 mg of acetaminophen demonstrated this statistically significant difference, as 1000 mg of acetaminophen was used in the present study. It is difficult to directly compare pain modulation of this study to the present study, as no explanation was made by Carnes and co-authors as to how pain was measured. It is also of worth to note Carnes et al. waited 45 minutes for drug absorption. Their findings support the present study in waiting 60 minutes to initiate treatment after drug administration. The significant findings by Carnes and co-authors may be explained by the way pain was rated, (which was not described in their study). Also, electric pulp testing was used in their study, while ice testing was the test of choice in the present study. It is possible that these two methods may have played a role in the statistically differing findings.

It has also been studied whether cold-induced pain, as is often used for dental diagnoses, would be affected by the administration of acetaminophen. Foss and co-authors (50) used a cold-pressor test to study the dose-related effects of acetaminophen on cold-induced pain. Eighteen healthy adult patients participated. Administration of doses of acetaminophen (325, 650, 1000 mg) or placebo was given at 4 different sessions per subject. Each session was separated by at least 48 hours. Each subject received each possible drug once. At the onset of each session one of the described doses or placebo
were administered randomly. The cold-pressor test was initiated 110 minutes after administration of the experimental drug. The cold-pressor test involved submerging the patients’ forearm in ice water for 180 seconds. Pain levels were recorded at 30, 70, 110, and 170 seconds after the immersion. They observed statistically significant differences of both dose and time (pain and bothersome ratings decreased with increasing drug dose and increased over time). However, in a pair wise comparison, only the highest dose of acetaminophen (1000 mg) compared to placebo reached statistical significance. This dose of acetaminophen is of significance, as this was the dose of acetaminophen administered in the present study. Thus, according to theses data, the 1000 mg of acetaminophen as used in the present study appears justified. It is also important to acknowledge that with recent changes in federal regulations, this dosage of acetaminophen is no longer available when combined with an opioid such as hydrocodone or oxycodone. Acetaminophen/hydrocodone combinations are no longer available in 5:500 mg (hydrocodone/acetaminophen) formulations. The amount of acetaminophen has been changed to a maximum of either a 300 mg or 325 mg per 5 mg of hydrocodone in available preparations. This is due largely to the fact that in the case of overdose, the accumulation of N-acetyl-p-benzoquinoneimine, a byproduct of acetaminophen, can cause serious harm to the liver. The dosage of 10 mg hydrocodone and 1000 mg acetaminophen was given for the present study because this was a commonly administered dose at the time this study was started, which was prior to these changes.
The combination of hydrocodone and acetaminophen was chosen for the experimental drug in the present study. Each of these drugs will be discussed separately.

Hydrocodone is a phenanthrene opioid that is similar in structure to codeine and morphine. It is primarily used as an oral analgesic. Parenterally administered analgesics are far less commonly used in a dental setting. As hydrocodone is normally used as an oral analgesic, it was a convenient choice for the present study. It is also used as an antitussive. Hydrocodone/acetaminophen combinations are the most prescribed analgesics in the United States. These are considered a Schedule III narcotic by the U.S. Drug Enforcement Administration (51). Hydrocodone, when prescribed alone is considered a Schedule II narcotic (63).

Recently Janecka and co-authors performed a review of the last 25 years of research on opioids (76). They explained that endogenous opioid peptides are molecules that are produced in the central nervous system (CNS) and in glands such as the adrenal glands and pituitary. These naturally occurring peptides produce the same effect as chemicals that are known as “classic alkaloid opioids” such as heroine and morphine. These peptides can function both as hormones and as neuromodulators. The ones that function as hormones are produced by a gland in the body, and then are transported to various distant sites in the body where they perform a function. The ones that function as neuromodulators are produced and secreted by nerve cells in the brain and spinal cord and they modulate the actions of other neurotransmitters. The development of the synthetic opioid receptor-specific ligands has become very important in the pharmaceutical industry (76).
Opioid receptors collectively belong to the large family of receptors known as G-protein coupled receptors (76). There are three main opioid receptors: mu (µ), kappa (κ), and delta (δ), although up to seventeen have been reported. Each receptor is distributed differently throughout the CNS and peripheral nervous system. The µ receptor is the site used for pure opioid agonists such as morphine and has the most potent analgesic effects. Considering the model of the present study is concerned with these analgesic effects, it is logical that an opioid (hydrocodone) acting on these µ receptors is a good choice as an experimental medication. The delta receptor is less efficacious in mediating pain relief. The kappa receptor mediates pain relief in peripheral tissues. When these agonists bind to these sites, analgesia is the result. This analgesia has been the most thoroughly studied among the many effects of opioids. We know that opioids acting at opioid receptors in spinal and supraspinal sites can produce clinically effective analgesia. The understanding that opioids work in the CNS came first, followed by documentation of direct peripheral analgesic actions of opioids (51).

It should also be noted that an “orphan” (ORL) receptor was recently identified (77). This receptor is quite different than the three previously discussed receptors in that they do not mediate typical opioid, but rather antiopioid effects (76). It may be of interest for future studies to further investigate the ORL receptor and its possible effects.

Opioid receptors are bound by small molecules called ligands. There are two types of ligands: alkaloids and peptides. Morphine was the first discovered opiate alkaloid. It was isolated from the poppy seed in 1803. (76) Morphine, and other similar opiates are regularly used in clinical practice to manage severe pain syndromes or for
anesthetic purposes (76). The hydrocodone in the present study is converted into hydromorphone (78), which is a more potent opioid because it has a stronger affinity to the µ receptor. This will be discussed in greater detail later. It is important to consider the similar properties of morphine and hydromorphone in the present study and to consider it is estimated to have a potency ten times greater than morphine (64).

Peptide ligands can be classified into two groups “typical” and “atypical” (79). Included in the list of “typical” opioid peptides are: enkephalins, dynorphins, and β-endorphins. The pre-cursor molecules for these peptides are all found in the CNS, however, it has been confirmed that they too are present in peripheral tissues (80). All of these endogenous peptides vary in their affinity for µ, δ, and κ opioid receptors. The “atypical” opioid peptides refer to those peptides that originate from a variety of precursor proteins and can have various amino acid sequences, thus they are “atypical” (76). Hemorphins are endogenous peptides that are generated when hemoglobin is hydrolyzed. Hemorphins occur naturally in the brain, plasma, and cerebrospinal fluid (81). Another example of atypical peptides have recently been isolated from the brain tissue, Tyr-MIF-1 (82) and Tyr-W-MIF-1 (83,84). These are very important as their binding is highly selective to µ compared with δ and κ receptors. A group of atypical peptides have also been isolated from amphibian skin that have an extremely high affinity for opioid receptors (85,86). Dermorphins are heptapeptides that have been isolated from the skin of the South American frog Phyllomedusa sauvagei (85) and is among the most potent opioid peptides to µ selectivity (77). Endomorphins are the first reported brain
peptides with high affinity and selectivity for the µ receptor and for this, endomorphins have been considered the endogenous µ opioid receptor ligand (77).

The mechanisms of action of opioids such as hydrocodone have been greatly studied. Three main mechanisms will be discussed here. First, peripheral receptors in skin, muscles, joints, and viscera respond to pain stimuli. These stimuli can be influenced at the site where they first synapse in the spinal, or medullary dorsal horn. This modulation of sensory stimuli relies on the binding of opioid receptors in the midbrain. This binding in the midbrain ultimately leads to the release of the neurotransmitters serotonin and norepinephrine which inhibit those pain stimuli coming from the skin, muscles, joints, and viscera. This is called the descending pain inhibitory system (51).

Secondly, opioids like hydrocodone can modulate pain by acting at opioid receptors in the brain that are not associated with the descending pain inhibitory system. Opioids bind to specific receptors in the nervous system and other tissues. This binding occurs at binding sites that involve the primary classes of opioid receptors, µ, κ, δ (mu, kappa, and delta). The action of opioids at these sites influences the emotional reaction to and interpretation of the pain stimulus (51).

Lastly, opioid agonists can act at receptors located on the terminals of specialized nerve fibers that connect the CNS and peripheral nervous systems. This type of action is seen when opioids are directly administered into, for example, a joint or intrathecal space (51).

When hydrocodone is given systemically, such as in this study, the opioids have access to all potential sites of action. With all of these mechanisms working together,
there is likely a synergistic effect resulting in increased potency, and consequently, less toxicity. Hydrocodone toxicity, however, is not of clinical concern when administered properly at a single and therapeutic dose, as was done in the present study (51).

For the present study, we must also understand that hydrocodone affects the CNS with a combination of stimulation and depression. The CNS effects include analgesia, drowsiness, euphoria, dysphoria, respiratory depression, suppression of cough reflex, pupillary constriction, suppression and or enhancement of pituitary hormones, and initial stimulation in the medulla depressing vomiting. A significant feature of opioid analgesics is that they are more effective against continuous, dull, aching pain than sharp, intermittent pain (51). The pain that patients experienced in the present study was during actual treatment which resulted in what would be described as “sharp” pain. This is a possible explanation as to why hydrocodone did not produce a significant decrease in the success of the IANB. In other words, the data of the present study suggest that even with a successful IANB, hydrocodone and acetaminophen combined is not enough to provide the needed analgesic effect to reach a significant increase in the success of the IANB.

It has been discussed that hydrocodone works on multiple levels, using many ligands which bind to numerous receptors. The complexity of this drug must be discussed because it is by these many mechanisms of action that the investigators suggest that it may increase the success rate of the IANB. The data of the present study suggest, however, that this is incorrect and even though the combination of acetaminophen and hydrocodone act on many levels and at numerous locations in the body, it did not prove enough to increase the success rate of the IANB.
Dosage used in the present study was determined considering the fact that it has been shown that the therapeutic dose of hydrocodone is 10 mg/150 kg of body weight. This dosage is commonly used for moderate-to-severe pain (51). Patient weight was not measured in this study, nor was it an inclusion or exclusion criterion. We must note, however, that according to the Centers for Disease Control and Prevention the average weight for men aged 20-74 years rose dramatically from 166.3 pounds in 1960 to 191 pounds in 2002, while the average weight for women the same age increased from 140.2 pounds in 1960 to 164.3 pounds in 2002 (88). It is possible that as weight increases, so should dosing of medication. It is unlikely, however, that an equivalent dosage increase of hydrocodone to compensate for increased weight would have made a significant difference in the present study. This is evident considering most people (75.7%) who received the drug reported side-effects of the treatment drug (Table 3).

The peripheral pharmacologic effects of hydrocodone are mainly on smooth muscle tone that can have therapeutic and toxic implications. It also affects gastrointestinal activity by reducing glandular secretions and by promoting absorption of fluid from the gastrointestinal tract. The peripheral analgesic effect of opioids has recently become more significant. Much of this effect is associated with opioid receptors located on the terminals of nociceptors. With tissue insult, opioid receptors upregulate. This up-regulation of opioid receptors can be taken advantage of by introducing exogenous opioid agonists that can then bind to these receptors producing analgesia at the very site of tissue insult (51). In the present study, hydrocodone was administered orally, and not placed at the very site of tissue insult – the pulp.
Most opioids, including hydrocodone, are much more effective when given parenterally rather than orally in the same doses. The large difference in effect after oral administration is caused by the first pass metabolism through the liver. The hepatic enzyme Cytochrome P450 2D6 (CYP2D6) converts hydrocodone into hydromorphone, which is a more potent opioid because it has a stronger affinity for the µ receptor. Analgesic effect by hydrocodone is highly dependent on metabolism to hydromorphone by CYP2D6 (78). In the general population, there are patients who are less responsive to hydrocodone. It has been shown that approximately 10% of caucasians fit this description (88). Recently, in a genotyping study, Jannetto and co-authors showed that these less responsive individuals have inherited polymorphisms in their CYP2D6 allele (89). These patients are considered as “poor or intermediate metabolizers” of opioid medications. It is possible these patients would need higher concentrations of opioids to experience the same therapeutic benefits as a person without the polymorphism in their CYP2D6 (89). There is also a population of what are considered, “rapid metabolizers” of hydrocodone. Approximately 7% of Caucasians fit this description. It is also quite interesting to note that up to 30% of Asian and African populations are rapid “metabolizers” due to rapid conversion.

Cytochrome CYP2D6 has been extensively investigated in relation to genetic polymorphism. Variation can be large between individuals for the enzyme activity of CYP2D6. For example, there is large variability in the CYP2D6 allele distribution among different ethnic groups. This results in variable percentages of poor, intermediate, or rapid metabolizers found in a given population. There are fully functional alleles,
with reduced function and null (non-functional) alleles, which demonstrate a wide range of enzyme activity, from no activity to very rapid metabolism of substrates. Lack of drug effect may occur as a consequence if standard doses are administered. Null alleles of CYP2D6 have no residual enzymatic activity because they do not encode a functional protein. Research shows that alleles 3, 4, 5, 6, 7, 8, 11, 12, 13, 14, 15, 16, 18, 19, 20, 21, 38, 40, 42, 44, 56 and 62 have no enzyme activity. These alleles are responsible when an individual demonstrates poor metabolism of opioids and other drugs when the alleles are present in homozygous or compound heterozygous situations. On the opposite spectrum the CYP2D6 gene can also copy number variations that are associated with rapid metabolizers. Decreases in drug concentrations have been shown in rapid metabolizers with drugs like tramadol and morphine (90). Genetic testing was not performed in the present study. Thus, there was no way of knowing if patients in the present study had polymorphisms in their CYP2D6 gene. It was clear, however, that hydrocodone had varying effects on the individual patients. It is interesting that 24.3% of patients who were given acetaminophen/hydrocodone reported not feeling any of the usual effects of the medication (euphoria, sleepiness, nausea). It is also of note that 33.3% of patients who were given a placebo, experienced a “placebo effect”, in that they reported effects consistent with administration of acetaminophen/hydrocodone (Table 3). Future, similar studies may explore in more depth these polymorphisms in participating patients. Clinically, however, this point may be moot as testing for alleles for each patient experiencing symptomatic irreversible pulpitis would take too long and be unreasonable.
Opioids when administered at therapeutic doses, not only produce analgesia, but also drowsiness and tranquilization (51). With this effect, opioids have an application not only for pain relief but for sleep induction provided that pain or coughing is the cause of sleeplessness. Opioids are often given to supplement benzodiazepines or other sedatives to facilitate moderate sedation, or with increasing doses, induce deep sedation or general anesthesia (51). It was believed by the investigators at the beginning of the present study that perhaps this sense of tranquilization from hydrocodone may play a role in increasing the success rate of the IANB. Lindemann et al. (99), however, demonstrated that 0.25 mg of sublingual triazolam, a commonly used sedative medication, did not statistically increase the success rate of the IANB in patients with irreversible pulpitis. Stanley et al. (100) demonstrated that the use of nitrous oxide (a commonly used sedative/analgesic inhalant) did significantly increase the success rate of the IANB. Stanley et al. attributed the increase in success to the analgesic effects of nitrous oxide rather than its sedative effects. These findings further support Lindemann et al.’s contentions. The present study also supports these two studies in that the sedative effects of hydrocodone did not prove of significance for increasing the success rate of the IANB.

Acetaminophen is the only aniline derivative currently in clinical use. Aniline is an organic compound that consists of a phenyl group and an amine group. It is used extensively as a precursor for making industrial chemicals, mainly polyurethane. Acetaminophen has analgesic and antipyretic activity that are comparable to aspirin (51).

The mechanism of action seems to be the inhibition of prostaglandin synthesis. However, the spectrum of COX enzymes that are targeted may differ than those of other
COX inhibitors. It is also believed that central nervous system (CNS) COX enzymes are more affected by acetaminophen than are enzymes located in the periphery (51). There are other proposed mechanisms of action of acetaminophen that include the activation of spinal serotonergic pathways and inhibition of nitric oxide synthase. When compared to aspirin, acetaminophen is a very weak anti-inflammatory agent. The effect of acetaminophen on inflammation is limited due to its inhibition in the presence of peroxides from leukocytes in inflamed tissues (51). Inflammation is known to be a large reason why symptomatic irreversible pulpitis can be severely painful. As this diagnosis was the pain model in the present study, it is likely the acetaminophen administered had little to no effect on the actively inflamed tissue in the tooth. This lack of effect was also demonstrated by Simpson et al. (34) when they showed that administration of ibuprofen plus acetaminophen did not significantly increase the success rate of the IANB. Thus, in the present study, neither acetaminophen, nor hydrocodone had a significant effect on the present inflammation. As inflammation was relatively unaddressed with the experimental medication, this could at least partially explain the lack of increase in the success rate of the IANB.

Acetaminophen is normally ingested orally in capsules or tablets. It is well absorbed in the small intestine. After oral administration, peak plasma concentrations are attained within 10-60 minutes (52). In the present study, treatment was initiated after 60 minutes. This appears to be at the far spectrum of time that the medication is at its peak plasma concentrations. It is possible that if a patient had peak plasma concentrations after 10 minutes, that acetaminophen could be less effective when treatment was initiated (52).
The main site of biotransformation of acetaminophen is the liver. Acetaminophen has a half-life of about 2 to 4 hours and broken down first by reaction with a cytochrome p450 enzyme, forming the highly toxic intermediate N-acetyl-p-benzoquinoneimine. By the addition of glutathione, a nontoxic product is formed (51). The toxic intermediate was not of concern in the present study as acetaminophen was only given one single time and at a therapeutic dose.

In the present study, a combination of the two discussed medications (acetaminophen and hydrocodone) was used. The beneficial theory of using a combination of drugs is that these medications alleviate pain using different mechanisms. By employing more than one mechanism of action, pain will theoretically be controlled on more than one level. Also, it is believed by some that the adverse side-effects of each medication are reduced by using reduced dosages, while still benefiting from similar analgesic effects (91). The data of the present study suggest, however, that even with the combined effects of acetaminophen and hydrocodone, as previously described, there was no significant increase in the success of the IANB.

Previous studies illustrate the location in the tooth when failure occurs. “Agarwala (105) reported 21% of subjects with irreversible pulpitis reported pain in dentin, 37% reported pain upon access to the pulp chamber, and 0% reported pain upon canal instrumentation in her Depo-Medrol group. Bigby (32) reported 60.1% of subjects with irreversible pulpitis recorded pain in the dentin, 34.8% upon entry into the pulp chamber, and 17.4% during instrumentation. Kennedy et al. (102) found that approximately half of the patients who reported pain during access of teeth with
irreversible pulpitis felt their pain when accessing into dentin. Claffey et al. (19), Reisman et al. (73), Nusstein et al. (107), and Kreimer et al. (106) reported the following percentages of pain in dentin: 14 of 35 (40%), 5 of 20 (25%), 6 of 33 (18%), and 1 of 24 (4%) in mandibular posterior teeth with irreversible pulpitis.” (101)

In the present study, it is interesting to note the anesthetic failure point for the IANB (Table 10). In the placebo group, 28% had no failure (considered a success), 46% failed while the operator was in dentin, 22% failed while the operator was in the pulp chamber, and 4% failed while the operator was instrumenting the canals. In the treatment group, 32% had no failure (considered a success), 46% failed while the operator was in dentin, 16% failed while the operator was in the pulp chamber, and 6% failed while the operator was instrumenting the canals. In the majority of cases, for both the placebo and experimental groups, the failed IANB occurred while the operator was still in the dentin of the tooth (46% for both groups). This is of great clinical significance as intrapulpal injections are impossible to perform at this stage of treatment.

It may be suggested that a buccal infiltration using 4% articaine may increase the success of pulpal anesthesia. The present study, however, demonstrated that articaine infiltrations resulted in only a 42% success rate for the placebo group, and 50% for the experimental group (Table 6 and Figure 2). These findings correlate well with those in previous studies. Oleson et al. (33) found that following a successful IANB, a buccal infiltration with 4% articaine with 1:100,000 epinephrine was successful 38% of the time for their experimental group and 24% of the time for the placebo group. Simpson et al. (34) also showed similar findings as the present study. Following a successful IANB a
buccal infiltration with 4% articaine with 1:100,000 epinephrine was successful 41% of the time for their experimental group, and 51% for the placebo group. Matthews et al. (101) evaluated the anesthetic efficacy of the supplemental infiltration injection of 4% articaine with 1:100,000 epinephrine in mandibular posterior teeth diagnosed with irreversible pulpitis when the conventional IANB failed. They found that 32 out of 55 (58%) patients had anesthetic success with the supplemental articaine infiltration. Stanley et al. (100) also found similar rates of success. They found that 61% of patient in the placebo group (did not receive nitrous oxide) achieved sufficient pulpal anesthesia while 72% of patient who received nitrous oxide achieved pulpal anesthesia. It is also interesting that in the present study, approximately 30% of these injections failed while the operator was drilling in the dentin (Table 10). These data suggest that supplemental injection techniques, such as an intraosseous (IO) or periodontal ligament injections may prove very beneficial.

In the present study the intraosseous injection successfully anesthetized the tooth 76% of the time for the placebo group, and 71% of the time for the experimental group (Table 6 and Figure 2). These findings also correlate well with the two previously discussed studies (33,34). Oleson et al. showed that the IO injection was successful 88% of the time in the experimental group, and 93% of the time for the placebo group (33). Simpson et al. showed that the IO was successful 81% of the time for the experimental group and 76% of the time for the placebo group (34). It is possible, then, that using the conventional IANB, achieving profound lip numbness, then proceding directly to a buccal infiltration with 4% articaine, then directly to an intraosseous injection may be
very beneficial in clinical cases of symptomatic irreversible pulpitis of a mandibular posterior tooth.

The pain of injection of the IAN block has been previously studied. “McCartney et al. (108) performed a retrospective analysis to determine the pain associated with needle insertion, placement, and solution deposition for the conventional IAN block in patients with irreversible pulpitis. One hundred two emergency patients with irreversible pulpitis received IAN block injections using 2% lidocaine with 1:100,000 epinephrine. The patients recorded pain of the 3 injection stages on a Heft-Parker visual analog scale (VAS). Moderate-to-severe pain occurred 57% to 89% of the time with the IAN block. Needle placement was significantly more painful than needle insertion for men and significantly more painful than either insertion or deposition for women. There was no statistical difference between the pain for men or women with respect to needle insertion, placement, or deposition pain. Deposition of 0.2 to 0.4 mL anesthetic during placement did not significantly reduce placement pain for either gender.” (101) Therefore, in the present study, anesthetic was not deposited during needle placement. “The study concluded that 57% to 89% of patients presenting with irreversible pulpitis have the potential for moderate to severe pain with the IAN block.” (101)

“Injعating local anesthetic slowly is the most important factor in the prevention of adverse drug reactions (109). Malamed states that it is extremely important to inject slowly with careful aspiration when giving inferior alveolar nerve blocks in order to minimize both the pain of injection and the possibility of a rapid intravascular injection. Aspiration allows the clinician to determine whether the needle tip lies within a blood
vessel lumen. Rapid intravascular injection of 1.8 mL of 2% lidocaine with 1:100,000 epinephrine will produce a blood level in excess of that required for overdose. Malamed states that a realistic goal for deposition of a 1.8 mL cartridge of anesthetic is 60 seconds. If this amount of anesthetic happened to be deposited intravascularly at this rate of injection it would produce levels below the minimum for overdose and if signs and symptoms did occur they would be less severe. Rapid injection is not only dangerous but also painful. If injected too quickly the anesthetic will tear the tissue rather than diffusing along the normal tissue planes leading to immediate discomfort followed by post-op discomfort and possibly trismus.

Kanaa et al. (111) investigated the speed of injection and the influence it had on the efficacy of the IAN block. The double-blind crossover trial studied the efficacy and discomfort associated with slow (60 seconds) and rapid (15 seconds) IAN block using 2% lidocaine with 1:80,000 epinephrine. Mandibular first molars, premolars and lateral incisors were evaluated in 38 healthy volunteers and the efficacy was determined by an electric pulp tester. Injection discomfort was self-recorded by the volunteers on a visual analog scale. Slow IAN block when compared to rapid IAN block produced more episodes of pulpal anesthesia as evaluated by the electric pulp tester. Slow IAN block was more comfortable than rapid IAN block.”

Table 12 and Figure 3 illustrate the pain of injection for the IANB. Table 13 illustrates the pain of injection for the buccal infiltration injection. No significant differences were found at any of the 3 stages of the injections when comparing the placebo group and acetaminophen/hydrocodone group for both the IANB and buccal
infiltration. Although there was no significant difference between the two groups for pain of injection, the solution deposition stage of the IANB was less painful for both the placebo and treatment groups with a mean VAS rating of 59.8 ± 42.5 mm compared to insertion and placement stages of the IANB which were 73.0 ± 36.1 mm and 74.6 ± 37.3 mm, respectively, for the placebo group. The VAS ratings for the experimental groups were very similar (Table 12 and Figure 3). A possible explanation is that anxiety may have decreased after the initial needle insertion and placement, which allowed the patient to rest more during the deposition phase resulting in a lower VAS rating for the deposition phase. This did not prove to be the same for the pain of injection with the buccal infiltration injection (Table 13). For both the placebo and treatment groups, the needle insertion, needle placement, and solution deposition pain ratings were very similar. It was also evident that the pain reported with the buccal infiltration was generally less than that reported during the IANB. This is likely due to the fact that the IANB was given at least 15 minutes before administration of the buccal infiltration. This time allowed for soft tissue anesthesia at the site of the buccal infiltration.

Patients in the present study who were administered acetaminophen/hydrocodone had a statistically significant higher mean satisfaction rating than did those receiving the placebo (P = 0.0409) (Table 14 and Figure 4). This may have been due to patients liking the euphoric feelings often associated with the administration of the experimental drug. Patients receiving the placebo may also have possibly felt disappointment for not having those feelings of euphoria. Scaling from 0 to 100, with 100 being completely satisfied and 0 being not satisfied, the mean satisfaction of the placebo group was 88.7 ± 17.9 mm
and the mean for the acetaminophen/hydrocodone group was 94.7 ± 10.6 mm. This finding is consistent with previous studies. Stanley et al. (100) showed satisfaction ratings of 95/96 mm (experimental group/placebo group). In the present study, the maximum rating for both groups was 100. The minimum rating for the placebo group was 24 mm while the minimum rating for the acetaminophen/hydrocodone group was 67 mm. All 50 participants in the acetaminophen/hydrocodone group were either moderately or completely satisfied. Forty-six participants in the placebo group were either moderately or completely satisfied, while three were somewhat satisfied, and only one was not satisfied. Of the four patients who were only somewhat, or not satisfied, none of them reported any type of symptom normally associated with the experimental drug. Both the placebo and acetaminophen/hydrocodone groups had high satisfaction ratings of 88.7 mm and 94.7 mm respectively (out of 100 mm). Again, these high satisfaction ratings correlate well with those of Stanley’s study with ratings of 95/96 (experimental group/placebo group) (100).

The results of the present study are lower than the results reported by Lindemann et al. (99), which used the same scale used in this study. “Lindemann et al. researched the same population as the current study and compared the effect of triazolam on the IAN block. Their results reported 100% patient satisfaction for both groups studied. These results are likely skewed as in Lindemann’s study patients were asked to complete the satisfaction form while the operator was still in the room, possibly impeding a truly honest response from patients.” (100) In the present study, it was strongly emphasized that the patient’s response on the survey would have no impact on the operator’s grade,
status as resident, or standing within the school/department. The patient was then given a clipboard with the satisfaction survey. The patients then completed the survey, turned the survey facedown on the clipboard they were given, and the clipboard was placed on the counter in the operatory. The patient then met the operator in the front of the clinic for dismissal. Thus, patients were left by themselves in a less pressured environment to complete the survey. It is interesting to note in the present studies results which showed high satisfaction ratings for both groups, although the satisfaction for the acetaminophen/hydrocodone group was higher at a level that was statistically significant. “This confirms the point that if patients feel they are properly cared for, they can experience moderate-to-severe pain and still be highly satisfied with the treatment received.” (100) It should also be noted that on the 100 mm scale used in the present study patients could only rate “completely satisfied” if they were to mark exactly on the 100 mm line. If there mark was made relatively high (80’s or 90’s), they were classified as “moderately satisfied.” It may be suggested in the future to use a more discerning scale to more accurately determine patients’ post-operative treatment satisfaction.
The purpose of the present study was to increase the success rate of the inferior alveolar nerve block in patients diagnosed with symptomatic irreversible pulpitis in a mandibular posterior tooth with the use of preoperative administration of an acetaminophen/hydrocodone combination medication. Past studies have used a variety of preoperative medications to increase this success rate and have reported varying findings (33-37). Acetaminophen/hydrocodone combinations have proven effective for moderate to severe pain models (41,43,45). It was hypothesized in the present study that administering acetaminophen and hydrocodone preoperatively to patients experiencing active, moderate to severe pain of irreversible pulpitis would increase the success rate of the inferior alveolar nerve block due to the multi-site and multi-action qualities of their mechanisms of action.

Although the combination of acetaminophen/hydrocodone may be acting on many levels regarding analgesia, there was no significant difference between the placebo and experimental groups. The success rate of the IANB for the placebo group was 28%, and
the success rate for the experimental group was 32%. Having found no significant
difference, we concluded that preoperative administration of 1000/10 mg of
acetaminophen/hydrocodone for patients diagnosed with symptomatic irreversible
pulpitis does not significantly increase the success rate of the inferior alveolar nerve
block.
APPENDIX A

GENERAL CONSENT FORM
The Ohio State University Consent to Participate in Research

Study Title: Preoperative acetaminophen/hydrocodone effect on the success of the inferior alveolar nerve block in patients with symptomatic irreversible pulpitis

Principal Investigator: Dr. Melissa Drum

Sponsor: NA

- **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 see if giving acetaminophen/hydrocodone before endodontic (root canal) treatment reduces pain during emergency endodontic treatment.

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

   One hundred and ten (110) people 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 and pain medication form and HIPPA authorization and consent form. If you are a female and 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 following part of the study is associated with the research. Sixty minutes before your doctor starts your root canal, you will be given capsules to swallow. The capsules will contain either hydrocodone/acetaminophen or a placebo drug (sugar). The capsules you receive will be chosen at random (by chance, like flipping a coin). Neither your doctor nor you will know which medication (hydrocodone/acetaminophen or placebo) you will receive. The purpose of this study is to see if hydrocodone/acetaminophen help your tooth get numb after you receive a numbing solution.

The study requires one appointment but you will need at least one additional appointment to finish the root canal if you elect to save your tooth.

The following procedures are needed for standard root canal treatment and will occur whether or not I take part in this study. You will be asked to rate the pain you are having prior to any treatment. You will also fill out a form to rate how anxious you are. The tooth causing you pain will first be tested to ensure an accurate diagnosis. It will 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 before root canal treatment. This test will be done once every 5 to 10 minutes prior to the start of treatment. You will also fill out a form to rate your pain every 5 to 10 minutes prior to the start of treatment.

An injection (shot) will be given in the back of your jaw to numb your lower teeth (inferior alveolar injection) using 2% lidocaine with 1:100,000 epinephrine which is an anesthetic (numbing solution) similar to Novocain. You will be asked to rate the amount of pain you feel when the injection is being given. You will do this by marking your pain with a pencil on a line graph.

Following the anesthetic injections (shots) the doctor will begin asking you every minute for 15 minutes whether you are experiencing lip numbness. At 15 minutes if your lip is not numb, you will be given extra anesthesia (shots). Next a small opening will be made
in the top of your tooth to begin the root canal. If you have moderate or severe pain, supplemental (extra) injections (shots) will be given directly beside your tooth. Routine emergency root canal treatment will then be completed.

Your participation or non-participation will have no effect on whether you will receive emergency root canal treatment. You understand that if you want to save the treated tooth (provided it is restorable or savable) further root canal treatment and restorative treatment such as a filling and or a crown will be needed. You are responsible for the emergency root canal fee.

4. How long will I be in the study?

You are aware that you will have one appointment, which will last approximately 120 minutes (60 minutes for the medication to work and then the root canal treatment will take about 60 minutes).

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?

The research risks with hydrocodone/acetaminophen would be: nausea, vomiting, constipation, lightheadedness, dizziness, drowsiness, flushing, vision changes, urticaria rash, hepatotoxicity and hypersensitivity reaction. The likelihood of adverse reactions is decreased because you are only receiving one dose.

The risks with standard root canal treatment would include: You may have pain associated with the local anesthetic (numbing solution) or soreness at the site of the injections (shots) for approximately two days. Where you receive the injection, you may have swelling (hematoma-a collection of blood in my 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. If you receive a placebo, you may require more local
anesthetic. 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 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 of the administration of pain medication during pregnancy. Patients/physicians differ in their acceptance of its use during pregnancy.

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

You may not directly benefit from this study. Patients who receive hydrocodone/acetaminophen may benefit by having less pain. Society may benefit if hydrocodone/acetaminophen reduces pain during endodontic treatment.

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

You may have the emergency endodontic procedure completed without taking hydrocodone/acetaminophen or the placebo drug. 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.

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?

Because routine endodontic treatment will be performed, other costs (emergency fees, parking) will not be reimbursed in this study. The study will pay for the cost of the study drugs (hydrocodone and acetaminophen or placebo) and urine pregnancy test.

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

Yes, you will be paid $75 for your participation.

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 or Dr. Spencer Fullmer 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 or Dr. Spencer Fullmer at 614-292-5399.
APPENDIX B

PATIENT PRIVACY FORM
Preoperative acetaminophen/hydrocodone effect on the success of the inferior alveolar nerve block in patients with symptomatic irreversible pulpitis

OSU Protocol Number:

Principal Investigator: Dr. Melissa Drum

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-ray 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.

Initials/Date: ________________
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 University 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.

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

- 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 Food and Drug Administration
  - The Office for Human Research Protections
  - The National Institutes of Health
  - The Ohio Department of Human 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.

Initials/Date_________
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 complete.

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. Henry Fischbach 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 Manju Ooman at the College of Dentistry, 305 w 12th avenue, The Ohio State University, Columbus, Ohio 43218.
- If you have any questions relating to the research, please contact Dr. Melissa Drum at the College of Dentistry, 305 w 12th avenue, The Ohio State University, Columbus, Ohio 43218.

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 [insert name of Principal Investigator] 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)
APPENDIX C

HEALTH HISTORY QUESTIONNAIRE
Medical History

1. Do you have or have you had any of the following?
   a. rheumatic fever or rheumatic heart disease…………………. NO YES
   b. heart murmur or mitral valve prolapse……………………… NO YES
   c. heart disease or heart attack………………………………… NO YES
   d. artificial heart valve………………………………………… NO YES
   e. irregular heart beat………………………………………….. NO YES
   f. pacemaker…………………………………………………… NO YES
   g. high blood pressure…………………………………………. NO YES
   h. chest pains or angina………………………………………… NO YES
   i. stroke………………………………………………………… NO YES
   j. artificial joint………………………………………………… NO YES
   k. hepatitis/liver disease……………………………………….. NO YES
   l. tuberculosis………………………………………………….. NO YES
   m. thyroid problem……………………………………………. NO YES
   n. kidney disease………………………………………………. NO YES
   o. diabetes (sugar)……………………………………………… NO YES
   p. asthma………………………………………………………. NO YES
   q. HIV or other immunosuppressive disease………………….. NO YES
   r. radiation or cancer therapy………………………………….. NO YES

2. Do you or have you had any disease, condition, or problem not listed here? NO YES

3. Have you ever been hospitalized? NO YES

4. Have you had excessive or prolonged bleeding requiring special treatment? NO YES

5. Have you had an allergic reaction to any drugs or medications?
   (Circle all that apply: penicillin; codeine; aspirin; anesthetics; other) NO YES

6. Are you currently under the care of a physician (M.D., D.O.)? NO YES
   When were you last seen by a physician?_____________________
   Name of Physician_______________________________________
   Street address___________________________________________
   City, State, and Zip Code________________________________
   Phone_________________________________________________

7. Are you pregnant or nursing? Estimated date of delivery_________ NO YES
8. Have you had any trouble associated with previous dental treatment? NO YES

9. How often do you have dental check ups? _________ Date of last Exam___________

10. Do you have any lumps or sores in your mouth now? NO YES

11. Do you smoke or use smokeless tobacco? NO YES

12. Are you currently taking any drugs or medications (such as antibiotics, heart medicine, birth control pills?) NO YES

**Current Medications**

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Generic Name</th>
<th>Dose/Frequency</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Summary of Patient’s Medical Status:**
____________________________________________________________________________
____________________________________________________________________________

**Medical Risk Assessment**

- ASA I (healthy individual) □ ASA III (severe disease but not incapacitating) □
- ASA II (mild systemic disease) □ ASA IV (incapacitating systemic disease)

**Medical Consultation Required**

- No (healthy and/or stabilized disease)

- Yes (ASA III or IV; cardiac murmur; vague hx; recent major disease; recent diagnosis/operation; uncontrolled disease; blood pressure; etc.)

To the best of my knowledge, the above information is correct and complete.

Patient’s Signature _______________________ Date _______________________
APPENDIX D

CORAH’S DENTAL ANXIETY QUESTIONNAIRE
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 your 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 E

PAIN MEDICATION FORM
Pain Medication Form

Have you taken any pain medications in the last 24 hours?

Yes  
No  

If you answered “Yes” to the above question please answer the following questions:

- What type of medication did you take? ________________.
- How much medication did you take? ________________.
- At what time did you take this medication? ____________.
APPENDIX F

PATIENT POST-TREATMENT SATISFACTION SCALE
Pt. Number:____________________

Satisfaction Rating

Mark a vertical line “│” on the point on the scale line that best describes your satisfaction.

Not Satisfied │ Somewhat Satisfied │ Moderately Satisfied │ Completely Satisfied

Treatment Pain Rating

Do you remember feeling pain during the treatment, if yes, what was the greatest amount of pain you felt?

1. Please place an “X” on the line below to rank the level of pain.

None │ Faint │ Weak │ Mild │ Moderate │ Strong │ Intense │ Maximum Possible
APPENDIX G

VISUAL ANALOG SCALE
0-54 mm ........ Mild pain

55-113 mm .......... Moderate Pain

114-170 mm .......... Severe Pain
APPENDIX H

TABLES AND FIGURES
Table 1. Initial Statistics
* Values analyzed using the Randomization test.
** Heft-Parker Visual Analog Scale.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th></th>
<th>Acet/Hydro</th>
<th></th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td>Min</td>
<td>Max</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50</td>
<td>35.7</td>
<td>12.7</td>
<td>18</td>
<td>61</td>
</tr>
<tr>
<td>Initial pain mm**</td>
<td>50</td>
<td>125.1</td>
<td>24.0</td>
<td>84</td>
<td>170</td>
</tr>
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</table>

Table 2. Initial Corah’s Dental Anxiety Scale Ratings.
* Values analyzed using the Mann-Whitney-Wilcoxon test.

<table>
<thead>
<tr>
<th></th>
<th>Low Anxiety</th>
<th>Moderate Anxiety</th>
<th>High Anxiety</th>
<th>Severe Anxiety</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo Group</td>
<td>16 (32%)</td>
<td>23 (46%)</td>
<td>4 (8%)</td>
<td>7 (14%)</td>
<td>0.2073*</td>
</tr>
<tr>
<td>Median: 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acet/Hydro Group</td>
<td>15 (30%)</td>
<td>16 (32%)</td>
<td>6 (12%)</td>
<td>13 (26%)</td>
<td></td>
</tr>
<tr>
<td>Median: 11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Initial Analysis by Tooth Type and Gender
* Value analyzed using the Fisher Exact test.
** Value analyzed using the Chi-Square test.

<table>
<thead>
<tr>
<th>Tooth Type</th>
<th>Placebo</th>
<th>N</th>
<th>%</th>
<th>Acet/Hydro</th>
<th>N</th>
<th>%</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Molar</td>
<td>28</td>
<td>56.0</td>
<td>26</td>
<td>52.0</td>
<td>0.3098*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd Molar</td>
<td>14</td>
<td>28.0</td>
<td>17</td>
<td>34.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd Molar</td>
<td>2</td>
<td>4.0</td>
<td>0</td>
<td>0.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st Premolar</td>
<td>2</td>
<td>4.0</td>
<td>0</td>
<td>0.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd Premolar</td>
<td>4</td>
<td>8.0</td>
<td>7</td>
<td>14.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male: 27</th>
<th>Female: 23</th>
<th>Male: 19</th>
<th>Female: 31</th>
<th>0.1085**</th>
</tr>
</thead>
</table>

| Food                 | No          | 22          | 44.0      | 20          | 40.0     | 0.6853** |
|----------------------|-------------|-------------|-----------|-------------|----------|
|                      | Yes         | 28          | 56.0      | 30          | 60.0     |          |

| Symptoms             | No          | 30          | 66.7      | 9           | 24.3     | 0.0001** |
|----------------------|-------------|-------------|-----------|-------------|----------|
|                      | Yes         | 15          | 33.3      | 28          | 75.7     |          |

Table 4. Preoperative Pain using Ice Stimulation (VAS Ratings in mm).
*Analyzed using the ANOVA and Tukey test.

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo (N=50)</th>
<th>Acet/Hydro (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIME (min.)</td>
<td>MEAN</td>
<td>SD</td>
</tr>
<tr>
<td>0</td>
<td>125.1</td>
<td>24.0</td>
</tr>
<tr>
<td>10</td>
<td>121.7</td>
<td>31.8</td>
</tr>
<tr>
<td>20</td>
<td>113.2</td>
<td>35.5</td>
</tr>
<tr>
<td>30</td>
<td>108.9</td>
<td>37.9</td>
</tr>
<tr>
<td>40</td>
<td>101.3</td>
<td>36.6</td>
</tr>
<tr>
<td>50</td>
<td>96.4</td>
<td>41.4</td>
</tr>
<tr>
<td>60</td>
<td>95.1</td>
<td>41.4</td>
</tr>
</tbody>
</table>

*Analyzed using the ANOVA and Tukey test.
Table 5. Preoperative Patient Reaction to Ice Stimulation (2 = severe reaction, 1 = mild/mod. reaction, 0 = no reaction).

<table>
<thead>
<tr>
<th>Time (min.)</th>
<th>Placebo (N=50)</th>
<th>Acet/Hydro (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>20</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td>30</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>40</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>50</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>60</td>
<td>0</td>
<td>33</td>
</tr>
</tbody>
</table>

Table 6. Success of Inferior Alveolar Nerve Block (IANB), Infiltration, and Intraosseous (IO) injections.
*Values analyzed using the Chi-Square test.
**Values analyzed using the Fisher Exact test.
<table>
<thead>
<tr>
<th>Tooth Type</th>
<th>Placebo Group (N=50)</th>
<th>Acet/Hydro Group (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Molar</td>
<td>9/28 (32%)</td>
<td>10/26 (38%)</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Molar</td>
<td>4/14 (29%)</td>
<td>4/17 (24%)</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; Molar</td>
<td>1/2 (50%)</td>
<td>0/0 (0%)</td>
</tr>
<tr>
<td>Premolars</td>
<td>0/6 (0%)</td>
<td>2/7 (29%)</td>
</tr>
</tbody>
</table>

Table 7. IAN Block Success by Group and Tooth Type

<table>
<thead>
<tr>
<th>Tooth Type</th>
<th>Placebo Group (N=34)</th>
<th>Acet/Hydro Group (N=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Molar</td>
<td>7/19 (37%)</td>
<td>5/16 (31%)</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Molar</td>
<td>5/10 (50%)</td>
<td>8/13 (62%)</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; Molar</td>
<td>0/1 (0%)</td>
<td>0/0 (0%)</td>
</tr>
<tr>
<td>Premolars</td>
<td>3/6 (50%)</td>
<td>4/5 (80%)</td>
</tr>
</tbody>
</table>

Table 8. Articaine Infiltration Success by Group and Tooth Type

<table>
<thead>
<tr>
<th>Tooth Type</th>
<th>Placebo Group (N=17)</th>
<th>Acet/Hydro Group (N=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Molar</td>
<td>8/12 (67%)</td>
<td>9/11 (82%)</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Molar</td>
<td>4/5 (80%)</td>
<td>2/5 (40%)</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; Molar</td>
<td>1/1 (100%)</td>
<td>0/0 (0%)</td>
</tr>
<tr>
<td>Premolars</td>
<td>3/3 (100%)</td>
<td>1/1 (100%)</td>
</tr>
</tbody>
</table>

Table 9. Intraosseous Success by Group and Tooth Type
<table>
<thead>
<tr>
<th>Anesthetic Failure Point</th>
<th>Placebo Group</th>
<th>Acet/Hydro Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAN Block</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>14/50 (28%)</td>
<td>16/50 (32%)</td>
</tr>
<tr>
<td>Dentin</td>
<td>23/50 (46%)</td>
<td>23/50 (46%)</td>
</tr>
<tr>
<td>Chamber</td>
<td>11/50 (22%)</td>
<td>8/50 (16%)</td>
</tr>
<tr>
<td>Canals</td>
<td>2/50 (4%)</td>
<td>3/50 (6%)</td>
</tr>
<tr>
<td>Articaine Infiltration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>15/36 (42%)</td>
<td>17/34 (50%)</td>
</tr>
<tr>
<td>Dentin</td>
<td>11/36 (31%)</td>
<td>10/34 (29%)</td>
</tr>
<tr>
<td>Chamber</td>
<td>7/36 (19%)</td>
<td>6/34 (18%)</td>
</tr>
<tr>
<td>Canals</td>
<td>3/36 (8%)</td>
<td>1/34 (3%)</td>
</tr>
<tr>
<td>I/O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>16/21 (76%)</td>
<td>12/17 (71%)</td>
</tr>
<tr>
<td>Dentin</td>
<td>1/21 (6%)</td>
<td>1/17 (5%)</td>
</tr>
<tr>
<td>Chamber</td>
<td>3/21 (14%)</td>
<td>2/17 (12%)</td>
</tr>
<tr>
<td>Canals</td>
<td>1/21 (5%)</td>
<td>2/17 (12%)</td>
</tr>
</tbody>
</table>

Table 10. Anesthetic Failure Point and Patient Distribution.
<table>
<thead>
<tr>
<th>Location of Failure:</th>
<th>Dentin (mean ± SD)</th>
<th>Chamber (mean ± SD)</th>
<th>Canals (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAN Block: (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>106 ± 26 (n=25)</td>
<td>101 ± 24 (n=11)</td>
<td>135 ± 47 (n=2)</td>
</tr>
<tr>
<td>Acet/Hydro</td>
<td>113 ± 32 (n=25)</td>
<td>109 ± 44 (n=8)</td>
<td>98 ± 40 (n=3)</td>
</tr>
<tr>
<td>Articaine: (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>118 ± 28 (n=12)</td>
<td>113 ± 18 (n=7)</td>
<td>76 ± 18 (n=3)</td>
</tr>
<tr>
<td>Acet/Hydro</td>
<td>113 ± 25 (n=10)</td>
<td>139 ± 20 (n=6)</td>
<td>85 ± 0 (n=1)</td>
</tr>
<tr>
<td>Intraosseous: (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>126 ± 0 (n=1)</td>
<td>139 ± 25 (n=3)</td>
<td>84 ± 0 (n=1)</td>
</tr>
<tr>
<td>Acet/Hydro</td>
<td>126 ± 0 (n=1)</td>
<td>153 ± 4 (n=2)</td>
<td>92 ± 30 (n=2)</td>
</tr>
</tbody>
</table>

Table 11. Location of Anesthetic Failure and Pain Ratings During Endodontic Treatment by Injection Type, Using Heft-Parker Visual Analog Scale (mm).
<table>
<thead>
<tr>
<th>GROUP</th>
<th>STAGE</th>
<th>N</th>
<th>MEAN</th>
<th>STD</th>
<th>MIN</th>
<th>MAX</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>INS</td>
<td>50</td>
<td>73.0</td>
<td>36.1</td>
<td>2</td>
<td>170</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>PLC</td>
<td>50</td>
<td>74.6</td>
<td>37.3</td>
<td>0</td>
<td>170</td>
<td></td>
</tr>
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<td>Placebo</td>
<td>DEP</td>
<td>50</td>
<td>59.8</td>
<td>42.5</td>
<td>0</td>
<td>170</td>
<td></td>
</tr>
<tr>
<td>Acet/Hydro</td>
<td>INS</td>
<td>50</td>
<td>74.1</td>
<td>42.9</td>
<td>0</td>
<td>143</td>
<td>0.5171*</td>
</tr>
<tr>
<td>Acet/Hydro</td>
<td>PLC</td>
<td>50</td>
<td>79.8</td>
<td>41.7</td>
<td>2</td>
<td>170</td>
<td></td>
</tr>
<tr>
<td>Acet/Hydro</td>
<td>DEP</td>
<td>50</td>
<td>59.0</td>
<td>43.9</td>
<td>0</td>
<td>170</td>
<td>0.5757*</td>
</tr>
</tbody>
</table>

Table 12. Pain of IAN Block Injection By Stage Using Heft-Parker Visual Analog Scale (mm)  
(INS = needle insertion, PLC = needle placement, DEP = solution deposition).  
*Analyzed using ANOVA.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>STAGE</th>
<th>N</th>
<th>MEAN</th>
<th>STD</th>
<th>MIN</th>
<th>MAX</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>INS</td>
<td>37</td>
<td>52.5</td>
<td>40.6</td>
<td>0</td>
<td>170</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>PLC</td>
<td>37</td>
<td>54.4</td>
<td>35.8</td>
<td>0</td>
<td>144</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>DEP</td>
<td>37</td>
<td>52.5</td>
<td>34.2</td>
<td>0</td>
<td>170</td>
<td></td>
</tr>
<tr>
<td>Acet/Hydro</td>
<td>INS</td>
<td>35</td>
<td>42.1</td>
<td>40.3</td>
<td>0</td>
<td>141</td>
<td></td>
</tr>
<tr>
<td>Acet/Hydro</td>
<td>PLC</td>
<td>35</td>
<td>55.5</td>
<td>40.5</td>
<td>0</td>
<td>143</td>
<td></td>
</tr>
<tr>
<td>Acet/Hydro</td>
<td>DEP</td>
<td>35</td>
<td>51.0</td>
<td>40.9</td>
<td>0</td>
<td>142</td>
<td>0.5757*</td>
</tr>
</tbody>
</table>

Table 13. Pain of Buccal Infiltration Injection By Stage Using Heft-Parker Visual Analog Scale (mm)  
(INS = needle insertion, PLC = needle placement, DEP = solution deposition).  
*Analyzed using ANOVA.
<table>
<thead>
<tr>
<th>Group (mean ± SD) mm</th>
<th>Not Satisfied</th>
<th>Somewhat Satisfied</th>
<th>Moderately Satisfied</th>
<th>Completely Satisfied</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean: 88.7 ± 17.9</td>
<td>1 (%)</td>
<td>3 (%)</td>
<td>27 (%)</td>
<td>19 (%)</td>
<td>0.0409*</td>
</tr>
<tr>
<td>n = 50 (min=24, max=100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acet/Hydro:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean: 94.7 ± 10.6</td>
<td>0 (%)</td>
<td>0 (%)</td>
<td>26 (%)</td>
<td>24 (%)</td>
<td></td>
</tr>
<tr>
<td>n = 50 (min=67, max=100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 14. Patient Post-Treatment Satisfaction Ratings.
* Values analyzed using the Randomization test.
Figure 1. Preoperative Pain By Ice Stimulation Using Heft-Parker Visual Analog Scale (mm).
Figure 2. Success of Inferior Alveolar Nerve Block (IA), Infiltration (INFLT), and Intraosseous (IO) Injections by Group: Placebo (PLC) and Acet/Hydro (Acetaminophen/Hydrocodone).
Figure 3. Pain of IANB Injection By Stage Using Heft-Parker Using Visual Analog Scale (mm)
Figure 4. Patient Post-Treatment Satisfaction Ratings Using Heft-Parker Visual Analog Scale (mm).
LIST OF REFERENCES


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48. Carnes PL, Cook B, Eleazer PD, Scheetz JP. Change in pain threshold by meperidine naproxen sodium, and acetaminophen as determined by electric pulp testing. Anesth Prog. 1999;45:139-42.


54. See http://fda.gov/AdvisoryCommittees/Calandar/ucm143083.htm


59. VICODIN 5 mg (hydrocodone)/500 mg (acetaminophen) [package insert]. North Chicago, IL: Abbott Laboratories.
60. VICODIN ES 7.5 mg (hydrocodone)/750 mg (acetaminophen) [package insert]. North Chicago, IL: Abbott Laboratories.

61. VICODIN HP 10 mg (hydrocodone)/660 mg (acetaminophen) [package insert]. North Chicago, IL: Abbott Laboratories.

62. VICODIN, VICODIN ES, VICODIN HP 5, 7.5, 10 mg (hydrocodone)/300 mg (acetaminophen) [package insert]. North Chicago, IL: Abbott Laboratories.

63. See http://www.deadiversion.usdoj.gov/schedules/index.html

64. See http://www.opiates.com/opiates/opiate-side-effects.html


68. See http://www.rxlist.com/vicodin-drug/clinical-pharmacology.htm


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87. See http://www.cdc.gov/obesity/data


