**THE EFFECT OF NITROUS OXIDE 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 in patients diagnosed with symptomatic irreversible pulpitis has low success rates. Anesthetic success rates may be affected by increased anxiety. Nitrous oxide has been shown to have both anxiolytic and analgesic properties. Therefore, the purpose of this prospective, randomized, double-blind, placebo-controlled study was to determine the effect of nitrous oxide on the anesthetic success of the inferior alveolar nerve block in patients experiencing symptomatic irreversible pulpitis. One hundred emergency patients diagnosed with symptomatic irreversible pulpitis of a mandibular posterior tooth were enrolled in this study. Each patient was randomly assigned to receive an inhalation regimen of nitrous oxide/oxygen mix or room air/oxygen mix (placebo) five minutes before administration of a conventional IAN block. Patients receiving nitrous oxide were titrated to a dose of 30%-50%. Endodontic access was initiated 15 minutes after the administration of the IAN block, assuming the patient had profound lip numbness. Anesthetic success was defined as no or mild pain (as recorded on a visual analog scale) upon access and instrumentation. The success rate for the IAN block in the nitrous oxide group was 50% and 28% for the placebo group. There was a statistically significant difference between the two groups ($p=0.0241$). In conclusion, for mandibular teeth diagnosed with symptomatic irreversible pulpitis, administration

of 30%-50% nitrous oxide resulted in a statistically significant increase in the success of the IAN block.

DEDICATION

To my wife, Laura, for her endless love and support. Thank you for all your hard work and sacrifice. Thank you for putting up with me. Thank you for being my best friend. You're my favorite.

ACKNOWLEDGEMENTS

Dr. Drum – Thank you for being you. Your insight, patience, perspective, and authenticity have made this experience something I will always treasure. Please know that all your hard work is appreciated and that you do make a difference, a big one. Thank you for making all of this fun.

Dr. Reader – Thank you for an incredible opportunity. Thank you for bringing me into the family you’ve made here. Your dedication to us, education, and this profession is rare and inspiring. Thank you for your humor and for helping me know that “It’ll be fine.” Thank you for the best educational experience of my life.

Dr. Nusstein – Thank you for being a good leader. Thank you for caring as much as you do. You have encouraged me to delve deeper and think more critically. You have also taught me the inherent, irreplaceable value of a hardcopy, specifically the JOE.

Dr. Meyers – Thank you for your dedication to this profession. Thank you for teaching me not only about endodontics, but about life, and helping me to always remember that “I don’t know what I don’t know.”

Dr. Beck – The word statistics is often hard for me to even spell, much less understand. Thank you for your tireless efforts and patience in helping me sort through and digest that mountain of information.

Anna, Brock, and Spencer – Thank you for making this process very memorable. Thank you for your consideration and support throughout the entire journey. Thank you for the laughs, memories, and fun. Thank you for your friendship.

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CHAPTER 1

INTRODUCTION

“The inferior alveolar nerve block is the most frequently used mandibular injection technique for achieving local anesthesia for endodontic treatment.

However, the inferior alveolar nerve block does not always result in successful pulpal anesthesia. Clinical studies in endodontics (1-11) have found failure with the inferior alveolar nerve block occurring 44% and 81% of the time. Therefore, it would be advantageous to improve the success rate of the inferior alveolar nerve block in endodontics.” (11)

Recently, Matthews et al., Oleson et al., and Simpson et al. (7, 10, 11) researched a supplemental buccal infiltration of 4% articaine with 1:100,000 epinephrine following an inferior alveolar nerve block in patients diagnosed with symptomatic irreversible pulpitis. The overall anesthetic success rate of an inferior alveolar nerve block in mandibular posterior teeth diagnosed with symptomatic irreversible pulpitis was only 33%, 35%, and 24%, respectively. They found that a supplemental buccal infiltration with 4% articaine will result in successful pulpal anesthesia in these teeth 58%, 41%, and 38% of the time, respectively.

Unfortunately, these modest success rates would not provide predictable pulpal anesthesia for all patients.

Many dental patients are anxious about dental treatment (12), and patients with pain reporting for emergency treatment may be even more anxious. Due to the nature of emergency treatment and the failure of the inferior alveolar nerve block, patients may benefit from sedation.

Lindemann et al. (8) conducted a study using the anxiolytic triazolam (Halcion) for patients with mandibular posterior teeth diagnosed with symptomatic irreversible pulpitis in an attempt to reduce anxiety and increase successful anesthesia. Despite high satisfaction ratings by patients, there was no significant difference in successful pulpal anesthesia gained with sublingual triazolam versus placebo.

Nitrous oxide is the most commonly used inhalation anesthetic in dentistry (13). It has an impressive safety record and is excellent for providing conscious sedation for apprehensive dental patients. Moreover, nitrous oxide provides a mild analgesic effect (13). The most common estimate of analgesic efficacy suggests 30% nitrous oxide is equivalent to 10-15 mg morphine (14). Nitrous oxide may have potential benefits because of its sedation and analgesic effects.

NITROUS OXIDE

Nitrous oxide is one of the oldest known general anesthetic agents. Nitrous oxide is the most commonly used inhalation anesthetic in dentistry (13). It is currently the only inorganic substance used as an anesthetic. Nitrous oxide is not a potent gas,

with a minimum alveolar concentration (MAC) of 104. Nitrous oxide also has minimal impact on cardiovascular or respiratory function, particularly when compared with other anesthetic inhalants (13). Nitrous oxide has low blood solubility. This characteristic allows anesthesia induction and awakening to occur very quickly. In dentistry nitrous oxide is typically administered in concentrations of 20% to 50%. Nitrous oxide typically induces a sense of relaxation, warmth, tingling of hands and/or feet, floating, auditory effects, or generalized euphoria. However, as the dosage increases, the patient is more likely to develop adverse symptoms such as nausea, anxiety, and uneasiness (15).

Nitrous oxide can be safely used on most patients in a typical dental setting. There are several contraindications, however. Individuals who are unable to use a nasal mask should not and cannot receive nitrous oxide sedation. These patients typically are in one of two categories: 1) patients who cannot tolerate wearing a nasal mask as a result of a psychological condition (cognitive impairment, severe phobias, etc.), or 2) patients who can't breathe adequately through their nose due to an anatomic variation or disease induced obstruction (upper respiratory/sinus infection, COPD, nasal polyp, deviated septum, etc.). Patients with diagnosed psychiatric or personality disorders may be at risk for adverse reactions with nitrous oxide sedation. Although it has been used successfully with these patients, caution should be used, especially when treating patients diagnosed with schizophrenia or bipolar disorder. Patients with a history of inner ear troubles or recent ear surgery should also be cautioned on nitrous oxide use. Use of nitrous oxide in these patients may lead to

pressure increases within the middle ear, which may result in tympanic membrane rupture (13).

Although it is commonly believed that nitrous oxide sedation is a definite contraindication during pregnancy, this is not necessarily fact. This belief arises from concern over adverse effects associated with long-term exposure to nitrous oxide. These adverse effects include altered metabolism, numbness/paresthesia, impaired fertility, and spontaneous abortion. Aside from chronic abusers, dental professionals are those individuals put at the highest risk of chronic exposure. Nitrous oxide scavenging devices greatly lower this risk, and thus are critical to the sedation process. Considering these points, pregnancy should be considered a relative contraindication to nitrous oxide sedation, because of the desire to avoid any drug administration or dental treatment during pregnancy. If drug induced sedation is to be considered on a pregnant patient, nitrous oxide sedation is the preferred sedative, and could be used for short procedures (13, 15).

Considering the above, nitrous oxide has an impressive safety record and is excellent for providing conscious sedation for apprehensive dental patients. Conscious sedation is defined as “A minimally depressed level of consciousness that retains the patient’s ability to independently and continuously maintain an airway and respond appropriately to physical stimulation or verbal command that is produced by a pharmacologic or nonpharmacologic method or a combination thereof” (9).

In 1967, Parbrook (16) classified nitrous oxide effects into four zones of analgesia. Zone I (~ 6-25% N₂O), moderate analgesia, consists of the full maintenance of contact with the patient. Zone II (~ 26-45% N₂O) is labeled

dissociation analgesia, and consists of patients beginning to experience psychological detachment from their environment and light sedation, but most patients are able to maintain full contact. Zone III (~ 46-65% N₂O), deemed analgesic anesthesia, consists of considerable inebriation and amnesia. However, patients are often able to maintain verbal contact in this zone.

Zone IV (~ 66-85% N₂O), which Parbrook called light anesthesia, produces light general anesthesia and contact with the patient is no longer possible. It should be noted that in Parbrook's study patients wore tight fitting masks or were intubated, which is contrary to methods used in dental practice (14).

Nitrous oxide also provides a mild analgesic effect (13). The most common estimate of analgesic efficacy suggests 30% nitrous oxide is equivalent to 10 to 15 mg of morphine (14).

Mechanism

The mechanism by which nitrous oxide produces its effects is not fully understood. It has been proposed that nitrous oxide has an effect on opiate receptors in the brain (17-19). This effect not only helps explain the central effects a sedated patient experiences, but may also explain the addictive qualities of nitrous oxide.

Although the exact mechanism of action of nitrous oxide is not known, it is known that nitrous oxide does not work through a single mechanism. Research indicates that nitrous oxide activates the analgesic effect by causing the release of endogenous opiate peptides and then subsequent activation of opioid receptors; however, this is not how the anxiolytic effect is reached. This involves the activation

of the GABA_A receptor through the binding site for benzodiazepines. The anxiolytic effect of nitrous oxide involves three key enzymes; nitric oxide synthase (NOS), soluble guanylyl cyclase, and cyclic GMP-dependent protein kinase (PKG). The inhibition of any of these enzymes blocks the anxiolytic effect of nitrous oxide. The anesthetic effect of nitrous oxide seems to be caused by the inhibition of N-methyl-D-aspartate (NMDA) glutamate receptors. NMDA typically incites an excitatory response in the nervous system; therefore, by blocking this effect, N₂O creates the desired anesthetic effect (20).

Emmanouil et al. (21) further researched the role of nitric oxide (NO) and nitric oxide synthase (NOS) in the antinociceptive properties of nitrous oxide. Because the blockage of NO production inhibits the antinociceptive properties of nitrous oxide, they conducted a study in an attempt to determine if NO function and the opioid receptors that determine nitrous oxide antinociception effects are found in the same location in the brain, specifically the periaqueductal gray (PAG) of the midbrain. This particular region of the midbrain has previously been proven to have involvement in the antinociceptive qualities of nitrous oxide. Two hundred and sixty-five mice were used in the study. The mice had this section of their midbrain injected with either saline or an opioid antagonist. They were then exposed to 70% nitrous oxide and an antinociception assessment was completed via an abdominal constriction test. The results showed that mice injected with a NOS-inhibitor, in this case 1-[2-trifluoromethylphenyl] imidazole (TRIM), had a dose-dependent relationship with inhibition of nitrous oxide induced antinociception. This led them

to conclude that both NO and opioid mechanisms are located in the PAG, based on the results of the abdominal constriction tests.

Zhang et al. (22) believed that the release of norepinephrine in the dorsal horn of the spinal cord was at least partially responsible for the analgesic action of nitrous oxide. In their experiment they took 104 male rats and transected their spinal cords at the level of T3-T4 before exposing the rat to 70% nitrous oxide. Analgesic response was measured with a tail flick latency response. A separate experiment was also conducted in rats, in which a dialysis fiber was placed in the dorsal horn of the spinal cord at the T12 level. This fiber was then filled with artificial cerebrospinal fluid and allowed to equilibrate. The animals were then exposed to 70% nitrous oxide. The rats were then pretreated with naltrexone and exposed to nitrous oxide again. In a third trial, the norepinephrine was depleted from the dorsal horn and exposed to 70% nitrous oxide. Analgesic response was measured. Zhang et al. determined that the analgesic effect of nitrous oxide was prevented by spinal cord transection; that there is a four fold increase in release of norepinephrine after exposure to nitrous oxide; that the administration of naltrexone inhibits the increased release of norepinephrine; and that depletion of norepinephrine obstructs any analgesic response to nitrous oxide; thus concluding that spinal norepinephrine is required for an analgesic response to nitrous oxide.

Substantia gelatinosa neurons receive nociceptive input from both A δ fibers and C-fibers, making them a major component of nociceptive processing. Georgiev et al. has shown in their research that nitrous oxide has a direct inhibitory effect on excitatory glutamergic transmission in the dorsal horn of rat spinal cords (23). They

(24) then further studied this inhibitory effect specifically in the synaptic transmission of substantia gelatinosa neurons of rats. After removing and preserving sections of spinal cord, the sections were placed in a biomimetic solution and impulses were made with an imbedded electrode. Nitrous oxide, in a concentration of 50%, was applied to the section by bubbling it through the solution. They concluded that nitrous oxide did not have any significant effect on inhibitory transmission in substantia gelatinosa neurons. “It seems that nitrous oxide facilitates inhibition at the spinal cord level not by a direct action on dorsal horn neurons, but through activation of descending inhibitory pathways and norepinephrine release in the dorsal horn” (24), which has been shown in previous studies (25). “In addition, as we found previously, nitrous oxide inhibits excitation through antagonism of ionotropic glutamatergic receptors in substantia gelatinosa neurons, thus exhibiting a dual analgesic mechanism” (24).

Dose

As mentioned previously, a 30% concentration of nitrous oxide is believed to have the analgesic effect of 10-15 mg of morphine (14). In dentistry, N₂O is typically administered in 20%-50% concentrations to obtain the desired effect (15). Parbrook (16) divided nitrous oxide sedation into four zones. Use in a day-to-day dental practice would likely restrict use to Zones I, II, and III with percent dose ranging from 6% to 65%. The majority of research completed in this area of focus used nitrous percentages ranging from 30% to 50% (26-38). There are exceptions to this.

Emmanouil et al. (21) and Zhang et al. (22) both used 70% in their research designs. However, both of these studies were laboratory based rather than clinically based.

Analgesia

Meskine et al. (37) conducted a prospective, randomized, double-blind controlled study investigating the analgesic effect of equimolar mixture of oxygen and nitrous oxide during percutaneous biopsy of focal liver lesions. Ninety-nine patients completed this study (50 experimental, 49 placebo). Patients each received 10 mg of diazepam and two tablets of Darvocet-N (paracetamol-dextropropoxyphene; 400 mg/30 mg) one hour prior to the procedure. Patients were then randomized into either experimental (50% nitrous) or placebo group. They inhaled the assigned regimen for 3 minutes prior to initiation and throughout the procedure. Ten milliliters of 2% lidocaine was administered locally and a needle biopsy was completed. Patients completed a preoperative and postoperative VAS pain scale (0-100 mm). Investigators defined analgesic control by the difference between postoperative and preoperative VAS pain ratings. It was concluded that patients receiving the 50% mixture of nitrous oxide experienced significantly better analgesic control than those who received placebo ($p=0.045$). Furthermore, they found that patients receiving the nitrous oxide were significantly more willing to undergo the same procedure again under the same conditions compared to placebo ($p=0.026$).

Reinoso-Barbero et al. (38) investigated the impact of equimolar nitrous oxide/oxygen (50% nitrous oxide) on procedural pain in children undergoing minor medical procedures. One hundred patients participated in this randomized, double-

blind study. All patients were aged 1 to 18 years and were randomly assigned to a treatment group (52 nitrous oxide, 48 placebo). Patients were scheduled for minor skin, muscle, or bone procedures. Three minutes before the procedure was to begin, patients began inhaling the assigned regimen and continued throughout the procedure. Some procedures included the administration of local anesthesia, but others did not. Pain was rated preoperatively and immediately postoperatively using two pain scales (0-10 scales). Patients 6 years of age and older were asked to rate their pain on the Faces Pain Scale-Revised (rFPS) (39), which is a 6 face scale that was converted to a 0-10 scale. Patients ages 5 and under had their pain rated by the procedure team on a Spanish version of an observational scale (LLANTO) (40). Results revealed that the nitrous oxide group had significantly more males than the placebo group ($p<0.04$). Additionally, the nitrous oxide group was older than the placebo group (8.0 vs 6.2 yrs; $p<0.021$). Pain scores were significantly reduced in the nitrous oxide group ($p<0.0003$). The pain levels of the nitrous oxide group were reduced by approximately 50% versus the placebo group, as determined by both scales. Patient cooperation, as rated by the procedure team, was also significantly better in the nitrous oxide group ($p<0.05$). They concluded that the inhalation of 50% nitrous oxide mixture was well accepted, had a potency of ~50%, and was safe to use in pediatric patients.

Paris et al. (27) completed a prospective, randomized, crossover, multicenter project, which compared the use of N₂O and morphine chlorhydrate for analgesic efficacy during the management/care of painful bedsores and ulcers. Thirty-three patients (53-96 yrs; mean = 84 yrs) completed the study with the inclusion criteria of:

1) 18 years or older; 2) more than 8 days inpatient stay; 3) presence of pressure ulcer(s) causing pain; and 4) able to give informed consent. Each patient received a sequence of three analgesic therapies over a period of six days. The regimens included: morphine, N₂O, and the combination of morphine and N₂O. Morphine was administered in a 1 mg/10 kg dose 30 minutes prior to start of treatment. The N₂O mixture was administered 5 minutes before and throughout treatment. Each treatment was administered once, in a random sequence, on Day 0, 2, or 4. Pain was measured by several methods. Pain was measured on a behavioral ECPA scale, typically used for evaluating behavior/pain in non-communicating elderly (0-32; 0=no pain/32=total pain); a GHES scale (1-4 scale; 1=comfortable/4=horrible); and a DOLOPLUS-2 scale, which asks a series of questions related to treatment received and the patient rates the difficulty of each question/stage of treatment on a 1-3 scale. Heart rate and mean arterial pressure were also measured before and after treatment. The ECPA, GHES, and DOLOPLUS-2 scales all revealed a statistically significant difference ($p<0.01$) between the morphine and N₂O groups and the combination group, with N₂O groups being statistically more effective in providing analgesia. There was no difference between the N₂O and N₂O/morphine group. They concluded that analgesia obtained with the N₂O was better than with morphine/chlorhydrate alone. Moreover, the combination of N₂O/morphine/chlorhydrate added no benefit, and that sex, age, or daily use of analgesic medication had no effect on these results.

Duarte et al. (41) compared the sedative, cognitive, and analgesic effects of nitrous oxide, sevoflurane, and ethanol. As a quick background, GABA is the principle inhibitory receptor found within the central nervous system and is the target

of most anesthetics. N₂O does not target these receptors, but instead targets NMDA sensitive receptors. NMDA antagonists, however, seem to have a greater effect on temporal summation pain or secondary pain, not acute pain (42). GABA and NMDA are part of a larger “cysteine-loop superfamily” and activation of either has an inhibitory effect. Ethanol and sevoflurane both target GABA and GABA_A receptors. Eight volunteers, 4 male and 4 female, ranging from age 19-28 years and weighing 47-87 kg (mean 66 kg) were recruited for this study. A nested, within-subjects design was used, and accomplished in four sessions. The treatments were administered in a random, double-blind manner, and included 1) N₂O, given in two 45 min. sessions with a 10 min. break in between at a dosage of 15% to 25%; 2) sevoflurane given in two 45 min. sessions with a 10 min. break in between at a dosage of 0.3% to 0.5%; 3) a single dose of EtOH, calculated to give the patient a peak plasma EtOH concentration of 80-100 mg per 100 mL; and 4) placebo. The EtOH was administered as vodka or water (placebo) mixed with orange juice. Patients were instructed not to eat for 4 hours before each session and not to consume alcohol for 24 hours prior to and after sessions, and were only permitted one cup of coffee or tea prior to session (no other caffeine sources). During each session, patients were asked to complete a series of tests including mazes, word list learning, logical working memory, visual analogue scales (to analyze mood), and pain sensitivity of pricking sensation on forearm (rated on a 10 cm VAS). Results showed that N₂O was more analgesic than the other drugs tested ($p < 0.05$). They also found that EtOH caused more of a drunken feeling ($p < 0.01$), but little analgesia.

Furuya et al. (28) attempted to find the dose of inhaled nitrous oxide required to reduce the pain felt by children during a venipuncture procedure. The prospective, randomized study included 72 patients undergoing surgery at Shizuoka Prefectural Children's Hospital. Kanagasundaram et al. (29) had previously published that N₂O concentrations of 50% to 70% were more effective in preventing pain in children older than 5 years of age. Therefore, all children were older than 5 years of age and were not premedicated. Each patient was assigned to 1 of 4 groups: 1) received 50% N₂O for 3 minutes; 2) received 50% N₂O for 5 minutes; 3) received 70% N₂O for 3 minutes; and 4) received 70% N₂O for 5 minutes. After the time for the assigned group passed, venipuncture was performed with a 24-gauge catheter on the back of the hand. Pain was measured by parents and/or nurse on the Bieri face scale (corresponds to a 0-10 metric scale; 0=no pain/10=max pain). Both parents and nurse were blinded to assigned treatment group. Results showed that there was no significant difference between groups with regard to age, sex, or weight. They also indicated that Group 3 experienced significantly less pain than Groups 1 and 2 ($p<0.005$), as rated by parents; Group 3 experienced significantly less pain than Group 1 ($p<0.005$), as rated by nurse; and that Group 4 experienced significantly less pain than Groups 1 and 2 ($p<0.05$), as rated by parents. This group concluded that the administration of 70% N₂O for 3 minutes reduced pain experienced during venous puncture.

Burnweit et al. (30) conducted a project to determine if N₂O analgesia for minor pediatric procedures was an effective alternative to conscious sedation. One hundred and forty-three patients, ages 1-20 years (mean 9.83 ± 4.92), ultimately

completed the study. All patients were recruited from Miami Children's Hospital in Miami, FL. Patients had to be overall healthy, with no contraindications, and were recruited from two pools: 1) patients requiring emergency interventions, such as abscess drainage or removal of a foreign body; and 2) patients undergoing minor elective procedures, such as mole removal. All patients were treated with topical anesthetic initially and then titrated on N₂O to a concentration of 20% to 50%. Once titrated, local anesthesia was then administered and pain was measured on a Wong-Baker face scale (43). This scale consists of six faces starting with a "smiley face" at zero pain progressing to a painful crying face at a pain score of five. The child was asked to rate pain on the Wong-Baker scale four times; preoperatively, at injection, during the procedure, and postoperatively. They reported that children who had abscesses had significantly more preoperative and postoperative pain than any of the other groups ($p<0.01$), and that other groups reported an increase in pain throughout the study. This was attributed to the fact that the other groups likely had little or no pain preoperatively. Parent satisfaction was 100%. It was concluded that N₂O was an efficacious alternative to conscious sedation, which provides for no postoperative monitoring of patient and a high level of satisfaction.

Maslekar et al. (34) conducted a randomized trial comparing N₂O sedation with intravenous midazolam-fentanyl for colonoscopy procedures. One hundred and thirty-one patients completed this study. Sixty-five patients received 50% N₂O and 66 received intravenous doses of midazolam and fentanyl, with both groups having the target of a 3 to 4 score on the Modified Observer's Assessment of Alertness of Sedation Scale (MOAAS scale) (44). Pain and satisfaction were reported on 0-100

mm VAS. Results showed that patients in the N₂O group reported significantly less pain ($p<0.001$) and higher satisfaction than patients receiving midazolam-fentanyl ($p=0.001$). It was concluded that N₂O sedation provides more effective pain relief and shorter recovery than midazolam-fentanyl; and therefore, N₂O is better for colonoscopy procedures.

Robinson et al. (45) conducted a study to compare the difference in analgesia provided by lidocaine, ethyl chloride, and nitrous oxide for intravenous cannulation. Two hundred and ninety patients completed this emergency department based project (Christchurch Hospital, New Zealand). All patients presented to the ED and required venous cannulation. They were randomly assigned to one of four groups: 1) cannulation without anesthesia; 2) 50% N₂O inhaled for 1 minute prior to and during cannulation; 3) ethyl chloride sprayed for 5-10 seconds on cannulation site; and 4) 0.1 mL 1% lidocaine delivered intradermally with a 26-gauge needle. Preoperative and postoperative pain scores were measured on a VAS as described by Ho et al. (46) and Scott (47). Patients receiving ethyl chloride spray or lidocaine injection were also asked to complete a VAS rating pain of that procedure. Results showed that all experimental groups reduced pain in comparison to control. However, lidocaine injection was the only treatment that produced a significant difference in pain experienced ($p<0.001$). Lidocaine injection was also significantly better than ethyl chloride and N₂O ($p<0.001$). Ethyl chloride and N₂O groups were not significantly different. It was concluded that although ethyl chloride and 50% N₂O may be effective in reducing pain experienced during venous cannulation, 0.1 mL of 1% lidocaine intradermally was more effective in reducing pain.

Claeys et al. (32) conducted a prospective, randomized, multicenter, open-label pilot study investigating the effectiveness of pain management with N₂O vs lidocaine-prilocaine cream (LPC) during debridement of leg ulcers. Patients were randomly assigned to 2 groups and received either lidocaine-prilocaine cream applied 30 minutes before debridement or 50% N₂O inhaled for 3 minutes prior to and then during debridement. Pain ratings were measured both preoperatively and immediately postoperatively via VAS (100 mm scale) and verbal rating scale (0-4 scale; 0=no pain/4=very intense pain). Forty-one patients completed this study (20 N₂O, 21 LPC). Results showed that the average pain rating in both groups rose significantly during treatment ($p<0.001$), but that postoperatively the LPC group had significantly less pain than the N₂O group ($p<0.001$). Early interruption of debridement via patient request was also significantly higher with the N₂O group ($p<0.002$). They concluded that LPC is superior to N₂O for controlling pain during mechanical debridement of leg ulcers.

Kan et al. (48) completed a prospective, randomized, double-blind control trial on the use of a 50:50 mixture of N₂O/O₂ in pain relief during suction evacuation of first trimester pregnancy terminations. Ninety women were recruited from the Department of Obstetrics and Gynecology at the University of Hong Kong Queen Mary Hospital. All women were older than 16 years and were within 12 weeks of gestation on day of recruitment. Patients were then randomly assigned to a treatment group (N₂O vs placebo). A project nurse not involved with the procedure evaluated each patient's pain and anxiety levels. Pain was measured on a 100 mm linear VAS. Baseline anxiety levels were measured on a State Anxiety Questionnaire. All other

anxiety levels from that point were measured on a 100 mm linear VAS. Sedation was measured with a scale proposed by Ramsay et al. (49). Satisfaction was measured on levels: unsatisfactory, fair, satisfactory, and excellent. Patients had baseline anxiety measured after arriving at the hospital, then pain measured during venipuncture, insertion of intravenous cannula, and vaginal exam. The patient was then asked to rate anxiety preoperatively. N₂O was then administered before intravenous administration of 2 mg midazolam and 25 µg fentanyl. The patient's sedation level was measured before the procedure began. Pain was measured during suction evacuation, and then one hour postoperatively. Anxiety was also measured postoperatively. The results showed that both groups were more nervous preoperatively, with no significant difference between groups. There was a positive correlation between preoperative anxiety and pain experienced during suction evacuation ($p < 0.042$). Neither age, sedation level, gestational age, nor socioeconomic status had effect on pain levels experienced. Approximately one third of patients rated their pain relief as unsatisfactory. However, more than half of patients in this study, regardless of group, said they would have the operation again under the same conditions. Overall, it was concluded that the N₂O/O₂ mixture did not reduce the pain levels experienced by patients in this study.

Babl et al. (31) conducted a prospective observational study to research the use of N₂O as a sole analgesic agent in procedures completed in a children's hospital emergency department. One hundred and twenty-four patients were recruited from a hospital in Melbourne, Australia. Patients reported for a wide range of emergencies ranging from arthrocentesis to joint dislocation reduction. The most common were

laceration repairs and orthopedic procedures. All patients received N₂O in a concentration of 50% to 70%, with the majority receiving 70% (100/124). Sedation was measured with a seven level scale ranging from 6 to 0 (6=anxious or in pain; 0=unresponsive to painful stimulus). Patient pain was measured several ways. For children 5 years and younger a 0-100 mm VAS was completed by the patient's parent. Children 5 to 6 years completed a Faces Pain Scale – Revised (FPS-R), which consists of six faces portraying increasing levels of pain or sadness. Children 7 years and older completed their own 0-100 mm VAS. Satisfaction of parents and staff members was measured postoperatively on a 5 point scale (very dissatisfied, dissatisfied, neither satisfied nor dissatisfied, satisfied, very satisfied). This group found that 1/3 of patients experienced an increase in pain throughout the procedure. One third of patients reported intra-procedural pain of 50 mm or greater, with 21% reporting pain of 70 mm or greater. Three procedures (24%) had to be abandoned due to inadequate anesthesia. Ninety percent of staff believed that the analgesia and sedation provided was adequate. Ninety-six percent of parents who responded to the survey were satisfied or very satisfied with the procedure completed. Ninety-two percent were satisfied with sedation and 93% would be willing to have their child have N₂O sedation again. They concluded that the use of N₂O for analgesia and sedation in the emergency department was effective and parents and staff were satisfied with the level of analgesia and sedation it provided. However, they also concluded that the analgesia obtained by N₂O sedation may not be adequate in all procedures.

Maslekar et al. (33) completed a study in which they compared N₂O sedation and modified patient-controlled propofol for sedation during colonoscopy procedures. One hundred patients completed this randomized trial. Fifty patients received an initial intravenous dose of propofol to induce a sedation score of 4 on the MOAAS (Modified Observer's Assessment of Alertness of Sedation Scale). These patients were then given a handset and were told to press the button if they wanted to feel more sleepy during the procedure. If the button was depressed, the patient was delivered an additional 200 µg/kg/mL bolus of propofol. The anesthetist was able to administer intravenous fentanyl to the patient if they had pain during the procedure. Fifty patients received 50% N₂O delivered via a demand mask. These patients breathed the N₂O throughout the procedure. When a sedation score of 4 on the MOAAS was obtained, the procedure was initiated and completed unless the patient was uncomfortable or experienced pain. If pain occurred, the anesthetist was able to deliver intravenous medication to aid with sedation and/or pain relief. Pain measurements were taken on a 0-100 mm VAS preoperatively, immediately post-operatively, every 15 minutes up to time of discharge, and 24 hours post-operatively. Satisfaction of patient and staff was also measured on a 0-100 mm VAS. Results reported indicate that there was no difference between the groups with regard to pain or satisfaction of patient or staff ($p < 0.05$). The median recovery time for resuming normal activities for the N₂O group was 2-4 hours versus the propofol group, which had a median of more than 6 hours. This group concluded that both N₂O and propofol provided equal sedation and analgesia allowing patients to easily be maneuvered during endoscopy procedures.

Welchman et al. (50) completed a systematic review of the use of nitrous oxide for lower gastrointestinal endoscopy versus intravenous sedation. The review identified 11 studies, which included 623 patients undergoing colonoscopy or flexible sigmoidoscopy. In the studies reviewed, overall there was no significant difference between N₂O sedation and no sedation during flexible sigmoidoscopy (possibly because N₂O was delivered on demand rather than continuously); there was also no significant difference between N₂O and intravenous sedation during colonoscopy, although several studies have shown a significant difference. In all the studies reviewed, N₂O sedation was associated with a quicker recovery time. Because there was no significant difference between the groups, they concluded that N₂O sedation is able to provide similar analgesia to that of intravenous sedation.

Uziel et al. (35) looked at the effects of nitrous oxide sedation for intra-articular injection in juveniles with idiopathic arthritis. Intra-articular injections with corticosteroids are often associated with pain and anxiety. Therefore, they conducted this study in order to evaluate the effectiveness and safety of N₂O during these procedures and evaluate patient and staff satisfaction. 43 patients participated in this study (mean age: 12.5 ± 4.8), which resulted in 54 procedures. Each patient had topical anesthetic (EMLA- Astra Zeneca, Wilmington, DE) placed at least one hour prior to procedure. Patients were titrated to 30% to 50% N₂O. There was no control group. Pain was measured by patient, parent, and staff members using a VAS with a 0-10 scale (51). Parent and staff satisfaction was measured on a 5 point Likert scale (5=best score). The median pain reported by patients, parents, and staff was 3. There was no significant difference between groups. Staff reported a median satisfaction

score of 5, whereas parents had a median satisfaction score of 3. This group concluded that N₂O provided safe and effective sedation for patients undergoing intra-articular injections for juvenile idiopathic arthritis.

Ong et al. (52) completed a prospective, randomized crossover study in which 36 patients had their bilateral impacted mandibular third molars extracted. The study investigated the preemptive analgesic effect of nitrous oxide. Patients had one side randomly assigned as pretreatment and the other as post treatment. The teeth were extracted at two separate appointments. The pretreatment side received 50% N₂O for 20 minutes preoperatively and 100% O₂ for 20 minutes postoperatively. The post treatment side received 100% O₂ preoperatively and 50% N₂O postoperatively, both for 20 minutes. Pain was measured on a 100 mm VAS hourly for 8 hours. They also measured time to first analgesic taken and total analgesic taken during the initial 48 hours. They detected no differences between groups in any variable measured.

Sedation

Al-Zahrani et al. (26) conducted a crossover study comparing the use of oral midazolam alone and oral midazolam combined with nitrous oxide inhalation to determine their effectiveness in the sedation of young dental patients. 30 healthy patients (17 males and 13 females), aged 4-6 years, were randomly selected from the pediatric dental screening clinics of the King Saud University College of Dentistry in Saudi Arabia. The children were all ASA-1, had no previous dental treatment, but required bilateral restorative treatment in the mandible. The midazolam was administered individually for each patient in a 0.6 mg/kg dosage. After 30 minutes,

the patient was moved to the treatment room, papoose, given local anesthesia, and restorative treatment of half of the lower arch was completed. The second appointment followed the same protocol as the first appointment, with the addition of nitrous oxide once the patient was brought to the treatment room. The nitrous oxide dosage was titrated 30% to 50% depending on the patient's need. This group found no significant difference between the groups in overall behavior, amnesia, and working time; but did find a significant improvement between groups in regard to sleep scale, movement scale, and crying scale ($p < 0.05$). They concluded that although midazolam/N₂O did not make a statistically significant difference in overall behavior versus midazolam alone, the midazolam/ N₂O combination did work better during stressful situations, including the administration of anesthesia and cavity preparation.

Crececius et al. (36) conducted a prospective, randomized, double-blind study investigating the influence of ethyl chloride on anxiety and pain during venous cannulation in patients sedated with nitrous oxide. Eighty-eight patients were recruited from the University of Washington School of Dentistry's Oral and Maxillofacial Surgery Department. All patients were scheduled to have dental surgery with N₂O and intravenous sedation. Subjects were divided into 2 groups randomly and placed on N₂O (median concentration of 50%). Subjects then received spray on their forearm of either distilled water or 10 seconds of ethyl chloride. The venipuncturist was not present during the spray, but then entered and completed venipuncture/cannulation. Pain and anxiety were measured on 100 mm VAS and were both measured 4 times: before N₂O administration, after N₂O sedation, after

spray application, and after venous cannulation. Patients reported greater pain and anxiety with the ethyl chloride spray than with placebo ($p < 0.001$). The total subject population displayed a statistically significant decrease in anxiety after the administration of N_2O ($p < 0.001$).

Zacny et al. (53) completed research investigating the changes in preoperative mood and anxiety associated with dental treatment after nitrous oxide sedation. Forty-six patients participated in this study. Each patient presented for routine dental care. The patients each completed a Dental Anxiety Scale (DAS) and a Profile of Mood States (POMS) before sedation and then again after sedation had been administered for at least 5 minutes. Based on the scoring of these anxiety tools, the patients were divided into three groups: low anxiety (LA); moderate anxiety (MA); and high anxiety (HA). Dosage of N_2O ranged from 10%-60%, and was determined by the dentist based on the patient's response to weekly alcohol use (higher EtOH use: higher dose administered) as well as patient response to sedation (sedation was increased if effects were little or none and decreased if patient was uncomfortable, nauseous, etc.). Results showed a statistically significant decrease in rated anxiety from preoperative period, to operative, and continuing in postoperative period for both the MA and HA groups.

Whalley and Brooks (54) conducted a study investigating nitrous oxide's enhancement of suggestibility and imaginative ability. Twenty-six patients fully participated in this study (mean age = 40.06 years). All patients completed the Sheehan-Betts Quality of Mental Imagery Scale (QMI) (55), the Stanford Hypnotic Susceptibility Scale Form C (SHSS:C) (56). Participants had two separate

appointments with approximately 2 weeks between sessions. Half of the patients received N₂O at the first appointment and half at the second. Patients were given a 25% concentration of N₂O at the treatment appointment and an O₂/air mixture at the placebo appointment. During the placebo appointment, the air intake valve remained open while oxygen was being delivered in order to obtain the mixture and also blind the patient by having gas flowing. During the study patients were asked to complete the QMI and SHSS:C surveys. The test administrator was not blinded to the treatment received. Results showed that only 36.7% of patients were able to correctly determine which session they received nitrous oxide, which is not significantly different from the result to be expected from chance alone (p=.201). This demonstrates that patients were unaware when they were receiving N₂O.

CORAH'S DENTAL ANXIETY SCALE

The Corah Dental Anxiety Scale (DAS) was developed by Normal Corah in 1968, based on observations of patient anxiety during video-simulated dental procedures (70).

Fagade et al. (57) conducted a study in Nigeria implementing the Corah scale preoperatively in patients undergoing single tooth extraction. One hundred and twenty-two patients completed the study and after completing a Corah scale they each received local anesthesia and underwent single tooth extraction. Post operatively they each completed a VAS pain scale (0-10 scale) rating the pain experienced during the procedure. They found a strong correlation between preoperative anxiety scores and

post operative VAS pain scores ($p=0.001$), leading them to conclude that high preoperative anxiety could lead to higher intra-operative pain perception.

Facco et al. (58) completed research with the aim of validating the effectiveness the visual analogue scale for anxiety (VAS-A) in 1114 consecutive patients presenting to the implantology clinic at the University of Padua in Italy. Each patient completed a VAS-A and a Corah Dental Anxiety Scale (DAS) preoperatively. This comparison was completed because the DAS is commonly used in research but has been criticized for its lack of ability to detect/discern intermediate levels of anxiety due to its limited range of scores compared with other measures, such as the VAS-A. After analyzing data statistically, it was determined that the VAS-A and DAS were closely correlated ($p<0.001$), but the VAS-A revealed higher sensitivity than the DAS. The authors suggested using the VAS-A exclusively or in conjunction with the DAS in an effort to better gauge patients' dental anxiety.

LOCAL ANESTHETICS

Inferior Alveolar Nerve Block Success with Irreversible Pulpitis

Claffey et al. (5) found success rate of an IAN block with 4% articaine to be 24% versus 23% success with lidocaine, in patients with irreversible pulpitis.

Tortamano et al. (59) also researched the efficacy of the IAN block with 4% articaine compared with 2% lidocaine, in patients with irreversible pulpitis. They reported no significant difference between the two solutions (60). Bigby et al. (6) compared the efficacy of an IAN block with lidocaine with epinephrine to an IAN block with

lidocaine with epinephrine and meperidine. They found no significant difference between the two groups ($p=0.28$).

Aggarwal et al. (9) performed a prospective, randomized, double-blind study comparing the anesthetic efficacy of a traditional IAN block injection, a Gow-Gates technique, Vazirani-Akinosi technique, and buccal plus lingual infiltrations in patients with irreversible pulpitis. Ninety-seven patients with active pain in a mandibular molar, a prolonged response to cold and EPT, and no periapical radiolucency were recruited to participate. The traditional IAN block was found to have a 36% success rate, compared to 52% success rate of the Gow-Gates, 41% of the Vazirani-Akinosi, and 27% of the infiltrations. There was no statistical difference between the IAN block and the Vazirani-Akinosi or infiltrations. However, in this study, the success rate of the Gow-Gates technique was statistically better than a traditional IAN block ($p<0.05$).

Aggarwal et al. (61) conducted a prospective, randomized, double-blind study investigating the effect of preoperative NSAIDs on anesthetic efficacy of the IAN block. Seventy-two patients were given either preoperative ibuprofen, ketorolac (Toradol), or a placebo. All patients were actively experiencing pain, had a prolonged response to cold testing, and had not taken pain altering medications. The placebo group had a 29% success rate, compared with the 27% and 39% success rate of ibuprofen and ketorolac, respectively. They concluded that the preoperative administration of the experimental NSAIDs had no significant effect on the success of the inferior alveolar nerve block.

Parirokh et al. (62) compared the success of the inferior alveolar nerve block in teeth with asymptomatic irreversible pulpitis after the preoperative administration of ibuprofen or indomethacin. The randomized, double-blind trial included 150 patients separated into three groups (placebo, ibuprofen, and indomethacin). The inclusion criteria included having a mandibular molar with normal radiographic appearance and an exaggerated painful response to cold. The overall success rates of the IAN block in each group was 32% for placebo, 78% for ibuprofen, and 62% for indomethacin. It was concluded that the preoperative administration ibuprofen or indomethacin significantly increased the success of the IAN block in teeth with asymptomatic irreversible pulpitis.

Matthews et al., Oleson et al., and Simpson et al. (7, 10, 11) studied the success of the inferior alveolar nerve block in patients diagnosed with symptomatic irreversible pulpitis. They found the success rates of the IAN block to be 33%, 35%, and 24%, respectively.

Mandibular Infiltration

Infiltration Success with Irreversible Pulpitis

Matthews et al. (7) researched the efficacy 4% articaine administered as a buccal infiltration after the failure of an IAN block. They reported an overall anesthetic success rate of 58%. In a similar population, Oleson (60) reported an articaine anesthetic success rate of 41%-52%, after premedication with 800 mg of ibuprofen. Rosenberg et al. (63) compared pain ratings of a buccal infiltration of 2%

lidocaine versus a buccal infiltration of 4% articaine. They reported no significant difference between the two solutions ($p>0.05$).

Parirokh et al. (64) evaluated the efficacy of combining a conventional IAN block with a buccal infiltration. They concluded that the combination of an IAN block and buccal infiltration provided more reliable anesthesia than the IAN block alone. However, the combination still only resulted in an anesthetic success rate of 65.4%.

Simpson et al. (11, 65) researched the effect of a combination of 800 mg ibuprofen and 1000 mg acetaminophen given preoperatively to patients diagnosed with symptomatic irreversible pulpitis. One hundred patients were given either 800 mg ibuprofen and 1000 mg acetaminophen or placebo 45 minutes before treatment was initiated. Anesthetic success was defined as no pain or mild pain as rated on a 170 mm Heft-Parker VAS. The success of the inferior alveolar nerve block was only 32% for the ibuprofen/acetaminophen group and 24% for placebo. Therefore, these patients required a supplemental buccal infiltration of 4% articaine with 1:100,000 epinephrine. Articaine infiltration success was 38% for the ibuprofen/acetaminophen group and 24% for the placebo group. The results showed no statistically significant difference between the groups ($p>0.05$).

Aggarwal et al. (66) examined the effect of a supplemental buccal infiltration in teeth diagnosed with irreversible pulpitis. Ninety-four subjects participated in this randomized clinical trial. Patients were randomly assigned to one of four groups: control; 1 cartridge 4% articaine with 1:100,000 epinephrine; 0.5 cartridge 4% articaine with 1:100,000 epinephrine plus 1 mL/30 mg of ketorolac tromethamine;

and 1 mL/4 mg dexamethasone. Each patient was first given an IAN block and then the supplemental buccal infiltration of their assigned group. After 20 minutes, if profound lip numbness was obtained, root canal treatment was initiated. The patient was instructed to raise their hand if they felt pain during the procedure. If so, they then rated the pain on a 170 mm VAS. Results showed successful anesthesia for control, articaine, articaine/ketorolac, and dexamethasone to be 39%, 54%, 62%, and 45%, respectively. The articaine and articaine/ketorolac groups both showed significantly higher anesthesia success compared with control ($p<0.05$).

Intraosseous Success with Irreversible Pulpitis

Pearce (67) 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. (68) 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. (2) 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. (69) evaluated the efficacy of the X-tipTM 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-

tipTM system. They found the intraosseous injection with the X-tipTM system to be 82% successful overall.

Oleson et al. (10, 60) 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. (11, 65) 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%).

No study has investigated the efficacy of nitrous oxide in increasing the success of the inferior alveolar nerve block in patients with irreversible pulpitis. Therefore, the purpose of this prospective, randomized, double-blind study was to determine the effect of nitrous oxide on the anesthetic success of the inferior alveolar nerve block in patients experiencing symptomatic irreversible pulpitis.

CHAPTER 2

MATERIALS AND METHODS

One hundred adult subjects participated in this study. All were emergency patients of The Ohio State University College of Dentistry and were in good health as determined by a health history and oral questioning. Patients were questioned regarding inclusion/exclusion criteria. Inclusion criteria were: age 18 or older; in good health (ASA classification I or II); informed consent granted. Exclusion criteria were: allergy to nitrous oxide; history of significant medical problem (ASA classification III or greater); schizophrenia or bipolar disorder; inability to use nasal mask (nasopharyngeal obstructions, respiratory infection, or sinusitis); have taken CNS depressants (including alcohol) or any analgesic medications within the last 8 hours; pregnancy; lactating; or inability to give informed consent. The Ohio State University Human Subjects Review Committee approved the study and written informed consent was obtained from each patient. After completion of the medical history and consent form, the subjects completed the Corah's Dental Anxiety Scale questionnaire (70-72) (Appendix D). Corah (70) developed a 4-item questionnaire

that asks patients about 4 dentally related situations. The scale yields a score ranging from 4-20.

To qualify for the study, each patient had a vital mandibular posterior tooth (molar or premolar), was actively experiencing moderate-to-severe pain, and had a prolonged response to cold testing with Cold Snap Freeze SprayTM (1,1,1,2 tetrafluoroethane; Benco Dental, Wilkes-Barre, PA). 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. Therefore, each patient had a tooth that fulfilled the criteria for a clinical diagnosis of symptomatic irreversible pulpitis.

Patients rated their presenting pain on a 170 mm Heft-Parker Visual Analog Scale (VAS) (73). The VAS was divided into four categories. No pain corresponded to 0 mm. Mild pain was defined as greater than 0 mm and less than or equal to 54 mm. Mild pain included the descriptors of faint, weak, and mild pain. Moderate pain was defined as greater than 54 mm and less than 114 mm. Severe pain was defined as equal to or greater than 114 mm. Severe pain included the descriptors of strong, intense and maximum possible.

A urine pregnancy test (Osom[®] Genzyme Corp, San Diego, CA) was offered to all eligible females before starting the study. If patients were sure they could not be pregnant, they were allowed to decline a pregnancy test. If there was a positive pregnancy test response, the patient was disqualified from the study. Zero patients were disqualified due to a positive pregnancy test.

The 100 patients randomly received either nitrous oxide/oxygen or oxygen/room air by nasal mask 10 minutes prior to the administration of local anesthesia. Each patient was randomly assigned a six-digit number to determine which inhalation regimen was administered. A trained operator not involved in the administration of local anesthesia or performing endodontic access was responsible for administering either the nitrous oxide/oxygen or oxygen/room air and was present during the time of the administration of the inhalation agent.

A master list of the six-digit numbers was supplied by the lead researcher and was not available to the operating doctor (WS) at any time during data collection. The master list provided identification of the inhalation regimen each patient received not only for blinding during the statistical analysis, but for the proper treatment in the case of a medical emergency during/following inhalation administration. To be certain that equal numbers of nitrous oxide/oxygen and placebo cases were used, the lead researcher (MD) periodically verified the six-digit numbers used to date to control for possible subject drop outs.

The nitrous oxide/oxygen was administered utilizing a scented nasal mask (Accutron, Inc., Phoenix, AZ) and nitrous oxide machine (McKesson Equipment Company, Chesterfield, UK). The scented mask helped to blind the subject to whether they were receiving the treatment or placebo. The patient and operator were further blinded by the covering of the air intake valve. A 1 cm diameter hole was drilled in one air intake hub of the nitrous oxide unit. This hub was used for those patients receiving the placebo. The hole allowed oxygen to flow through the intake opening, while also allowing room air to be breathed in and mixed with the flowing

oxygen. The hub, whether experimental or placebo, was covered during each procedure with a round molded dental mask (Mydent International, Hauppauge, NY), trimmed to a size similar to the intake hub, in order to keep the operator (WS) blinded to the treatment received. Moreover, the nitrous delivery unit (O₂/N₂O flowmeter) was directed away from the blinded operator and patient. It was only visible to the practitioner administering the inhalation regimen.

Oxygen was given for five minutes both before and after the administration of the nitrous oxide/oxygen or room air/oxygen. The nitrous oxide/oxygen was then titrated over a 5-minute period until a 30% to 50% concentration was achieved. Malamed states that “The first sign of clinical evidence of the effect of nitrous oxide is usually the feeling of light-headedness” (74). He also states that this is typically followed by a tingling sensation in the arms or legs or a “feeling of warmth, floating, or heaviness” (74). This relative analgesic state is typically achieved with nitrous oxide concentrations of 30% to 50% (74). The practitioner responsible for administering the nitrous oxide/placebo monitored the patient for these changes. This practitioner asked the patient every minute if they were “feeling alright” and “do you feel any changes at all?” When and if the patient stated they were feeling any “changes” or sedation symptoms, the patient was then maintained at the N₂O/O₂ level for 5 minutes prior to the injection of local anesthetic. The patient rated their perceived level of sedation prior to local anesthetic injection on a 0-100 mm VAS (Appendix E). When the experimental procedure was completed, the patient was placed on 100% oxygen for at least 5 minutes.

The patients receiving placebo treatment were treated in the same manner as those receiving nitrous oxide. The only difference in setup was the altered gas exchange hub, described previously. The patient was maintained on room air/oxygen mixture for 10 minutes prior to injection of local anesthetic to mimic the amount of time necessary for those receiving experimental treatment. Five minutes after beginning, the operator administering the gas would come into the room and mimic changes to the delivery system. This was accomplished by the practitioner informing the patient “you’ll hear me making some changes here, but just continue to relax and breathe through your nose.” The practitioner then mimicked changing the delivery system and pushed the air flush button to produce an auditory change in environment. These patients were also monitored and questioned for any changes, just as the experimental group.

After the administration of either the nitrous oxide/oxygen or oxygen/room air mixture, the operator passively placed anesthetic gel (20% benzocaine, Patterson Dental Supply, Inc., St. Paul, MN) at the IAN block injection site for 60 seconds using a cotton tip applicator. A single operator administered all injections (WS).

Patients then received a standard IAN block given in the manner described by Fischer (75) and modified by Jorgensen and Hayden (76) using a standard aspirating syringe and a 27-gauge 1¼-inch needle (Monoject; Tyco Healthcare Group LP, Mansfield, MA). The solution given was 1.8 mL 2% lidocaine with 1:100,000 epinephrine (Xylocaine; Astra Zeneca LP, Dentsply, York, PA). After initial needle penetration (needle insertion), the needle was advanced to the target site (needle placement). After gentle contact with the bone, the needle was withdrawn 1 mm,

aspiration was performed, and 1.8 mL of the anesthetic solution was deposited over a 1-minute period (deposition of solution).

Before the injection, each subject was informed of the pain ratings for needle insertion, needle placement, and deposition of solution and was shown the visual analog scale (VAS) they were to complete. After solution deposition was complete, the needle was removed. Each subject was immediately asked to rate the discomfort of the three phases of the IAN block injection (needle insertion, needle placement and solution deposition) using the VAS (Appendix G). The patients then received an additional 1.8 mL 2% lidocaine with 1:100,000 epinephrine using the standard IAN block technique mentioned above and using the same standard aspirating syringe and a new 27-gauge 1¼-inch needle. Pain was not rated during the second IAN block. The patient was then asked every 3 minutes for 15 minutes whether they were experiencing lip numbness. If his/her lip was not numb, the patient was given additional local anesthetic at the inferior alveolar nerve site. No patients required additional injections due to lack of lip numbness. If lip numbness was never achieved (failed block), the patient was excluded from the study. No patients were excluded due to failure to achieve lip numbness. The operator commenced the endodontic procedure 20 minutes after administration of nitrous oxide/oxygen or placebo and 15 minutes after local anesthetic delivery.

The tooth requiring treatment was isolated with a clamp and rubber dam and endodontic access was performed. Each patient was instructed to definitively rate any pain felt during endodontic treatment using a VAS similar to the one used to rate injection pain (Appendix G). There were three phases of the treatment: access into

dentin, access into the pulp chamber, and instrumentation of the canals. If discomfort was reported by the patient, the operator recorded the phase of treatment the pain was experienced. The patient was then instructed to rate the pain on the appropriate VAS. If a patient experienced moderate-to-severe pain (VAS rating greater than 54 mm) during access into dentin, when entering the pulp chamber, or upon instrumentation of canals, the IAN block was considered a failure and treatment was stopped. The patient then received a supplemental buccal infiltration injection using 1.8 mL 4% articaine with 1:100,000 epinephrine. If the patient experienced no or mild pain (VAS rating less than 54 mm) during access and instrumentation, the IAN block was considered successful.

The mandibular infiltration injection was administered using a standard cartridge of 4% articaine with 1:100,000 epinephrine (Septocaine, Septodont, New Castle, DE) using a standard aspirating syringe equipped with a 27-gauge 1-inch needle (Monoject; Sherwood Medical, St. Louis, MO). After rubber dam removal, with the subject in a reclined position, the mandibular infiltration injection was administered. No topical was placed prior to the infiltration. The target site was centered buccally to the treatment tooth. The needle was inserted 2 mm beneath the mucosa (needle insertion). The needle was then placed to the periosteum and withdrawn 1 mm, leaving the needle in an area that was estimated to be just superior to the apex of the tooth (needle placement). Following aspiration, one cartridge of anesthetic solution was deposited over 1 minute (solution deposition). Immediately following the infiltration injection, the subject was asked to rate the discomfort of the three phases of the supplemental injection. The operator waited five minutes before

continuing with root canal treatment to give the anesthetic solution sufficient onset time (96, 97).

After rubber dam replacement, endodontic treatment was continued. The success of the supplemental infiltration injection was defined as the ability to access the pulp chamber, place initial files, 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 experienced moderate-to-severe pain (VAS rating greater than 54 mm) during access or initial instrumentation, the supplemental infiltration injection was judged as a failure and an intraosseous injection was administered with the technique described by Nusstein et al. (1). If the initial intraosseous injection was not successful, a second intraosseous injection was administered at a different site. If this was not successful, periodontal ligament (PDL) and/or intrapulpal injections were administered.

Stainless steel, K-type, hand files and nickel titanium rotary files (ProFile[®] GT[®] Dentsply Tulsa Dental, Tulsa, OK) were used to prepare the canals. Glyde lubricant (Dentsply Tulsa Dental, Tulsa, OK) was used during rotary instrumentation. Working length determination was completed with the Root ZX Apex Locator (J. Morita Mfg. Corp., Irvine, CA) and/or a digital periapical radiograph that was taken to confirm lengths. All canals were irrigated with 3.0% sodium hypochlorite and dried. A cotton pellet was placed into the access opening and Cavit (3M ESPE, St. Paul, MN) was used for the temporary restoration. Post-operative instructions and appropriate post-operative medications were prescribed. The patient was then paid \$75.00 for participating in the research study.

With 100 subjects (50 in each group) and a non-directional alpha risk of 0.05, the power of the Chi-square test to detect a difference of +/- 30 percentage points in anesthetic success was 86%. Comparisons were considered to be significant if $p < 0.05$. The data from this study was collected and statistically analyzed. Comparisons between the nitrous oxide/oxygen and placebo groups for anesthetic success, gender, previous experience with nitrous oxide, and tooth type were analyzed using the chi-square test or, if expected frequencies were less than 5, the Fisher exact test. The Corah dental anxiety scale, age, initial pain, block time, and access time were analyzed using the Randomization test. Injection pain ratings and instrumentation pain ratings were assessed using the randomization test and the step-down Bonferroni method of Holm.

CHAPTER 3

RESULTS

One hundred adult patients completed this study. The treatment group (nitrous oxide) included 50 patients, of which 30 were female (60%) and 20 were male (40%). The placebo group also included 50 patients, of which 27 were female (54%) and 23 were male (46%). The mean age of the treatment group was 33 (+/-11) years and the mean age for the placebo group was 35 (+/-13) years.

Table 1 outlines the preoperative spectrum of all patients. There were no statistically significant differences between the two groups with regard to gender, age, history of nitrous oxide use, initial pain, anxiety level, time to access after anesthesia, treatment time, or tooth type ($p>0.27$)

Table 2 shows VAS ratings for initial pain. All subjects reported moderate-to-severe pain, regardless of group. There was no statistically significant difference between the two groups ($p=0.6814$).

Table 3 displays the dental anxiety scale ratings. There were no statistically significant differences between the treatment or placebo groups on the whole ($p=1.0000$) or by gender (female: $p=0.3629$, male: $p=0.4131$).

Anesthetic success rates are detailed in Table 4. With regard to the IAN block, 25 out of 50 subjects (50%) in the treatment group achieved anesthetic success, while only 14 out of 50 subjects (28%) in the placebo group had anesthetic success with the IAN block. This was a statistically significant difference ($p=0.0241$).

Sixty-one patients required additional anesthesia after the IAN block. These patients received a buccal infiltration of articaine. In the treatment group, 18 of 25 patients (72%) had anesthetic success, where 22 out of 36 patients (61%) had success in the placebo group. There was no statistically significant difference between the groups ($p=0.3787$).

Twenty-one subjects required additional anesthesia after the articaine buccal infiltration. These patients were given an intraosseous injection of lidocaine. In the treatment group, 4 out of 7 subjects (57%) had anesthetic success, and 13 of 14 subjects (93%) had success in the placebo group. There was no statistically significant difference between the two groups ($p=0.0877$).

Anesthetic successes achieved by method and tooth type are outlined in Tables 5-7. In each table and group the majority of teeth were first and second molars.

Tables 8, 9, and 10 outline the VAS pain ratings for the IAN block (Table 8), articaine infiltration (Table 9), and intraosseous injection (Table 10). There were no statistically significant differences for type or stage of injection ($p>0.05$).

Table 11 lists the anesthetic failure points and patient distribution. The failure points are shown for the IAN block, articaine infiltration, and I/O injection.

Anesthetic failure point was recorded as none, dentin, chamber, or canals. The anesthetic failure point occurred in dentin in 14 out of 50 subjects (28%) in the treatment group and in 22 out of 50 subjects (44%) in the placebo group. Overall, anesthetic failure in dentin was 47 out of 100 (47%). The majority of failures of the IAN block and articaine infiltration in both groups occurred before canal instrumentation.

Visual analogue scale pain ratings for the failure point/treatment pain of the IAN block, articaine infiltration, and intraosseous injection are displayed in Tables 12, 13, and 14, respectively. The pain ratings were recorded as access in dentin, access into the chamber, and instrumentation of canals. There was no statistically significant difference between the groups ($p>0.05$).

Table 15 shows patient post-treatment satisfaction ratings, as rated on a 100 mm scale ranging from not satisfied (0 mm) to completely satisfied (100 mm). There was no statistically significant difference between the groups ($p>0.05$). The majority of subjects in each group reported either moderate or complete satisfaction with the treatment received.

CHAPTER 4

DISCUSSION

The results from this project are displayed in Tables 1-15. Table 1 outlines the preoperative distribution of patients in both the nitrous oxide and placebo groups. Fifty patients were included in each group. The nitrous oxide group was composed of 30 females (60%) and 20 (40%) males, and the placebo group was composed of 27 females (54%) and 23 males (46%). There was no statistically significant difference between these two groups with respect to the genders that composed them ($p=0.5445$).

This near equal distribution was important because Liddell and Locker (77) found that women are significantly more affected by pain than men ($p<0.0001$). Moreover, they concluded that females have a lower acceptance of pain, a greater fear of pain, and avoid pain more than males ($p<0.0001$). Fillingim et al. (78) also conducted a gender pain study and found that women had significantly lower thresholds for pain detection and tolerance than males ($p<0.001$). Therefore, having a statistically significant difference with regard to gender in a pain study could skew the results. This was not the case for our study.

The mean age of patients in the nitrous oxide group was 33 (+/- 11) years and the placebo group was 35 (+/-13) years. A study by Nordenram et al. (79) found that anesthetics were more effective in an older group of patients versus a younger group. There was no statistically significant difference between the two groups with regard to age in this study ($p=0.5006$).

Thirty-five percent of patients in the nitrous oxide group and 47% of patients in the placebo group reported having experienced nitrous oxide sedation in the past. There was no significant difference between the two groups ($p=0.2724$). Malamed (74) stated the symptoms of nitrous oxide sedation could include: a feeling of warmth, light-headedness, tingling, floating feeling, feeling of heaviness, relaxation, or tiredness. These are the conditions we used in the current study to determine if a patient was experiencing “sedation symptoms.” Blinding was a significant concern in this project. If a patient had experienced nitrous oxide sedation previously, they may have been able to discern which regimen they were assigned and inadvertently bias their responses. However, in our study there was no difference between the groups with regard to people who had been given nitrous oxide previously ($p=0.2724$).

Another concern was the placebo effect. The placebo effect is a unique response that has been documented in medicine. It is defined as “a reaction to a placebo manifested by a lessening of symptoms or the production of anticipated side effects.” (98) In relation to placebo-induced analgesia, Beecher (80) reported in 1955 that 30% of patients would respond positively to placebo. Levine et al. (81) reported that 39% of patients responded positively to a placebo in their evaluation of

postoperative pain after dental extraction. More recently, Vase et al. (82) stated that results of placebo analgesia are impacted by patient knowledge of the possibility of receiving a placebo. This means that patients who are aware of the possibility of receiving a placebo are less likely to show a placebo induced effect than patients who are fully expecting an actual treatment/medication. This is important because in the current study patients were informed of the possibility of receiving a placebo during the informed consent process.

Out of the 50 patients in the placebo Group, 9 patients (18%) reported symptoms similar to those patients that received nitrous oxide. They reported feeling “relaxed, warm, and having tingly hands and fingers,” all possible descriptions of symptoms while using nitrous oxide (of these nine patients, 4 had IAN block success, 4 had success with supplemental articaine, and 1 required intrapulpal injections after the failure of the I/O injection. Of the 9 patients in the placebo group who reported sedation symptoms, 4 patients (44%) experienced IAN block success). Although it could be argued that this percentage is similar to the success rate found in the nitrous oxide group, we do not believe this to be a true placebo effect, but rather the success rate based on small sample size and chance alone. If it had been a true placebo effect we would expect that the patients would also have lower injection pain ratings and this was not the case. The majority of the patients experiencing sedation symptoms in the placebo Group rated injection pain greater than the group mean.

Of the 50 patients who received the nitrous oxide regimen, 3 patients (6%) reported that they experienced no sedation symptoms during treatment. The question could be raised, would a higher dosage of nitrous oxide with increasing dosage until

symptoms are apparent, change the results? Two of the patients without sedation symptoms achieved anesthetic success with the IAN block, and the third only obtained anesthetic success after intrapulpal injection. In regard to the one patient requiring intrapulpal injections, this was after the failure of two I/O injections and PDL injections.

Whalley and Brooks (54) conducted a study in which participants were exposed to 25% nitrous oxide or placebo and asked to complete several questionnaires. The study was completed in two separate appointments and the treatment received (nitrous vs placebo) was randomized. The results showed that only 36.7% of patients were able to correctly discern which treatment they received. This percentage was not significantly different from the results expected from chance alone ($p=.201$). Their study showed that despite patients being exposed to nitrous oxide previously, patients were not able to reliably determine when they were being exposed to nitrous oxide. We did not specifically question our patients as to whether they believed they were receiving nitrous oxide or placebo. Although there are patients that are not able to discern whether they are receiving nitrous oxide, the percentage is not as high as reported by Whalley and Brooks. In the current study, 9 patients (18%) reported sedation symptoms despite being in the placebo group. This discrepancy may be based upon the fact that in Whalley and Brooks' study (54) they only used a nitrous oxide concentration of 25% compared to the 30%-50% used in our study. In future studies, it may be useful to have patients indicate which treatment they believe they are receiving, especially for higher dosages of nitrous oxide, to further analyze a possible placebo effect.

Whalley and Brooks (54) also delivered a room-air/oxygen mixture to their patients during the placebo visit of the study, similar to what was done in the current study. It has been conjectured that pure oxygen (100%) could have a mild euphoric effect. However, Bren (100) stated in an FDA publication that although oxygen has been claimed to have many effects, there are no well-controlled, long-term clinical studies showing oxygen's beneficial effects in healthy people.

One of the goals of this study was to analyze the analgesic effect of nitrous oxide on mandibular teeth with irreversible pulpitis. However, the more commonly known property of nitrous oxide is that of sedation. After the patients in this study were randomly assigned to a treatment group they were fitted with a nasal mask and placed on oxygen for 5 minutes followed by 5 minutes of the assigned sedation regimen. After 10 minutes, before the administration of the IAN block, each patient was asked to rate on a 100 mm scale his or her sedation level and to verbally describe any symptoms they were experiencing. This was done to not only analyze the types of responses the nitrous oxide induced, but also to analyze patients' responses to monitor for possible placebo effect. Patients were also instructed to breathe through their nose, rather than their mouth, to gain greater effect from the gas. Placement of the rubber dam during treatment may have further encouraged breathing through the nose, as rubber dam placement likely made mouth breathing more difficult.

We found that the patient self-reported sedation ratings did not correspond to anesthetic success of the IAN block ($p=0.1712$). Upon further review, it was noted that simply having some type of sedation symptom was the most significant predictor of success ($p=0.0145$). These symptoms ranged from "sleepy, laughing, drunk, light,

relaxed, warm, woozy, and tingly” to “heavy, and floaty like Jimi Hendrix.” History of nitrous oxide sedation ($p=0.5783$), sedation rating ($p=0.1712$), and Corah DAS score ($p=0.1786$) had no significant correlation with IAN block success. However, the presence of sedation symptoms was significantly correlated with IAN block success ($p=0.0145$). This is important for a couple of reasons. One, it displays that the self-reported sedation scale used in this experiment may be unreliable. This may be a result of inadequate wording of the scale, making it difficult for all patients to understand and interpret what they should report. Sedation was defined as “the calming of mental excitement or abatement of physiological function, especially by the administration of a drug” (83). Perhaps changing the wording on the scale to include more broad terminology or vernacular would have been of benefit. It may also have been a result of patients not having a good grasp of how they were feeling or having any frame of comparison in relation to deeper sedation techniques. Some patients may have had prior exposure to deep sedation, remember what that feels like, and realize they were in a lighter state of sedation; versus someone who had never had any sedation and received nitrous oxide for the first time. The self-reported sedation rating was never seen by the operator and the nitrous oxide dose was not altered by the assistant after the sedation scale was completed. A more effective procedure for the current study could have been to have the assistant question the patient and increase the nitrous oxide percentage until sedation symptoms were noted, and then have the operator enter to begin the treatment procedure. If this were the case, there would have been a need for an alternate script for the placebo patients, as

they did not receive nitrous oxide. The procedure followed in the current study had the assistant follow identical scripts for each group in an effort not to bias the patient.

Secondly, this shows us that dosage for nitrous oxide may not be as simple as a single number or percentage for all patients. According to this study's findings, it may be more important to titrate the dose of N₂O until the patient begins experiencing symptoms of sedation to gain the desired analgesic effects. Patients in this study did have their dose of nitrous oxide titrated, however no patients were titrated beyond a 50% dose, per the protocol of this study.

Patients were asked to rate their initial pain upon presentation to the Graduate Endodontic clinic on a 170-mm visual analog scale. The mean pain rating for the nitrous Group was 128 +/-25 mm and the mean for the placebo Group was 130.1 +/- 23 mm. There was no statistically significant difference between the groups ($p=0.6814$). The distribution of pain and group is noted in Table 2. All patients in both groups presented with moderate or severe pain, and had a diagnosis of symptomatic irreversible pulpitis. This was essential because previous studies have shown decreased anesthetic success rates in symptomatic teeth. If one of the groups was in less pain than the other, that may have biased the results of the project.

Dunbar et al. (84) studied the success of the inferior alveolar nerve block on asymptomatic teeth and found success to be 38%-42%. Other studies completed on mandibular posterior teeth diagnosed with irreversible pulpitis have found the success rate of the IAN block to be lower than the rate in asymptomatic teeth, ranging from 12% to 35% (2, 5-7, 10, 11, 61). The population recruited for the current study was the same as those used in these previous studies (2, 5-7, 10, 11, 61). Therefore, we

expected the success rate of the IAN block to be lower than the rate expected in asymptomatic teeth. This was confirmed when the results showed an overall anesthetic success rate for the IAN block of 28% for the placebo Group.

The results of the Corah Dental Anxiety Scale (DAS) are found in Table 3. The Corah DAS is a well-accepted, often used scale to measure patients' dental anxiety (58). Although it has been criticized for not discerning between intermediate levels of anxiety, it does offer the ability to place patients on a spectrum and gain some insight into their feelings about dental treatment (58).

Anxiety is known to be directly related to pain. Jackson et al. (12) stated that patients in pain are often anxious and afraid of dental treatment. Ploghaus et al. (85) found in their event-related Functional Magnetic Resonance Imaging (fMRI) study that anxiety, and specifically pain-related anxiety, can increase the perception of pain severity. Fagade et al. (57) showed in their research that higher preoperative Corah DAS scores led to significantly higher postoperative pain ratings ($p=0.001$), which lead them to conclude high preoperative anxiety could lead to higher intra-operative pain perception. Preoperative anxiety could therefore be a potential confounder. However, the preoperative Corah DAS scores for the groups in this study were not significantly different, and therefore were not expected to bias the results. All patients enrolled in the current study were actively experiencing pain, and were emergency patients of the College of Dentistry, which may have further increased anxiety. The elevated pain and anxiety levels would lead us to believe that this population would have lower anesthetic success rate as well as increased pain perception.

The mean Corah DAS score for the nitrous oxide Group was 11 +/- 4 and the score for the placebo Group was also 11 +/- 4. The Corah DAS ranges in score from 4-20. A score of 9-12 is described as moderate anxiety, 13-14 is described as high anxiety, and 15-20 is described as severe anxiety. In the nitrous oxide Group 26% of patients were categorized as low anxiety, 40% as moderate anxiety, 14% as high anxiety, and 20% as severe anxiety. In the placebo Group 30% were categorized as low anxiety, 36% as moderate anxiety, 10% as high anxiety, and 24% as severe anxiety. There were no statistically significant differences between the two groups ($p=1.0000$), which should decrease the effect of anxiety on the difference in success of the IAN block between the groups. However, the highest percentage of patients in each group had moderate or higher anxiety (74% in the nitrous oxide group; 70% in the placebo group).

Table 4 outlines anesthetic success. The IAN block was successful in 25 out of 50 patients (50%) in the nitrous oxide Group and 14 out of 50 patients (28%) in the placebo Group. The difference in success of the IAN block between the two groups was statistically significant ($p=0.0241$).

The success of the IAN block in the placebo group (28%) was similar to rates found in previous studies with the same definition of anesthetic success involving mandibular teeth with irreversible pulpitis (2, 5-7, 10, 11), and was not considered to be adequate clinically in order to complete endodontic therapy.

The success of the IAN block in the nitrous oxide Group (50%) was significantly better than that of the placebo Group. It was also higher than IAN block success rates found in recent studies by Matthews et al. (7), Oleson et al. (10), and

Simpson et al. (11), who reported IAN block success rates in mandibular posterior teeth with irreversible pulpitis to be 33%, 35%-41%, and 24%-32%, respectively. However, even with a success rate of 50%, this was not clinically significant, because half of the patients in this group still required the administration of supplemental anesthesia to complete the treatment. The success rate of the IAN block in the nitrous oxide Group in the current study is similar to the success rate of the IAN block in Lindemann et al.'s (8) study on mandibular teeth with irreversible pulpitis. Lindemann et al. used oral sedation with sublingual triazolam in an attempt to increase the success of the IAN block. They reported an IAN block success rate of 43% with triazolam and 57% with placebo. They concluded that there was no statistically significant difference between the triazolam and placebo group. It should be noted that Lindemann's study had a smaller sample size than the current study, with 30 patients in the triazolam group and 28 in the placebo group. This smaller sample size may explain the relatively high success rates of the IAN block in their population compared to more recent studies with larger population samples, such as Oleson et al. (35-41%) (10), Simpson et al. (24-32%) (11), and the current study (28-50%). More importantly, even though the success rates were higher in Lindemann's study, there was no increase in success of the IAN block with triazolam use, whereas the current study showed significantly higher success rates with nitrous oxide use.

Triazolam causes a sedative effect in patients, much like nitrous oxide.

However, sedation is not an effective means of pain control. This was shown by Lindemann et al.'s research (8) as well as other previous studies by Young et al. (86), Aissaoui et al. (87), and Payen et al. (88), who researched pain in unconscious and

sedated patients in ICU and critical care patients. Their research implemented a Behavioral Pain Scale (BPS) to evaluate both painful and non-painful procedures performed on these patients. They concluded that both sedated and unconscious patients cannot only detect painful/noxious stimuli, but they can also respond to these stimuli. Patients were not able to remember the pain because of their altered consciousness, yet the physiologic response remained.

Therefore, if sedation were the only benefit of nitrous oxide, we would not expect a significant effect. Fortunately, in addition to sedation, nitrous oxide also has an analgesic effect (13). This is the effect that we hypothesized may increase the success of the IAN block. Moreover, nitrous oxide has a quick onset and recovery time; it is titratable (meaning the dose administered can be specifically controlled); and patients do not require driver accompaniment, as they would with oral or IV sedation. Furthermore, if a patient becomes nauseous while under nitrous oxide sedation, the flow of nitrous is stopped, the patient is placed on 100% oxygen and they typically recover within seconds to minutes. Three patients (6%) from the nitrous oxide Group experienced nausea during the procedure. All of them experienced nausea during the instrumentation phase, were not experiencing any pain, and therefore did not have to be removed from the study. All patients recovered and returned to normal within 2 minutes after being placed on 100% oxygen. All of these patients left the appointment without nausea.

Although the exact mechanism of nitrous oxide is not known, it is known that nitrous oxide does not work through a single mechanism. Research indicates that nitrous oxide activates its analgesic effect by causing the release of endogenous

opiate peptides and then subsequent activation of opioid receptors; however, this is not how the anxiolytic effect is reached. This involves the activation of the GABA_A receptor through the binding site for benzodiazepines. The anxiolytic effect of nitrous oxide involves three key enzymes; nitric oxide synthase (NOS), soluble guanylyl cyclase, and cyclic GMP-dependent protein kinase (PKG). The inhibition of any of these enzymes blocks the anxiolytic effect of nitrous oxide. The analgesic effect of nitrous oxide seems to be caused by the inhibition of N-methyl-D-aspartate (NMDA) glutamate receptors. NMDA typically incites an excitatory response in the nervous system; therefore, by blocking this effect, N₂O creates the desired analgesic effect (20). A large advantage of nitrous oxide in this study is that it targets both opiate receptors and NMDA receptors to increase the analgesia and pain control experienced by patients.

The percentage of 30%-50% nitrous oxide was chosen for this study for two reasons. Jastak and Donaldson (14) theorized that a 30% dose of nitrous oxide is equivalent to a 10-15 mg dose of morphine. Secondly, a dose range of 25%-50% nitrous oxide has been commonly used in previous studies researching nitrous oxide sedation and analgesia (26-38, 74).

The literature shows that this dose range of nitrous oxide has resulted in adequate or improved analgesia during painful procedures. Meskine et al. (37) showed that 50% nitrous oxide use during liver biopsy resulted in significantly better analgesia versus Darvocet-N ($p=0.045$). Paris et al. (27) found nitrous oxide sedation to be significantly better than morphine chlorhydrate in managing analgesia during the treatment of painful bedsores ($p<0.01$). Maslekar et al. (34) conducted a

randomized trial comparing sedation and pain control with 50% nitrous oxide with intravenous midazolam and fentanyl. They found that patients in the N₂O group reported significantly less pain ($p<0.001$) and higher satisfaction than patients receiving midazolam-fentanyl ($p=0.001$). These studies show that the dose of nitrous oxide administered in the current study has been shown to provide improved analgesia in previous research designs.

Other studies in the literature have shown that higher doses of nitrous oxide are also effective in producing analgesia. In their laboratory studies, Emmanouil et al. (21) and Zhang et al. (22) both used 70% nitrous oxide to monitor the analgesic effect of nitrous oxide in mice. Henderson et al. (89) conducted a study measuring the pain and behavior of children under 50% and 70% nitrous oxide sedation during venous cannulation. One hundred and sixty-five patients ranging from 3 months to 18 yrs of age were recruited from a pool of patients scheduled for elective surgery. Patients were randomly assigned to a treatment group of 50% nitrous oxide, 70% nitrous oxide, 100% oxygen, or no mask. Patients were monitored by a calibrated observer, who recorded any record of previous surgery, whether the patient had attended the preoperative explanation class, any behavioral problems, the patients behavior while separated from parents, relaxation during the application of the monitoring equipment, whether or not they accepted the sedation mask, relaxation during venipuncture, a pain score, and any side effects. Results showed that both 50% and 70% nitrous oxide resulted in significant improvement of relaxation during venipuncture and pain scores compared with the 100% oxygen and no mask groups ($p<0.05$). Additionally, they found that 70% nitrous oxide showed a statistically

significant improvement in pain scores compared to all other treatment groups ($p < 0.05$). However, 70% nitrous oxide also resulted in significantly more side effects (nausea and vomiting) than any other group ($p < 0.05$).

Furuya et al. (28) followed the work by Henderson (89) and used dosages of 50%-70% nitrous oxide in their pediatric study of pain felt by children, ages 6-15 years, during venipuncture. They concluded that 70% nitrous oxide for 3 minutes reduced pain experienced during venipuncture procedures in children. Patient pain was measured by parents and nurses that were present during the procedure, on a 0-10 face scale, which ranged from no pain (0) to very painful (10). Because the patient did not rate the pain, but instead had it rated by a parent or nurse, the ratings may not be as accurate as if they had been self-reported.

The results of the current study showed a statistically significant increase in success of the IAN block with the administration of five minutes of 30%-50% nitrous oxide. We believe this increase in success is a result of the combined anxiolytic, and maybe more importantly, analgesic effects of nitrous oxide. Patient anxiety may have been decreased along with anxiety-related pain experience. This reduction in anxiety coupled with the analgesic component, described earlier, may have contributed to higher success rates in the nitrous oxide group.

Although this increase in success was statistically significant, the modest gain alone would not be deemed satisfactory for the completion of treatment (i.e. without supplemental anesthesia). Nonetheless, the results showed that nitrous oxide sedation did increase the success of an IAN block, and therefore is a useful technique to add to the armamentarium used in the treatment of teeth with irreversible pulpitis.

Furthermore, if a patient were to present with irreversible pulpitis of a mandibular tooth and severe anxiety, requesting sedation, this study confirmed the fact that nitrous oxide sedation may be preferable and more successful than oral sedation with triazolam. As mentioned previously, with nitrous oxide sedation the dose is titratable, the patient would not require a driver to accompany them, nor would they be sedated beyond the length of the treatment appointment.

The results also beg the question, would an increase in nitrous oxide dosage result in even higher success of the IAN block? Theoretically, a higher dose of nitrous oxide could result in greater analgesic effect, and therefore, higher anesthetic success. The concern with administering higher doses of nitrous oxide is the risk of patients becoming too sedated and unable to manage their own airway. Parbrook (16) described nitrous oxide sedation in four zones. Zones I and II included nitrous oxide concentrations of 6%-45%, and caused the patient to experience “light sedation,” but remain in full contact with the operator. Zones III included nitrous oxide dose range of 46%-65% and was deemed analgesic anesthesia, and patients were often able to maintain verbal contact while in this zone. The dosages administered in this study may have fallen within Zone III, depending on the patient. Zone IV, as described by Parbrook, ranged in dosage from 66%-85%, was called light anesthesia, and produced “light general anesthesia.” Moreover, he noted that in this zone contact with the patient was no longer possible.

Therefore, although a higher dose of nitrous oxide may produce greater analgesia and warrants more research, caution must be exercised and patient safety must also be considered. Deep sedation requires more preparation and advanced

training to insure the patient is properly monitored, well cared for, and safe.

Additionally, Henderson et al. (89) and Yagiela (15) noted an increase in untoward, undesired side effects with 70% nitrous oxide compared with a 50% dose. Noting these facts, we designed our study to remain in a 30%-50% dose range.

Sixty-one patients required a supplemental buccal infiltration of 4% articaine with 1:100,000 epinephrine. The articaine infiltration was successful in 18 of 25 subjects (72%) in the nitrous oxide Group and 22 of 36 subjects (61%) in the placebo Group. There was no significant difference between the two groups ($p=0.3787$). The success rate of 61% in the placebo Group is similar to the rate of 58% reported by Matthews et al. (7) when studying the success rate of a supplemental articaine in mandibular posterior teeth with symptomatic irreversible pulpitis. The success rate of 72% in the nitrous oxide Group was higher than rates previously reported by Matthews et al. (7), Oleson et al. (10), Simpson et al. (11), or Aggarwal et al. (66) in similar populations. This higher success rate in this study may be attributed to the relatively low sample size of 25 patients in this group. The previously mentioned studies by Matthews (7), Oleson (10), and Simpson (11) included 55 teeth, 29 teeth, and 34 teeth, respectively, in their treatment groups, all of which are more than in this study. Tooth type also cannot be to blame, as the current study included a very similar number of premolar teeth (4) in the treatment group as the previously cited studies (Matthews and Simpson: 6 premolars; Oleson: 4 premolars) This study also included comparable numbers of 1st and 2nd molars to these previous studies (Matthews: 41 1st molars, 29 2nd molars; Oleson: 45 1st molars, 27 2nd molars; Simpson: 46 1st molars, 40 2nd molars). One may argue that the nitrous oxide had a

similar effect on the articaine infiltration efficacy as it did on the IAN block. However, the p-value derived from the Chi-Square test reveals no significant difference between the nitrous oxide and placebo groups with regard to the articaine supplemental infiltration. Success by tooth type for the articaine supplemental infiltration in the nitrous oxide Group was 10 out of 15 (67%) for the 1st molar, 4 out of 6 (67%) for the 2nd molar, and 3 out of 4 (75%) for the premolars. In the placebo Group, the success rates were 9 out of 17 (53%), 9 out of 13 (69%), 0 out of 1 (0%), and 4 out of 5 (80%) for the 1st molar, 2nd molar, 3rd molar, and premolars, respectively. The differences between these previous studies and the current study with regard to success by tooth type can be attributed to a smaller sample size in the current study.

A supplemental intraosseous injection of 2% lidocaine with 1:100,000 epinephrine was administered if adequate anesthesia was not achieved with the buccal infiltration of 4% articaine. The intraosseous injection was successful in 4 of 7 patients (57%) in the nitrous oxide Group and 13 of 14 patients (93%) in the placebo Group. There was no significant difference between the two groups ($p=0.0877$), and the large difference in success percentages is due to the discrepancy in sample size. The success rate of 93% in the placebo Group is quite high and comparable to previous reports of success in studies investigating the same population included in this study (1, 10, 11). The modest success rate of 57% in the nitrous oxide Group is lower than intraosseous success rates reported in previously mentioned studies and may be attributed to the small sample size of 7 patients. Success by tooth type for the nitrous oxide group was 3 out of 5 (60%) for the 1st molar, and 1 out of 2 (50%) for

the 2nd molar. There were no premolars in this group. The placebo Group success rates for the I/O injection were 8 out of 8 (100%) for the 1st molar, 3 out of 4 (75%) for the 2nd molar, 1 out of 1 (100%) for the 3rd molar, and 1 out of 1 (100%) for the premolars. Repeat I/O injections were completed if the initial I/O injection failed. However, repeat I/O injection did not result in an increased success rate, as teeth that failed required PDL injections followed by intrapulpal injections. Again, the lower success rates by tooth type seen in the nitrous oxide Group are a result of the increased success rate of the IAN block and thus a smaller sample size.

Anesthetic success of the IAN block by tooth type is displayed in the Table 5. The majority of the teeth were 1st and 2nd molars, however broad comparisons become difficult because the sample sizes become small when teeth are categorized by type. The 1st molar had an IAN block success rate of 50% in the nitrous oxide Group and 26% in the placebo Group. The 2nd molar had success of 45% in the nitrous oxide Group and 24% success in the placebo Group. The premolars sampled had 56% success in the nitrous oxide Group and 44% success in the placebo Group.

The success rates found in the current study are similar or higher than rates reported by previous studies researching the same teeth with the same clinical parameters. Oleson et al. (10) reported success rates of the IAN block in the 1st molar, 2nd molar, and premolars to be 29-36%, 21-25%, and 54-60%, respectively. Matthews et al. (7) found success rates of the IAN block in those same groups to be 37%, 21%, and 50%, respectively. Simpson et al. (11) found reported IAN block success rates to be 17-35%, 33-37%, and 14-25% for 1st molars, 2nd molars, and premolars, respectively. Although the quantity of teeth per group was relatively low,

the results show similar success rates between groups. The success of the IAN block in the 2nd molar in our study was higher than the previously mentioned studies. This is likely reflection of the impact of nitrous oxide on the IAN block for the nitrous oxide Group. The success rate of 24% for the 2nd molar in the placebo Group is comparable to the 2nd molar success rate of 27% reported by Reisman et al. (2), in a study completed on mandibular teeth with irreversible pulpitis. The current study was designed to evaluate the impact of nitrous oxide on the success of the IAN block. It was not designed to gauge the effect of nitrous oxide on supplemental injections of articaine or I/O injections, because a study of that nature would require a much larger sample size for that comparison. The data was included in this study because it would be a waste of resources and data to not collect information on supplemental anesthesia success for future compilation and analysis.

Table 6 displays the success rates of a supplemental buccal infiltration of 4% articaine by tooth type and group. Sixty-one teeth required a supplemental articaine infiltration. The success rate for the 1st molar was 67% for the nitrous oxide group and 53% for the placebo group. The 2nd molar success rate was 67% for the nitrous oxide group and 69% for the placebo group. The premolar success rate was 75% for the nitrous oxide group and 80% for the placebo group. All of these values were comparable or higher than success rates found in similar studies. The higher success rate, again, is likely due to the decreased sample size as a result of the increased success of the IAN block.

Matthews et al. (7) reported articaine infiltration success rates of 58%, 48%, and 100% for the 1st molar, 2nd molar, and premolars, respectively. Oleson et al. (10)

reported success rates of 39-42% for the 1st molar, 17-53% for the 2nd molar, and 67-100% for premolars. Simpson et al. (11) found that supplemental articaine resulted in a success rate of 16-40% in 1st molars, 21-25% in 2nd molars, and 67% in the premolars. As mentioned previously, the differences noted here are likely due to the differences in sample size of tooth type and patient population, particularly in regard to the premolars. It is worth noting that the current study found a higher success in 2nd molars (67%-69%) than the previously mentioned studies reported for 2nd molars.

If anesthetic success was not achieved with the supplemental articaine infiltration, a supplemental intraosseous injection of 2% lidocaine with 1:100,000 epinephrine was administered. Table 7 displays these results. The 1st molar had a success rate of 60% in the nitrous oxide Group and 100% in the placebo Group. The 2nd molar had a success rate of 50% in the nitrous oxide Group and 75% in the placebo Group. The premolars had a success rate of 100%.

Simpson et al. (11) reported success rates of 88-89%, 73-89%, and 0-67% in the 1st molar, 2nd molar, and premolars, respectively. Oleson et al. (10) found anesthetic success with an intraosseous injection at a rate of 91-100%, 80-86%, and 100% for the 1st molar, 2nd molar, and premolars, respectively. The results of the placebo Group in the current study are similar to these previous studies. However, the success rate in the nitrous oxide Group was lower than expected. This is likely due to a very small sample set, caused by significantly higher success of the IAN block in this group.

Pain ratings for the IAN block are shown in Table 8. Each patient was asked to rate their pain for each of the three stages on a 170 mm VAS (Appendix G).

Needle insertion was rated first. There were no statistically significant differences between the groups ($p=1.0000$). The majority of all patients (64%) rated the pain of needle insertion as none or mild, with 36% of patients rating the pain as moderate-to-severe. Needle placement was also rated by each group. There were no statistically significant differences between the groups ($p=1.0000$). Fifty-five percent of patients rated the pain of needle placement as none or mild and 45% rated it as moderate or severe. Regarding solution deposition, there were no statistically significant differences between the groups ($p=1.0000$). Fifty-four percent of patients rated the pain of solution deposition as none or mild, and 46% of patients rated the pain as moderate-to-severe.

McCartney et al. (90) reported that patients with irreversible pulpitis have a 57%-89% chance of experiencing moderate-to-severe pain during an IAN block. They also stated that needle placement and deposition were more painful than needle insertion. This was similar to results of the current study. These pain levels were higher than levels expected in asymptomatic conditions. Steinkruger et al. (91) reported injection pain of the IAN block in asymptomatic patients. They found that patients experienced none-to-mild pain 84.3-92.2% of the time. These ratings are lower than pain ratings of the IAN block in the current study. The patients included in the current study presented to the Graduate Endodontic clinic actively experiencing moderate-to-severe pain. This state was associated with changes in pain thresholds and the possibility of patients being hyperconscious of anything taking place in the vicinity. The combination of these factors resulted in increased injection pain.

Table 9 reveals the patient pain ratings for each stage of the supplemental buccal infiltration of articaine. Sixty-one patients required the supplemental injection of articaine. A long buccal infiltration/block was not administered before the supplemental injection of articaine. There were no differences between the nitrous oxide and placebo groups in regard to pain ratings for needle insertion, placement, or solution deposition. Seventy-seven percent of patients receiving the buccal infiltration of articaine rated the pain of insertion as none-to-mild, while 23% rated the pain as moderate-to-severe.

In regard to the pain ratings for needle placement during articaine infiltration, 69% of patients rated the pain as none-to-mild, and 30% rated the pain as moderate-to-severe. Sixty-nine percent of patients rated solution deposition as none-to-mild pain, while 31% of patients rated the pain of solution deposition as moderate-to-severe.

Overall, the majority of all patients receiving an articaine infiltration rated the pain of each stage as none-to-mild. These results are similar to Matthews et al. (7) and Oleson et al. (10), both of which studied the same population as the current study.

These results are higher than a study by Haase (92), in which the efficacy of a buccal infiltration of 2% lidocaine versus a supplemental infiltration of 4% articaine were compared in asymptomatic teeth after the administration of an IAN block. They found that 92% of pain ratings were none-to-mild. Martin et al. (93) evaluated the efficacy of 1.8 mL versus 3.6 mL of 4% articaine administered as a primary buccal infiltration in asymptomatic mandibular teeth. Results showed that 94.1%, 84.9%, and 82.6% of patients rated pain as none-to-mild for needle insertion, needle

placement, and solution deposition, respectively. The pain ratings in these two studies were slightly lower than the rates in the previously cited studies, but that was to be expected as they were conducted on asymptomatic patients.

Pain ratings for the I/O injection are found in Table 10. Twenty-one patients required an I/O injection, 7 in the nitrous oxide Group and 14 in the placebo Group. There were no statistically significant differences between the groups for any stage of the injection. Eighty percent of patients rated I/O insertion as none-to-mild pain. Eighty-five percent of patients rated the pain of I/O placement as none-to-mild. Fifty percent of patients rated the pain of I/O solution deposition as none-to-mild.

Kennedy et al. (4) and Bigby et al. (94) both measured pain ratings of the I/O injection. Kennedy reported that patients experience moderate-to-severe pain 27% of the time, and Bigby reported that the frequency of moderate-to-severe pain experience was 21.6%. These results are very similar to the findings of the current study with regard to I/O insertion and placement. However, solution deposition resulted in a 50% frequency of moderate-to-severe pain experience (70% moderate, 30% severe). This may be partially due to the low sample size of 20 patients. Moreover, the buccal infiltration of articaine likely influenced the lower pain levels rated during insertion and placement since the soft tissues where the I/O perforation was made were most likely already numb. Despite this decreased pain during the needle insertion and placement stages of the injection, lack of adequate anesthesia was noted during solution deposition. Rate of injection may be the cause of this increased pain, since rate was not standardized for this study. Rate varied between 30 seconds and 1 minute in this study due to the varying degree of force/pressure needed

during solution deposition. Because of the uncontrollable variance in intraosseous perforation sites, an injection given with a computer controlled, pressure-feedback device such as the Wand (Milestone Scientific, Deerfield, IL) may improve this pain as it would slowly deliver a controlled amount of anesthetic over a set amount of time. Susi et al. (99) measured change in heart rate during different deposition rates of a computer controlled I/O injection, but they did not measure pain of injection.

Table 11 outlines the anesthetic failure point and patient distribution for both groups. The pain ratings during endodontic treatment are displayed in Tables 12-14. These ratings are divided into pain felt during instrumentation of dentin, pulp chamber, and canals for the IAN block, articaine infiltration, and I/O injection. Although the IAN block was significantly more successful in the nitrous oxide Group, there was no statistically significant difference between groups with regard to pain ratings during failure. This was also true of the articaine supplemental infiltration and I/O injection. Pain level ratings for access through dentin, into the pulp chamber, and instrumentation of canals were not significantly different between the groups.

The majority of failures of the IAN block occurred in dentin for both groups (28% in nitrous oxide Group; 44% in placebo Group). Fourteen percent of IAN blocks in the nitrous oxide Group occurred when reaching the pulp chamber, whereas 24% of failures in the placebo Group occurred in the chamber. This is likely a reflection of the higher success rate of the IAN block in the nitrous oxide Group, and therefore, lower remaining numbers to draw upon. Additionally, failure levels changed as the treatment progressed, because as treatment moved from IAN block, to

articaine supplemental infiltration, to I/O injection it allowed the operator to progress more apically in the canals. In the nitrous oxide Group the supplemental articaine infiltration failed upon accessing dentin 12% of the time and the pulp chamber 16% of the time. In the placebo Group the supplemental articaine injection failed upon accessing dentin 22% of the time and 11% of the time entering the pulp chamber. In regard to the I/O injection, there were only 4 failures, thus making comparisons difficult. There were 3 failures in the nitrous oxide Group, 1 upon access of the pulp chamber and 2 instrumenting the canals; and there was one failure in the placebo Group, which occurred instrumenting the canals.

These results were similar to and within the range what has been found in previous studies by Claffey et al. (5), Nusstein et al. (1), Reisman et al. (2), and Kreimer et al. (95), which reported pain ratings drilling into dentin after the administration of an IAN block to be 40%, 18%, 25%, and 4%, respectively. The findings in the nitrous oxide Group in the current study are lower than the frequencies reported in studies by Matthews et al. (7) and Simpson et al. (11), which reported 30% and 34% experienced moderate-to-severe pain drilling into dentin and 36% and 31% moderate-to-severe pain upon entry into the pulp chamber. These differences could be partially attributed to the increased success of the IAN block in the nitrous oxide Group and/or smaller sample size. It may also be attributed to operator differences in evaluation of level of access and/or interpretation of patient symptoms/pain.

Table 15 summarizes the patient post-treatment satisfaction ratings. Patients were asked to rate their satisfaction with their experience/treatment on a 100 mm

(Appendix F) scale broken into four categories of: not satisfied, somewhat satisfied, moderately satisfied, and completely satisfied. The mean satisfaction rating of the nitrous oxide Group was 95 +/-7 mm and the mean rating of the placebo Group was 96 +/-10 mm. There was no significant difference between the two groups. One patient in the nitrous oxide Group elected not to respond to the satisfaction survey and because the patient was left alone to anonymously complete the form, this lack of response was not noted until the patient had left the clinic. Sixty-three percent of the nitrous oxide Group rated that they were moderately satisfied with the treatment they received, and 37% rated that they were completely satisfied with the treatment received. Fifty-eight percent of the patients in the placebo Group rated their satisfaction as moderately satisfied, and 40% rated their experience as completely satisfied. Only one person (2%) in the placebo Group rated their satisfaction as somewhat satisfied. The patient who rated their satisfaction as somewhat satisfied gave a rating of 48 mm on the 100 mm satisfaction scale. This person also had IAN block success. Conversely, of the four patients in the entire study that required intrapulpal injections to achieve anesthesia, not one of them rated their satisfaction lower than 97 mm on the 100 mm scale. 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. In addition, on the 100 mm scale used in the current study the only way a patient could rate “completely satisfied” is if they were to mark exactly on the 100 mm line. Otherwise, although their mark may have been in the high 80’s or 90’s in mm, they were classified as “moderately satisfied.”

In the future a more discerning scale should be considered to more accurately determine patients' post-operative treatment satisfaction.

These results are lower than the results reported by Lindemann et al. (8), 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. In the current study, before patients were given a satisfaction survey, it was strongly emphasized that the patient's response on the survey would have no impact on the operator's (WS) grade, status as resident, or standing within the school/department. The patients were then asked to complete the survey as honestly as they could, turn the survey facedown on the clipboard they were given, and then meet the operator in the front of the clinic for dismissal. Patients were then left by themselves in a less pressured environment to complete the survey. Moreover, the results of the current study show that despite nitrous oxide providing significantly higher success rates for the IAN block as well as sedation, patients in the placebo Group, who experienced less anesthetic success, were generally satisfied, despite experiencing anesthetic failure and moderate-to-severe pain more often than the nitrous oxide Group.

CHAPTER 5

SUMMARY AND CONCLUSIONS

The current study was designed with the aim of improving the anesthetic success rate of the inferior alveolar nerve block in patients diagnosed with symptomatic irreversible pulpitis of a mandibular posterior tooth. Anxiety may be related to increased anesthetic failure. However, previous work by Lindemann et al. (8) has shown that the management of anxiety alone does not result in increased success of the IAN block. Nitrous oxide has been shown to have both anxiolytic and analgesic properties. Therefore, it was our hypothesis that this combination of anxiolysis and analgesia may result in an increased success of the IAN block.

We found that the success of the IAN block in the nitrous oxide Group was 50% compared with 28% success in the placebo Group. There was a statistically significant difference between the two groups ($p=0.0241$). Although 50% success is a relatively modest improvement, we believe, when used in combination with other supplemental anesthetic techniques, administration of nitrous oxide could be useful clinically in patients with symptomatic irreversible pulpitis.

APPENDIX A
GENERAL CONSENT FORM

The Ohio State University Consent to Participate in Research

Study Title: Effect of nitrous oxide on the success of the inferior alveolar nerve block in patients with irreversible pulpitis.

Principal Investigator: Dr. Melissa Drum

Sponsor: Not applicable

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

1. Why is this study being done?

The purpose of this study is to see if nitrous oxide improves the success of anesthesia during emergency endodontic treatment.

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

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

3. What will happen if you 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. Ten minutes before your doctor starts your root canal, you will breathe a mixture of gas through a nasal mask. The gas mixture will be either a mixture of nitrous oxide and oxygen or a mixture of room air and oxygen. Nitrous oxide is sometimes referred to as “laughing gas,” and is a gas that is used to reduce anxiety. The mixture you receive will be chosen at random (by chance, like flipping a coin). Neither your doctor nor you will know which one you will receive. Nitrous oxide (laughing gas) has been used in the dental office and has been approved by the Food and Drug Administration (FDA) for dental and medical use. The purpose of this study is to see if nitrous oxide helps your tooth get numb after you receive a numbing solution.

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

You will be asked to rate the pain you are having prior to any treatment. You will also fill out a form to rate how anxious you are. The tooth causing you pain will first be tested to insure an accurate diagnosis. It will first be tested with a cold cotton pellet chilled with an ice spray. Your tooth may hurt for a few moments after being tested with the cold. The cold pellet will be removed immediately after you feel the sensation in your tooth. The cold test is used routinely before root canal treatment.

Before you get an injection (shot) of numbing solution, you will fill out a form which asks how relaxed you feel.

One 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 novocaine. 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 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 feel pain, you will raise your hand and will be asked to rate the pain. If you have moderate or severe pain, a supplemental (extra) injection (shot) of 4% articaine with 1:100,000 epinephrine will then be given directly beside your tooth (under the gums). This may be uncomfortable. Routine emergency root canal treatment will then be completed. You will then be asked to rate your satisfaction with the treatment you received.

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 you be in the study?

You are aware that you will have one appointment, which will last approximately 120 minutes.

5. Can you 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 you expect from being in the study?

- 1.
2. You are aware that nitrous oxide (laughing gas) may cause: a feeling of nausea, which is rare; light-headedness, a tingling sensation in your arms or legs; feeling of warmth, floating, or heaviness. The effects of nitrous oxide (laughing gas) are short term. You will be placed on oxygen for five minutes after treatment to ensure that the nitrous oxide is removed from your body.
3. 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 your mouth) or a bruise may develop. You may experience a feeling of anxiety, lightheadedness or fainting, and or a temporary

increase in your heart rate. Your toothache may stay the same or worsen during the study. The tingling sensation and/or slight discomfort (pain) produced by the cold ice spray may be uncomfortable to you. You may have an allergic reaction to the local anesthetic (itching or hives, very rare), or have an unexpected infection (rare) which could result in permanent nerve damage. You may have soreness of your gum tissue for a few days or a possible altered sensation of your lip or tongue that may last up to a few weeks. Your tooth may feel sore to bite on for a few days.

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

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

You will not directly benefit from this study except for the \$75.00 paid to you for your participation.

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

You may have the emergency endodontic procedure completed without having nitrous oxide or placebo administered.

You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled.

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

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 urine pregnancy test.

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

Yes, you will be paid \$75.00 for your participation.

By law, payments to subjects are considered taxable income.

12. What happens if you are injured because you 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 your rights if you 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 your questions about the study?

For questions, concerns, or complaints about the study you may contact Dr. Melissa Drum or Dr. William Stanley 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. William Stanley at 614 – 292-5399.

Signing the consent form

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

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

Printed name of subject

Signature of subject

Date and time AM/PM

Printed name of person authorized to consent for subject
(when applicable)

Signature of person authorized to consent for subject
(when applicable)

Relationship to the subject

Date and time AM/PM

Investigator/Research Staff

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

Printed name of person obtaining consent

Signature of person obtaining consent

Date and time

AM/PM

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

Printed name of witness

Signature of witness

Date and time

AM/PM

Printed name of witness

Signature of witness

Date and time

AM/PM

APPENDIX B
PATIENT PRIVACY FORM

THE OHIO STATE UNIVERSITY

AUTHORIZATION TO USE

Personal Health Information In Research

Title of the Study: Effect of nitrous oxide on the success of the inferior alveolar nerve block in patients with 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. Other Ohio State University staff not involved in the study but who may become involved in your care for study-related treatment will have access to your information.
- 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. Stanley Vermilyea at the College of Dentistry, 305 w 12th avenue, the Ohio State University, Columbus, Ohio 43218.

- Signing this authorization also means that you will not be able to see or copy your study-related information until the study is completed. This includes any portion of your medical records that describes study treatment.

Contacts for Questions

- If you have any questions relating to your privacy rights, please contact Dr. Stanley Vermilyea 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 Dr. Melissa Drum and the others listed on this form to use and share my personal health information for this study. I will be given a copy of this signed form.

Signature _____

(Subject or Legally Authorized Representative)

Name _____

(Print name above)

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

Date _____ Time _____ AM / PM

APPENDIX C
HEALTH HISTORY QUESTIONNAIRE

Date of Birth _____

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

Trade Name	Generic Name	Dose/Frequency	Reason

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

Pt. #: _____
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
PATIENT SEDATION SCALE

Pt. Number: _____

Sedation Rating

Mark a vertical line “|” on the point on the scale line that best describes your sedation.

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.

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.

APPENDIX G
VISUAL ANALOG SCALE

0-54 mm Mild pain

55-113 mm Moderate Pain

114-170 mm ... Severe Pain

APPENDIX H

TABLES

	Nitrous Oxide Group	Placebo Group	P-value
Total Subjects	50	50	
Total Analyzed	50	50	
Gender	Female 30/50 (60%) Male 20/50 (40%)	Female 27/50 (54%) Male 23/50 (46%)	0.5445*
Age (Mean +/- SD) yrs	33 (+/-11)	35 (+/-13)	0.5006**
History of Nitrous Oxide Use	Yes 15/43 (35%) No 28/43 (65%)	Yes 20/43 (47%) No 23/43 (53%)	0.2724*
Initial Pain (Mean +/- SD) mm	128 (+/-25)	130.1 (+/-23)	0.6814**
Corah Dental Anxiety (Mean +/- SD)	11 (+/-4)	11 (+/-4)	1.0000**
Access Time after IAN Block (Mean +/- SD) min	15.2 (+/-0.7)	15.2 (+/-0.7)	0.8687**
Tx Time (After 5 min O ₂ admin) (Mean +/- SD) min	45.0 (+/-8.7)	45.6 (+/-10.7)	0.7469**
Tooth Type	30 1 st Molars (60%) 11 2 nd Molars (22%) 0 3 rd Molars (0%) 2 1 st Premolars (4%) 7 2 nd Premolars (14%)	23 1 st Molars (46%) 17 2 nd Molars (34%) 1 3 rd Molars (2%) 1 1 st Premolars (2%) 8 2 nd Premolars (16%)	0.4786***

Table 1. Initial Statistics for Nitrous Oxide & Placebo Groups

* Values analyzed using Chi-Square Test

** Values analyzed using the Randomization Test

*** Values analyzed using the Fisher Exact Test

	None	Mild	Moderate	Severe	P-value
Nitrous Oxide Group	0 (0%)	0 (0%)	22 (44%)	28 (56%)	
Mean: 128 +/-25 (mm)					
n = 50					0.6814*
Placebo Group	0 (0%)	0 (0%)	17 (34%)	33 (66%)	
Mean: 130 +/-23 (mm)					
n = 50					

Table 2. Initial Pain VAS

* Values Analyzed using the Randomization Test

	4-8 Low Anxiety	9-12 Moderate Anxiety	13-14 High Anxiety	15-20 Severe Anxiety	P-value
Nitrous Oxide Group Mean: 11 +/-4 n = 50	13 (26%)	20 (40%)	7 (14%)	10 (20%)	1.0000*
Placebo Group Mean: 11 +/-4 n = 50	15 (30%)	18 (36%)	5 (10%)	12 (24%)	

Table 3. Initial Corah's Dental Anxiety Scale Ratings

* Values Analyzed using the Randomization Test

	Nitrous Oxide Group	Placebo Group	P-value
IAN Block Success n = 100	25/50 (50%)	14/50 (28%)	0.0241*
Articaine Success n = 61	18/25 (72%)	22/36 (61%)	0.3787*
I/O Success n = 21	4/7 (57%)	13/14 (93%)	0.0877* *
PDL Success n = 4	0/3 (0%)	0/1 (0%)	
Intrapulpal Success n = 4	3/3 (100%)	1/1 (100%)	

Table 4. Distribution of the Experimental Groups by Type of Anesthetic Success

* Values Analyzed using the Chi-Square Test

** Value Analyzed using the Fisher Exact Test

	Nitrous Oxide Group	Placebo Group
1st Molar	15/30 (50%)	6/23 (26%)
2nd Molar	5/11 (45%)	4/17 (24%)
3rd Molar	0/0 (0%)	0/1 (0%)
Premolars	5/9 (56%)	4/9 (44%)

Table 5. IAN Block Success by Group and Tooth Type (n = 100)

	Nitrous Oxide Group	Placebo Group
1st Molar	10/15 (67%)	9/17 (53%)
2nd Molar	4/6 (67%)	9/13 (69%)
3rd Molar	0/0 (0%)	0/1 (0%)
Premolars	3/4 (75%)	4/5 (80%)

Table 6. Articaine Infiltration Success by Group and Tooth Type (n = 61)

	Nitrous Oxide Group	Placebo Group
1st Molar	3/5 (60%)	8/8 (100%)
2nd Molar	1/2 (50%)	3/4 (75%)
3rd Molar	0/0 (0%)	1/1 (100%)
Premolars	0/0 (0%)	1/1 (100%)

Table 7. I/O Success by Group and Tooth Type (n=21)

Group (mean +/- SD) mm	None	Mild	Moderate	Severe	P-value
Needle Insertion					
Nitrous Oxide: 48 +/-40 n = 50	6 (12%)	27 (54%)	13 (26%)	4 (8%)	1.0000*
Placebo: 54 +/-33 n = 50	0 (0%)	31 (62%)	17 (34%)	2 (4%)	
Needle Placement					
Nitrous Oxide: 48 +/-40 n = 50	9 (18%)	21 (42%)	16 (32%)	4 (8%)	1.0000*
Placebo: 61 +/-34 n = 50	2 (4%)	23 (46%)	25 (50%)	0 (0%)	
Solution Deposition					
Nitrous Oxide: 55 +/-46 n = 50	6 (12%)	21 (42%)	18 (36%)	5 (10%)	1.0000*
Placebo: 58 +/-42 n = 50	4 (8%)	23 (46%)	20 (40%)	3 (6%)	

Table 8. Pain Ratings for IAN Block Injection (n=100)

* Values analyzed using the Randomization Test and the Step-Down Bonferroni Method of Holm

Group (mean +/- SD) mm	None	Mild	Moderate	Severe	P-value
Articaine Infiltration Insertion					
<i>Nitrous Oxide:</i> 33 +/-34 n = 25	6 (24%)	13 (52%)	6 (24%)	0 (0%)	1.0000*
<i>Placebo:</i> 34 +/-32 n = 36	6 (17%)	22 (61%)	7 (19%)	1 (3%)	
Articaine Infiltration Placement					
<i>Nitrous Oxide:</i> 31 +/-33 n = 24	8 (32%)	11 (44%)	5 (20%)	0 (0%)	1.0000*
<i>Placebo:</i> 42 +/-32 n = 36	3 (8%)	20 (56%)	13 (36%)	0 (0%)	
Articaine Infiltration Deposition					
<i>Nitrous Oxide:</i> 38 +/-43 n = 25	7 (28%)	10 (40%)	6 (24%)	2 (8%)	1.0000*
<i>Placebo:</i> 45 +/-39 n = 36	2 (6%)	23 (64%)	8 (22%)	3 (8%)	

Table 9. Pain Ratings for Articaine Infiltration Injection (n=61)

* Values analyzed using the Randomization Test and the Step-Down Bonferroni Method of Holm

Group (mean +/- SD) mm	None	Mild	Moderate	Severe	P-value
I/O Insertion					
Nitrous Oxide: 23 +/-18 n = 7	1 (14%)	6 (86%)	0 (0%)	0 (0%)	1.0000*
Placebo: 26 +/-36 n = 13	4 (31%)	5 (38%)	4 (31%)	0 (0%)	
I/O Placement					
Nitrous Oxide: 24 +/-24 n = 7	1 (14%)	5 (71%)	1 (14%)	0 (0%)	1.0000*
Placebo: 23 +/-35 n = 13	4 (31%)	7 (54%)	2 (15%)	0 (0%)	
I/O Deposition					
Nitrous Oxide: 58 +/-54 n = 7	1 (14%)	3 (43%)	2 (29%)	1 (14%)	1.0000*
Placebo: 57 +/-50 n = 13	4 (31%)	2 (15%)	5 (38%)	2 (15%)	

Table 10. Pain Ratings for I/O Injection (n=20)

* Values analyzed using the Randomization Test and the Step-Down Bonferroni Method of Holm

Anesthetic Failure Point	Nitrous Oxide Group	Placebo Group
IAN Block		
None	25/50 (50%)	14/50 (28%)
Dentin	14/50 (28%)	22/50 (44%)
Chamber	7/50 (14%)	12/50 (24%)
Canals	4/50 (8%)	2/50 (4%)
Articaine Infiltration		
None	18/25 (72%)	22/36 (61%)
Dentin	3/25 (12%)	8/36 (22%)
Chamber	4/25 (16%)	4/36 (11%)
Canals	0/25 (0%)	2/36 (6%)
I/O		
None	4/7 (57%)	13/14 (93%)
Dentin	0/7 (0%)	0/14 (0%)
Chamber	1/7 (14%)	0/14 (0%)
Canals	2/7 (29%)	1/14 (7%)

Table 11. Anesthetic Failure Point and Patient Distribution

Group (mean +/- SD) mm	None	Mild	Moderate	Severe	P-value
IAN Block Dentin					
<i>Nitrous Oxide:</i> 37 +/- 50 n = 38	17 (45%)	7 (18%)	12 (32%)	2 (5%)	0.0810*
<i>Placebo:</i> 71+/-49 n = 36	6 (17%)	6 (17%)	19 (53%)	5 (14%)	
IAN Block Chamber					
<i>Nitrous Oxide:</i> 27 +/- 42 n = 31	14 (45%)	9 (29%)	6 (19%)	2 (6%)	0.2686*
<i>Placebo:</i> 60 +/-54 n = 23	4 (17%)	6 (26%)	10 (43%)	3 (13%)	
IAN Block Canals					
<i>Nitrous Oxide:</i> 24 +/- 44 n = 27	14 (52%)	8 (30%)	2 (7%)	3 (11%)	1.0000*
<i>Placebo:</i> 39 +/-48 n = 15	4 (27%)	6 (40%)	4 (27%)	1 (7%)	

Table 12. IAN Block Failure Pain Ratings During Endodontic Treatment

* Values analyzed using the Randomization Test and the Step-Down Bonferroni Method of Holm

Group (mean +/- SD) mm	None	Mild	Moderate	Severe	P-value
Articaine Infiltration Dentin					
Nitrous Oxide: 18 +/-35 n = 20	11 (55%)	6 (30%)	3 (15%)	0 (0%)	1.0000*
Placebo: 37 +/-54 n = 25	12 (48%)	5 (20%)	5 (20%)	3 (12%)	
Articaine Infiltration Chamber					
Nitrous Oxide: 23 +/-39 n = 21	10 (48%)	7 (33%)	4 (19%)	0 (0%)	1.0000*
Placebo: 18 +/-37 n = 22	13 (59%)	5 (23%)	4 (18%)	0 (0%)	
Articaine Infiltration Canals					
Nitrous Oxide: 6 +/-13 n = 18	12 (67%)	6 (33%)	0 (0%)	0 (0%)	1.0000*
Placebo: 14 +/-32 n = 20	14 (70%)	4 (20%)	1 (5%)	1 (5%)	

Table 13. Articaine Infiltration Treatment Pain Ratings

* Values analyzed using the Randomization Test and the Step-Down Bonferroni Method of Holm

Group (mean +/- SD) mm	None	Mild	Moderate	Severe	P-value
I/O Dentin					
Nitrous Oxide: 0.3 +/- 0.6 n = 3	2 (67%)	1 (33%)	0 (0%)	0 (0%)	1.0000*
Placebo: 0.2 +/-0.4 n = 10	8 (80%)	2 (20%)	0 (0%)	0 (0%)	
I/O Chamber					
Nitrous Oxide: 24 +/-48 n = 4	2 (50%)	1 (25%)	1 (25%)	0 (0%)	1.0000*
Placebo: 0.8 +/-2.3 n = 12	10 (83%)	2 (17%)	0 (0%)	0 (0%)	
I/O Canals					
Nitrous Oxide: 54 +/- 73 n = 5	2 (40%)	1 (20%)	0 (0%)	2 (40%)	1.0000*
Placebo: 16 +/- 40 n = 12	9 (75%)	1 (8%)	1 (8%)	1 (8%)	

Table 14. I/O Treatment Pain Ratings

** Values analyzed using the Randomization Test and the Step-Down Bonferroni Method of Holm

Group (mean +/- SD) mm	Not Satisfied	Somewhat Satisfied	Moderately Satisfied	Completely Satisfied	P-value
Nitrous Oxide					
Mean: 95 +/-7 n = 49	0 (0%)	0 (0%)	31 (63%)	18 (37%)	0.7751*
Placebo					
Mean: 96 +/-10 n = 50	0 (0%)	1 (2%)	29 (58%)	20(40%)	

Table 15. Patient Post-Treatment Satisfaction Ratings

* Values analyzed using the Randomization Test

Nitrous Oxide % Dose	30-35%	36-40%	41-45%	46-50%
# of Patients	4	22	8	13
Mean Dosage Std. Dev.	43% 5			

Table 16. Nitrous Oxide Dosages Administered

LIST OF REFERENCES

1. Nusstein J, Reader A, Nist R, Beck M, Meyers WJ. Anesthetic efficacy of the supplemental intraosseous injection of 2% lidocaine with 1:100,000 epinephrine in irreversible pulpitis. *J Endod.* 1998;24:487-91.
2. Reisman D, Reader A, Nist R, Beck M, Weaver J. Anesthetic efficacy of the supplemental intraosseous injection of 3% mepivacaine in irreversible pulpitis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1997;84:676-82.
3. Cohen HP, Cha BY, Spangberg LS. Endodontic anesthesia in mandibular molars: a clinical study. *J Endod.* 1993;19:370-3.
4. Kennedy S, Reader A, Nusstein J, Beck M, Weaver J. The significance of needle deflection in success of the inferior alveolar nerve block in patients with irreversible pulpitis. *J Endod.* 2003;29:630-3.
5. Claffey E, Reader A, Nusstein J, Beck M, Weaver J. Anesthetic efficacy of articaine for inferior alveolar nerve blocks in patients with irreversible pulpitis. *J Endod.* 2004;30:568-71.

6. Bigby J, Reader A, Nusstein J, Beck M. Anesthetic efficacy of lidocaine/meperidine for inferior alveolar nerve blocks in patients with irreversible pulpitis. *J Endod.* 2007;33:7-10.
7. Matthews R, Drum M, Reader A, Nusstein J, Beck M. Articaine for supplemental buccal mandibular infiltration anesthesia in patients with irreversible pulpitis when the inferior alveolar nerve block fails. *J Endod.* 2009;35:343-6.
8. Lindemann M, Reader A, Nusstein J, Drum M, Beck M. Effect of sublingual triazolam on the success of inferior alveolar nerve block in patients with irreversible pulpitis. *J Endod.* 2008;34:1167-70.
9. Aggarwal V, Singla M, Kabi D. Comparative evaluation of anesthetic efficacy of Gow-Gates mandibular conduction anesthesia, Vazirani-Akinosi technique, buccal-plus-lingual infiltrations, and conventional inferior alveolar nerve anesthesia in patients with irreversible pulpitis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2010;109:303-8.
10. Oleson M, Drum M, Reader A, Nusstein J, Beck M. Effect of preoperative ibuprofen on the success of the inferior alveolar nerve block in patients with irreversible pulpitis. *J Endod.* 2010;36:379-82.
11. Simpson M, Drum M, Nusstein J, Reader A, Beck M. Effect of combination of preoperative ibuprofen/acetaminophen on the success of the inferior alveolar nerve block in patients with symptomatic irreversible pulpitis. *J Endod.* 2011;37:593-7.
12. Jackson DL, Johnson BS. Conscious sedation for dentistry: risk management and patient selection. *Dent Clin N Am* 2000;46:767-80.

13. Becker DE, Rosenberg M. Nitrous oxide and the inhalation anesthetics. *Anesth Prog.* 2008;55:124-30.
14. Jastak JT, Donaldson D. Nitrous oxide. *Anesth Prog.* 1991;38:142-53.
15. Yagiela JA, Dowd FJ, Johnson BS, Mariotti AJ, Neidle EA. *Pharmacology and Therapeutics for Dentistry 6th Edition*. St. Louis: Mosby Elsevier. 2011;281-298,758-770.
16. Parbrook G. The Levels of Nitrous Oxide Analgesia. *Brit J Anaesth.* 1967;39:974-82.
17. Quock RM, Kouchich FJ, Tseng LF. Does nitrous oxide induce release of brain opioids peptides? *Pharmacology.* 1985;30:95-9.
18. Zuniga JR, Joseph SA, Knigge KM. The effects of nitrous oxide on the central endogenous pro-opiomelanocortin system in the rat. *Brain Res.* 1987;420:57-65.
19. Zuniga JR, Joseph SA Knigge KM. The effects of nitrous oxide on the secretory activity of pro-opiomelanocortin peptides from basal hypothalamic cells attached to cytodex beads in a superfusion in vitro system. *Brain Res.* 1987;420:66-72.
20. Emmanouil DE, Quock Rm. Advances in understanding the actions of nitrous oxide. *Anesth Prog.* 2007;54:9-18.

21. Emmanouil DE, Dickens AS, Heckert RW, Ohgami Y, Chung E, Han S, Quock RM. Nitrous oxide-antinociception is mediated by opioid receptors and nitric oxide in the periaqueductal gray region of the midbrain. *Eur Neuropsychopharmacol.* 2008;18:194-99.
22. Zhang C, Davies MF, Guo TZ, Maze M. The analgesic action of nitrous oxide is dependent on the release of norepinephrine in the dorsal horn of the spinal cord. *Anesthesiology.* 1999;91:1401-7.
23. Georgiev SK, Kohno T, Ikoma M, Yamakura T, Baba H. Nitrous oxide inhibits glutamatergic transmission in spinal dorsal horn neurons. *Pain.* 2008;134:24-31.
24. Georgiev SK, Baba H, Kohno T. Nitrous oxide and the inhibitory synaptic transmission in rat dorsal horn neurons. *Eur J Pain.* 2010;14:17-22.
25. Sawamura S, Kingery WS, Davies MF, Agashe GS, Clark JD, Kobilka BK, Hashimoto T, Maze M. Antinociceptive action of nitrous oxide is mediated by stimulation of noradrenergic neurons in the brainstem and activation of [alpha] 2B adrenoceptors. *J Neurosci.* 2000;20:9242-51.
26. Al-Zaharani AM, Wyne AH, Sheta SA. Comparison of oral midazolam with a combination of oral midazolam and nitrous oxide-oxygen inhalation in the effectiveness of dental sedation for young children. *J Indian Soc Pedod Prev Dent.* 2009;27:9-16.
27. Paris A, Horvath R, Basset P, Thierry S, Couturier P, Franco A, Bosson JL. Nitrous oxide-oxygen mixture during care of bedsores and painful ulcers in the elderly: a randomized, crossover, open-label pilot study. *J Pain Symptom Manage.* 2008;35:171-6.

28. Furuya A, Ito M, Fukao T, Suwa M, Nishi M, Horimoto Y, Sato H, Okuyama K, Ishiyama T, Matsukawa T. The effective time and concentration of nitrous oxide to reduce venipuncture pain in children. *J Clin Anesth.* 2009;21:190-3.

29. Kanagasundaram SA, Lne LJ, Cavalletto BP, Keneally JP, Cooper MG. Efficacy and safety of nitrous oxide in alleviating pain and anxiety during painful procedures. *Arch Dis Child.* 2001;84:492-5.

30. Burnweit C, Diana-Zerpa JA, Lankau CA, Weinberger M, Malvezzi L, Smith L, Shapiro T, Thayer K. Nitrous oxide analgesia for minor pediatric surgical procedures: an effective alternative to conscious sedation? *J Pediatr Surg.* 2004;39:495-9.

31. Babl FE, Oakley E, Puspitadewi A, Sharwood LN. Limited analgesic efficacy of nitrous oxide for painful procedures in children. *Emerg Med J.* 2008;25:717-21.

32. Claeys A, Gaudy-Marqueste C, Pauly V, Pelletier F, Truchetet F, Boye T, Aubin F, Schmutz JL, Grob JJ, Richard MA. Management of pain associated with debridement of leg ulcers: a randomized, multicentre, pilot study comparing nitrous oxide-oxygen mixture inhalation and lidocaine-prilocaine cream. *J Eur Acad Dermatol Venereol.* 2011;25:138-44.

33. Maslekar S, Balaji P, Gardiner A, Culbert B, Monson JRT, Duthie GS. Randomized controlled trial of patient-controlled sedation for colonoscopy: Entonox vs modified patient-maintained target-controlled propofol. *Colorectal Dis.* 2011;13:48-57.

34. Maslekar S, Gardiner A, Hughes M, Culbert B, Duthie GS. Randomized clinical trial of Entonox versus midazolam-fentanyl sedation for colonoscopy. *Br J Surg.* 2009;96:361-8.
35. Uziel Y, Chapnick G, Rothschild M, Tauber T, Press J, Harel L, Hashkes PJ. Nitrous oxide sedation for intra-articular injection in juvenile idiopathic arthritis. *Pediatr Rheumatol Online J.* 2008;6:1-4.
36. Crecelius C, Rouhfar L, Beirne OR. Venous cannulation and topical ethyl chloride in patients receiving nitrous oxide. *Anesth Prog.* 1999;46(3):100-3.
37. Meskine N, Vullierme MP, Zappa M, d'Assignies G, Sibert A, Vilgrain V. Evaluation of analgesic effect of equimolar mixture of oxygen and nitrous oxide inhalation during percutaneous biopsy of focal liver lesions: a double-blind study. *Acad Radiol.* 2011;18:816-21.
38. Reinoso-Barbero F, Pascual-Pascual SI, de Lucas R, Garcia S, Billoet C, Dequenue V, Onody P. Equimolar nitrous oxide/oxygen versus placebo for procedural pain in children: a randomized trial. *Pediatrics.* 2011;127:e1464-70.
39. Hicks CL, von Baeyer CL, Spafford PA, van Korlaar I, Goodenough B. The faces pain scale-revised: toward a common metric in pediatric pain measurement. *Pain.* 2001;93:173-83.
40. Reinoso-Barbero F, Lahoz Ramon AI, Duran Fuente MP, Campo Garcia G, Castro Parga LE. LLANTO scale: Spanish tool for measuring acute pain in preschool children. *An Pediatr (Barc).* 2011;74:10-4.

41. Duarte R, McNeill A, Drummond G, Tiplady B. Comparison of the sedative, cognitive, and analgesic effects of nitrous oxide, sevoflurane, and ethanol. *Br J Anaesth.* 2008;100:203-10.
42. Ilkjaer S, Dirks J, Brennum J, Wernberg M, Dahl JB. Effect of systemic N-methyl-D-aspartate receptor antagonist (dextromethorphan) on primary and secondary hyperalgesia in humans. *Br J Anaesth.* 1997;79:600-5.
43. Wong D, Baker C. Pain in children: Comparison of assessment scales. *Pediatr Nurs.* 1988;14:9-17.
44. Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. *J Clin Psychopharmacol.* 1990;10:244-51.
45. Robinson PA, Carr S, Pearson S, Frampton C. Lignocaine is a better analgesic than either ethyl chloride or nitrous oxide for peripheral intravenous cannulation. *Emerg Med Australas.* 2007;19:427-32.
46. Ho K, Spence J, Murphy MF. Review of pain measurement tools. *Ann Emerg Med.* 1996;27:427-32.
47. Scott J, Huskisson EC. Graphic representation of pain. *Pain.* 1976;2:175-84.
48. Kan ASY, Caves N, Wong SYW, Ng EHY, Ho PC. A double-blind, randomized controlled trial on the use of a 50:50 mixture of nitrous oxide/oxygen in pain relief during suction evacuation for the first trimester pregnancy termination. *Hum Reprod.* 2006;21:2606-11.

49. Ramsay MAE, Savege TM, Simpson BRJ, Goodwin R. Controlled sedation with alphaxalone-alphadolone. *Br Med J*. 1974;2:656-9.
50. Welchman S, Cochrane S, Minto G, Lewis S. Systematic review: the use of nitrous oxide for lower gastrointestinal endoscopy. *Aliment Pharmacol Ther*. 2010;32:324-33.
51. McGrath PA, Seifert CE, Speechley KN, Booth JC, Stitt L, Gibson MC. A new analogue scale for assessing children's pain: an initial validation study. *Pain*. 1996;64:435-43.
52. Ong KS, Seymour RA, Tan JML. A prospective randomized crossover study of the preemptive analgesic effect of nitrous oxide in oral surgery. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2004;98:637-42.
53. Zacny JP, Hurst RJ, Graham L, Janiszewski DJ. Preoperative dental anxiety and mood changes during nitrous oxide inhalation. *J Am Dent Assoc*. 2002;133:82-8.
54. Whalley MG, Brooks GB. Enhancement of suggestibility and imaginative ability with nitrous oxide. *Psychopharmacology (Berl)*. 2009;203:745-52.
55. Sheehan PW. A shortened form of Betts' questionnaire upon mental imagery. *J Clin Psychol*. 1967;23:386-89.
56. Weitzenhoffer AM, Hilgard ER. Stanford hypnotic susceptibility scale, Form C. Consulting Psychologists. 1962.
57. Fagade OO, Oginni FO. Intra-operative pain perception in tooth extraction – possible causes. *Int Dent J*. 2005;55:242-6.

58. Facco E, Zanette G, Favero L, Bacci C, Sivolelle S, Cavallin, Manani G. Toward the validation of visual analogue scale for anxiety. *Anesth Prog.* 2011;58:8-13.
59. Tortamano IP, Siviero M, Costa CG, Buscariolo IA, Armonia PL. A comparison of the anesthetic efficacy of articaine and lidocaine in patients with irreversible pulpitis. *J Endod.* 2009;35:165-8.
60. Oleson ML. The effect of preoperative ibuprofen on the efficacy of the inferior alveolar nerve block in patients with irreversible pulpitis. Masters Thesis: The Ohio State University; Columbus OH, 2009.
61. Aggarwal V, Singla M, Kabi D. Comparative evaluation of effect of preoperative oral medication of ibuprofen and ketorolac on anesthetic efficacy of inferior alveolar nerve block with lidocaine in patients with irreversible pulpitis: a prospective, double-blind, randomized clinical trial. *J Endod.* 2010;36:375-8.
62. Parirokh M, Ashouri R, Rekabi AR, Nakhaee N, Pardakhti A, Askarifard S, Abbot P. The effect of premedication with ibuprofen and indomethacin on the success of inferior alveolar nerve block for teeth with irreversible pulpitis. *J Endod.* 2010;36:1450-4.
63. Rosenberg PA, Amin KG, Zibari Y, Lin LM. Comparison of 4% articaine with 1:100,000 epinephrine and 2% lidocaine with 1:100,000 epinephrine when used as a supplemental anesthetic. *J Endod.* 2007;33:403-5.

64. Parirokh M, Satvati SA, Sharifi R, Rekabi AR, Gorjestani H, Nakhaee N. Efficacy of combining a buccal infiltration with an inferior alveolar nerve block for mandibular molars with irreversible pulpitis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2010;109:468-73.
65. Simpson MG. The effect of preoperative ibuprofen and acetaminophen on the efficacy of the inferior alveolar nerve block in patients with irreversible pulpitis. Masters Thesis: The Ohio State University; Columbus OH, 2010.
66. Aggarwal V, Singla M, Rizvi A, Miglani S. Comparative evaluation of local infiltration of articaine, articaine plus ketorolac, and dexamethasone on anesthetic efficacy of inferior alveolar nerve block with lidocaine in patients with irreversible pulpitis. *J Endod.* 2011;37:445-9.
67. Pearce JH. Intraosseous injection for profound anesthesia of the lower molar. *J Colo Dent Assoc.* 1976;54:25-6.
68. Parente SA, Anderson RW, Herman WW, Kimbrough WF, Weller RN. Anesthetic efficacy of the supplemental intraosseous injection for teeth with irreversible pulpitis. *J Endod.* 1998;24:826-8.
69. Nusstein J, Kennedy S, Reader A, Beck M, Weaver J. Anesthetic efficacy of the supplemental X-tip intraosseous injection in patients with irreversible pulpitis. *J Endod.* 2003;29:724-8.
70. Corah NL. Development of a dental anxiety scale. *J Dent Res.* 1969;48:596.
71. Corah NL, Gale EN, Illig SJ. Assessment of a dental anxiety scale. *J Am Dent Assoc.* 1978;97:816-9.

72. Newton JT, Buck DJ. Anxiety and pain measures in dentistry: A guide to their quantity and application. *J Am Dent Assoc* 2002;131:1449-57.
73. Heft MW, Parker SR. An experimental basis for revising the graphic rating scale for pain. *Pain*. 1984;19:153-61.
74. Malamed SF. *Sedation, A Guide To Patient Management*. St. Louis: Mosby.; 1985:226.
75. Fischer G. *Lokale Anesthesia*. Berlin: Herman Meuser; 1919.
76. Jorgensen NB, Hayden J. *Sedation, Local and General Anesthesia in Dentistry 2nd ed*. Philadelphia, PA: Lea and Febiger.; 1967.
77. Liddell A, Locker D. Gender and age differences in attitudes to dental pain and dental control. *Community Dent Oral Epidemiol*. 1997;25:314-8.
78. Fillingim RB, Edwards RR, Powell T. The relationship of sex and clinical pain to experimental pain responses. *Pain*. 1999;83:419-25.
79. Nordenram A DK. Local anaesthesia in elderly patients. An experimental study of oral anaesthesia. *Swed Dent J*. 1990;14:19-24.
80. Beecher HK. The powerful placebo. *J Am Med Assoc*. 1955;159:1602-6.
81. Levine JD, Gordon NC, Bornstein JC, Fields HL. Role of pain in placebo analgesia. *Proc Natl Acad Sci USA*. 1979;76:3528-31.

82. Vase L, Riley JL, Price DD. A comparison of placebo effects in clinical analgesia trials versus studies on placebo analgesia. *Pain*. 2002;99:443-52.
83. Sedation. Dictionary.com. *Dictionary.com Unabridged*. Random House, Inc. <http://dictionary.reference.com/browse/sedation> (accessed: June 30, 2011).
84. Dunbar D, Reader A, Nist R, Beck M, Meyers WJ. Anesthetic efficacy of the intraosseous injection after an inferior alveolar nerve block. *J Endod*. 1996;22:481-6.
85. Ploghaus A, Narain C, Beckmann CF, Clare S, Bantick S, Wise R, Matthews PM, Rawlins JNP, Tracey I. Exacerbation of pain by anxiety is associated with activity in a hippocampal network. *J Neurosci*. 2001;21:9896-903.
86. Young J, Siffleet J, Nikoletti S, Shaw T. Use of a behavioral pain scale to assess pain in ventilated, unconscious and/or sedated patients. *Intensive Crit Care Nurs*. 2006;22:32-9.
87. Aissaoui Y, Zeggwagh AA, Zekraoui A, Abidi K, Abouqal R. Validation of a behavioral pain scale in critically ill, sedated, and mechanically ventilated patients. *Anesth Analg*. 2005;101:1470-6.
88. Payen JF, Bru O, Bosson JL, Lagrasta A, Novel E, Deschaux I, Lavagne P, Jacquot C. Assessing pain in critically ill sedated patients by using a behavioral pain scale. *Crit Care Med*. 2001;29:2258-63.
89. Henderson JM, Spence DG, Komocar LM, Bonn GE, Stenstrom RJ. Administration of nitrous oxide to pediatric patients provide analgesia for venous cannulation. *Anesthesiology*. 1990;72:269-71.

90. McCartney M, Reader A, Beck M. Injection pain of the inferior alveolar nerve block in patients with irreversible pulpitis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2007;104:571-5.
91. Nusstein J, Steinkruger G, Reader A, Beck M, Weaver J. The effects of a 2-stage injection technique on inferior alveolar nerve block injection pain. *Anesth Prog.* 2006;53:126-30.
92. Haase AJ. The anesthetic efficacy of articaine and lidocaine for a buccal infiltration of the mandibular first molar following an inferior alveolar nerve block. Masters Thesis: The Ohio State University; Columbus OH, 2007.
93. Martin M, Nusstein J, Drum M, Reader A, Beck M. Anesthetic efficacy of 1.8 mL versus 3.6 mL of 4% articaine with 1:100,000 epinephrine as a primary buccal infiltration of the mandibular first molar. *J Endod.* 2011;37:588-92.
94. Bigby J, Reader A, Nusstein J, Beck M, Weaver J. Articaine for supplemental intraosseous anesthesia in patients with irreversible pulpitis. *J Endod.* 2006;32:1044-7.
95. Kreimer T. The anesthetic efficacy of a combination of lidocaine and mannitol with infiltration in teeth with irreversible pulpitis. Masters Thesis: The Ohio State University; Columbus OH, 2001.

96. Robertson D. The anesthetic efficacy of articaine in buccal infiltration of mandibular posterior teeth: A prospective, randomized, double-blind study comparing the anesthetic efficacy of an injection of an articaine solution to a lidocaine solution in mandibular posterior teeth. Masters Thesis: The Ohio State University; Columbus OH, 2006.
97. Robertson D, Nusstein J, Reader A, Beck M, McCartney M. The anesthetic efficacy of articaine in buccal infiltration of mandibular posterior teeth. *J Am Dent Assoc.* 2007;138:1104-12.
98. Placebo effect. Dictionary.com. *Dictionary.com Unabridged.* Random House, Inc. <http://dictionary.reference.com/browse/placeboeffect> (accessed: June 30, 2011).
99. Susi LW. Heart rate changes after intraosseous injection of 2% lidocaine with 1:100,000 epinephrine using a computer-assisted local anesthetic delivery system. Masters Thesis: The Ohio State University; Columbus OH, 2005.
100. Bren L. Oxygen bars: is a breath of fresh air worth it? *FDA Consum.* 2002;36:9-11.