A prospective randomized, double-blind study of the anesthetic efficacy of buffered articaine as a primary buccal infiltration of the mandibular first molar.

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Abstract

Several studies have demonstrated that 4% articaine with 1:100,000 epinephrine is a superior local anesthetic when used as a primary mandibular buccal infiltration when compared to 2% lidocaine with 1:100,000 epinephrine. However, the anesthetic success has been reported as less than 100% and not predictable enough for routine use. Buffered local anesthetics have been shown to improve anesthetic success, reduce pain of injection, and decrease time to onset of anesthesia. No objective study has addressed the success rate of buffering articaine in a mandibular primary buccal infiltration of the first molar. Therefore, the purpose of this study was to compare the degree of pulpal anesthesia obtained with a buffered 64.8 mg articaine with 16.2 µg epinephrine formulation versus a non-buffered 72.0 mg articaine with 18.0 µg epinephrine formulation as a primary infiltration in the mandibular first molar.

Using a crossover design, 80 adults received mandibular buccal infiltrations using 64.8 mg articaine with 16.2 µg epinephrine buffered with 8.4% sodium bicarbonate, and 72 mg articaine with 18 µg epinephrine plain. An electric pulp tester (EPT) was used to test the first molar for pulpal anesthesia every 30 seconds for the first 5 minutes, and every minute for the remaining 55 minutes. Successful pulpal anesthesia was defined as two consecutive 80/80 readings with the EPT. Pain ratings for each injection and postoperative pain were recorded. Onset time of pulpal anesthesia was recorded. Data
were statistically analyzed.

For the buffered articaine formulation, the anesthetic success rate was 71%. For the non-buffered articaine formulation the anesthetic success rate was 65%. There was no significant difference for anesthetic success between buffered articaine and non-buffered articaine (P>0.05). No significant differences were discovered between the two formulations for pain of injection, or onset of anesthesia. Mean anesthesia onset time for buffered articaine and non-buffered articaine was 5.9 min and 5.4 min, respectively. There was a significant difference between anesthetic formulations for female participants regarding postoperative pain ratings for Days 1, 2, and 3 (P=0.000). The highest mean pain ratings were on Day 1 and were slightly in the moderate pain category.

The anesthetic efficacy of buffered articaine was not better than non-buffered articaine. The buffered articaine did not provide a decrease in injection pain nor decrease time of onset of anesthesia compared to the non-buffered articaine. Buffered articaine does not provide any advantage over non-buffered articaine for anesthetic efficacy, pain of injection and onset of anesthesia for the mandibular first molar after a primary buccal infiltration.
Dedication

To my Father in Heaven and my Savior: All I have is because of Thee. May I live to give Thee glory.

To Sheena: Thank you for who you are and your love. You are my life. You make my life.

To Riley, Sadie, and Weston: I love you. Keep playing hard.

To my parents, brothers and sisters: Thank you for my foundation in life.
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To Jared, Taryn, and Raquel: My friends, as we part ways, shed no tears of sorrow. Rather rejoice that friendships shall endure the distance. Thanks for becoming part of my family. I’ll miss seeing your smug mugs each day.

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Chapter 1

Introduction

Several studies have demonstrated that 4% articaine with 1:100,000 epinephrine is a superior local anesthetic when used as a primary mandibular buccal infiltration when compared to 2% lidocaine with 1:100,000 epinephrine as a primary mandibular buccal infiltration (1-11). The average success rate (no subject response to two consecutive 80 readings with the electric pulp tester) for the primary buccal infiltration is 67% with a range of 54% to 87%, depending on the tooth and injection location. Unfortunately, the success rate of this primary mandibular buccal infiltration is not a highly predictable clinical modality in providing profound pulpal anesthesia.

Most dental local anesthetic formulations have an acidic pH ranging from 3.0 to 6.5 (12, 13). Articaine HCl is one of these formulations and is in the amide local anesthetic family. The formulation contains epinephrine as a vasoactive agent rendering the pH around 3.5 to 4.0. Articaine, at a molecular level exists in two forms within this formulation: a de-ionized, uncharged free base form and an ionized, charged cationic form (14, 15). The de-ionized form of the local anesthetic is the active lipid soluble form that enters the nerve membrane and blocks nerve conduction (16). A sufficient amount of de-ionized free base anesthetic is necessary to achieve adequate anesthesia.
Generally, articaine with epinephrine enters the body at a lower pH (3.5-4.0) than that of the physiologic pH of 7.4. The ionized charged form predominates at this lower pH, requiring the body to buffer and convert enough anesthetic to the active de-ionized form to produce anesthesia (17, 18).

Buffering local anesthetic formulations increases the pH, making the formulation closer to physiologic pH. Theoretically, once buffered, the anesthetic formulation will have a higher pH upon injection and more de-ionized base form will be available to penetrate the nerve sheath and provide anesthesia. Thus, buffered anesthetic formulations may be more efficient in achieving anesthesia for the mandibular buccal infiltration injection.

Injection pain may also be reduced if a higher proportion of de-ionized articaine could be administered at the time of injection (19). Galindo and co-authors (20) used pH-adjusted local anesthetic formulations (pH of 7.4) in epidural injections, peripheral nerve blocks and regional anesthesia. They found that higher pH formulations established anesthesia of better quality. Several authors (21-25) have found faster onset with buffered anesthetic formulations. These reported successes have been within medical models for dermatologic injections, epidural anesthesia, hemodialysis infiltration, and peripheral nerve studies within humans and rats (21-25). The dental model studies are more ambiguous as to the efficacy of buffering local anesthetic. Several authors report improvement of success rate (no subject response to two consecutive 80 readings with the electric pulp tester) and less injection pain when buffering dental local anesthetic formulations (13, 26-28). The types of injections used were the inferior alveolar nerve block (IANB) and maxillary and mandibular buccal infiltration injections. The patients
included in the studies were asymptomatic and symptomatic. However, several other authors report no advantage to buffering local anesthetics in asymptomatic and symptomatic models (29-31). These studies also used the IANB and maxillary and mandibular buccal infiltration injections.

Several mechanisms have been proposed explaining the improved results of buffered local anesthetics. One proposed mechanism states that the irritation from conventional non-buffered formulations is due to their inherent acidity. By increasing the pH of the injected formulation they should be less irritating (32). Another mechanism states that the de-ionized anesthetic, which is in greater quantity at higher pH, will enter the nerve sheath more quickly, and result in a faster onset of anesthesia (33). Anesthetic formulations are generally buffered with sodium bicarbonate. Mixing sodium bicarbonate (NaHCO₃) with anesthetic formulations produces water and carbon dioxide through interaction with hydrochloric acid in the formulation (34). The combination of carbon dioxide with lidocaine produces a depressant effect upon the nerve axon, an accumulation of the anesthetic inside the nerve and the changing of the charge of the anesthetic once inside the nerve. Each result helps to potentiate nerve blockade and produce anesthesia (35). Thus an increase in pH and CO₂ formation may increase local anesthetic success with comparison to non-alkalinized formulations.

No objective study has addressed the success rate of buffering articaine in a mandibular primary buccal infiltration of the first molar. Therefore, the purpose of this prospective randomized, double-blind, crossover study was to compare the degree of pulpal anesthesia obtained with a buffered 64.8 mg articaine with 16.2 µg epinephrine formulation versus a non-buffered 72 mg articaine with 18 µg epinephrine formulation as
a primary infiltration in the mandibular first molar. We also recorded the pain of injection and postoperative pain.
Chapter 2

Literature Review

Local Anesthetics: Mechanism of Action

The sensation of pain is blocked by local anesthetics that reversibly interfere with peripheral nerve impulse propagation. Local anesthetics bind to receptor sites within the sodium ion (Na\(^+\)) channel that spans the neuron cell membrane or axolemma. Action potential generation and conductance are inhibited by this interference. Generally, the axolemma is impermeable to sodium ion (Na\(^+\)) diffusion at rest. The intracellular environment is negatively charged while the extracellular environment is positively charged. The difference in charge is created via active transport of Na\(^+\) and the inability of larger negatively charged molecules (protein) to cross the axolemma. Potassium ions (K\(^+\)) freely move across the axolemma toward the negatively charged intracellular environment as well as being transported via active transport with the Na\(^+\). This creates a high K\(^+\) concentration gradient intracellularly, and a high Na\(^+\) concentration gradient extracellularly. The differences in charges across the axolemma result in a -70 to -90 mV resting potential. When stimuli (chemical, thermal, mechanical, electrical) excite the free endings of sensory neurons, the Na\(^+\) channels will temporarily increase Na\(^+\) permeability and conductance. Sodium ion conductance causes the neuron to be less electronegative,
permitting the difference in charge between the extracellular and intracellular environments to increase. If a critical threshold (-50mV to -60mV) is reached, the depolarization of the axolemma becomes self-generating; enabling more Na\(^+\) channels to sequentially open along the axolemma and propagate the impulse proximally down the neuron toward the CNS. An action potential is created (36-39).

After depolarization, the nerve is unable to propagate any signal. In other words, the axolemma is unable to depolarize and generate an action potential. This is termed the refractory period. It allows the impulse to be carried in only one direction down the nerve. The charge across the membrane at the end of depolarization is approximately +40 mV. Repolarization of the axolemma to its resting potential (-70 to -90 mV) occurs within the refractory period. Potassium channels open and K\(^+\) efflux to the extracellular environment occurs, decreasing the charge across the axolemma. The neuron continues to reestablish the electronegative resting potential (-90 mV) by closing and resetting the Na\(^+\) and K\(^+\) channels. It pumps out Na\(^+\) and pumps in K\(^+\) via active transport. Once the resting potential is re-established, the neuron is ready to create another action potential. The entire cycle occurs in one millisecond (ms). Depolarization occurs in 0.3 ms. Repolarization occurs in 0.7 ms (36-39).

The signals or impulses (from nociceptive and thermal sensory afferents on the trigeminal nerve from maxillary and mandibular teeth, or branches V\(_2\) and V\(_3\)) move proximally along primary afferent neurons reaching the presynaptic terminal. The sensory neurons synapse with second-order neurons in the medullary dorsal horn of the subnucleus caudalis. The subnucleus caudalis is within the medulla, which is the most inferior portion of the brainstem. The depolarization allows for presynaptic calcium ion
(Ca\(^+\)) influx, releasing neurotransmitters, which act upon postsynaptic terminals (second-order neurons). The neurotransmitters binding to the postsynaptic terminal cause depolarization of the ascending neuronal tracts. This impulse, carried by second-order neurons, crosses the midline and ascends to the thalamus via the trigeminothalamic tract. The impulse is relayed in the thalamus to the cerebral cortex via third-order neurons on the thalamocortical tract. Once in this higher center of the brain, the impulse is processed for perception and response (40–42).

Local anesthetics block action potential creation and propagation by decreasing the rate and degree of axolemma depolarization, thereby slowing Na\(^+\) conductance into the intracellular environment of the neuron. Local anesthetics interact directly within the Na\(^+\) channel that spans the axolemma and blocks ion conductance. They exert their effect by binding to sites within the Na\(^+\) transmembrane channel, and freezing the channel in an inactivated configuration. The anesthetic molecule can also act as a plug within the channel. By changing the Na\(^+\) channel configuration or by plugging the channel, Na\(^+\) intracellular conductance is impeded. If depolarization of the axolemma is retarded to the point that repolarization develops before the critical threshold potential is met for action potential generation and propagation, conductance fails and nerve blockade is successful (36–38).

**Articaine Hydrochloride (HCl)**

Articaine's commercial chemical formula is 3-N-Proplyamino-propionylamino-2-carbomethoxy-4-methylthiophene hydrochloride. Ferger et al (43) and Muschaweck et al (44) first characterized the drug carticaine (articaine) before the Food and Drug
Administration (FDA) approved it for clinical use in the United States in April 2000 (45).

The structural formula of articaine HCl is:

![Articaine HCl Structural Formula](image)

There are three basic components to local anesthetic molecules: 1) an aromatic group, 2) the intermediate chain, and 3) the amino terminus. Articaine is considered an amide local anesthetic. The amide anesthetic family is classified as such for their intermediate chain: R-NHCOH-R, an amide. The ester anesthetic family has the intermediate chain, R-COO-R. Knowing the composition of the intermediate chain is useful due to differences in potential allergenicity and metabolism. Specifically, amide anesthetics are considered less allergenic when compared to the ester anesthetics because they are not metabolized to an ester derivative, *para*-aminobenzoic acid (PABA). PABA has been shown to form immunogenic complexes, which can elicit an allergic reaction (47).

Within the amide anesthetic family, articaine has several unique molecular structure components. It is the only amide anesthetic with a thiophene ring (a five carbon structure) as the aromatic group. All other amide anesthetics have a benzene ring (a six
carbon ring) as the aromatic group. The aromatic portion of the molecule confers lipophilic properties. Lipophilicity allows for nerve sheath penetration. Without this property the anesthetic could not gain access to the Na⁺ ion channels to exert its effect. Articaine also has an ester group as part of the intermediate chain. The ester group allows for articaine to be metabolized in the tissue and blood by plasma esterases. Articaine is also metabolized in the liver, as are the other amide anesthetics. The tissue and blood metabolism property decreases articaine’s relative toxicity (38, 48).

Articaine HCl also exhibits intramolecular hydrogen bonds that confer greater lipophilicity for nerve sheath penetration and anesthetic efficacy (49, 50). Skjevik et al (49) and Kuhn et al (50) reported that articaine HCl exerts these properties due to a molecular folding that renders the molecule smaller, also allowing for greater nerve sheath and bone penetration. The amine nitrogen and ester carbonyl oxygen groups within articaine form the hydrogen bond (49).

Local anesthetics cause peripheral vasodilation via direct relaxation of vascular smooth muscle tissue (51). Vasodilatory effect of articaine is similar to lidocaine. Most clinical preparations of local anesthetics use vasoconstrictive additives (i.e. epinephrine) to overcome this vasodilatory effect, allowing for longer therapeutic results. Articaine HCl is highly protein bound (95%) (52). Highly protein bound molecules use the cationic portion of their molecular structure to firmly adhere to proteins at receptor sites, increasing duration of local anesthetic action (52, 53).

The pKₐ of articaine is 7.9, with a pH of 7.35 (46). Commercially prepared formulation of articaine HCl with epinephrine has a pH between 3.5 – 4.0. The pH
decreases with the addition of the vasoconstrictive agent, epinephrine, and associated preservative, sodium metabisulfite.

Metabolism of articaine HCl occurs in plasma, tissue and liver. It is excreted by the kidneys unchanged and also as a metabolite. Degradation (hydrolysis) of the ester group by plasma and tissue esterases, and hepatic microsomal enzymes produce the primary metabolite, articainic acid. This molecule is pharmacologically inactive. Further biotransformation into articainic acid glucuronide occurs in the kidneys for excretion. Due to the ester group metabolism, articaine HCl has a shorter half-life (27 minutes) than lidocaine HCl (1.5-2 hours). Shorter half-life for articaine indicates a decrease in potential plasma or tissue accumulation and toxicity, as well as a shortened time to therapeutic steady state (45).

Articaine HCl is available in the United States as Septocaine® (Septodont, Saint Maur des Fossés, France) in 1.7 mL cartridges as the following formulations: 4% Articaine HCl 1:100,000 epinephrine, and 4% Articaine HCl 1:200,000 epinephrine. Septocaine® contains articaine HCl (40 mg/mL), epinephrine (1:200,000 or 1:100,000) (as epinephrine bitartrate), sodium chloride (1.6 mg/mL), and sodium metabisulfite (0.5 mg/mL). The product is formulated with a 15% overage of epinephrine to account for any loss of active epinephrine to oxidation over time. Sodium metabisulfite is an antioxidant to eliminate oxygen (O₂) species from the cartridge. The pH of this formulation is adjusted with sodium hydroxide to 3.5-4.0. Sodium chloride is added to achieve isotonicity of the aqueous formulation (46).
**Dosage and Safety**

The maximum recommended dose for adult and pediatric patients is 7.0 mg/kg. Adults (70 kg) can receive approximately 7 cartridges of articaine. Children (25 kg) can receive about 2 cartridges of articaine (38, 46). Articaine HCl is a pregnancy category C drug which indicates that “animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks” (38, 54). Several authors evaluated articaine with other local anesthetics for toxicity, bioavailability, systemic effects and complications both in adults and children. They concluded that articaine is safe when used according to the prescribing information by the manufacturer and the FDA (46, 55-64).

Although rare, articaine HCl has a potential to produce methemoglobinemia in patients with breathing problems such as asthma and emphysema (65). Local anesthetic induced methemoglobinemia occurs when large doses of local anesthetic are administered. Methemoglobin (ferric state iron molecule) normally consists of about 1-3% of hemoglobin molecules in erythrocytes. Methemoglobin binds oxygen more firmly than the predominating hemoglobin (ferrous state). If the percentage of methemoglobin rises, oxygen cannot release properly to body tissues and signs of cyanosis and respiratory distress may develop (41, 55, 65).

Several studies have reported articaine to cause permanent and temporary neuropathies of the lip and/or tongue following nonsurgical dental treatment with administration of the local anesthetic. The inferior alveolar nerve block was reported as the injection with the highest incidence of paresthesia (94.5% of cases involving
paresthesia) (55, 66-71). Articaine and prilocaine have been reported to have an incidence of paresthesia five times higher than lidocaine and mepivacaine (66, 68). Haas and Lennon (66) reported an articaine-associated incidence for paresthesia at 1: 785,000 injections. Gaffen and Haas (72) reported an incidence of paresthesia for articaine of 1: 410,000 injections compared to lidocaine paresthesia incidence at 1: 2,580,000 injections between 2006 to 2008. Garisto et al (71) reported the incidence of paresthesia for a twelve year (1997 – 2008) period for the following local anesthetic drugs: articaine – 1:4,159,848; lidocaine – 1:181,112,900. Though the incidence for articaine associated paresthesia is higher than for lidocaine, it is still a rare clinical event (66, 69, 71, 73, 74). Garisto et al (71) determined that the concentration of prilocaine and articaine, both a 4% concentration of local anesthetic drug, might be the reason for the higher incidences. They also believe that administration of the IANB and possible direct trauma to neuronal tissues during administration contributes to the majority of reported paresthesias being associated with the use of the IANB injection for treatment.

With the local anesthetic mechanism for blocking pain stimuli, and the specific attributes of articaine described, how articaine specifically fairs using primary and supplemental buccal infiltration injections needs to be articulated. By reviewing the historical data in relation to efficacy and pain of injection for buccal infiltration injections, the acquired knowledge may allow for further improvement to achieve less painful and more efficacious anesthetic modalities.
Primary Mandibular Buccal Infiltration Injections with Articaine HCl –

Asymptomatic Patients

Historically, mandibular buccal infiltrations have been used as primary and supplemental injections to provide anesthesia in order to conduct surgical and nonsurgical dental treatment. The mandibular buccal infiltration injection is administered as a supraperiosteal deposition of a local anesthetic formulation in the mucobuccal fold (mandibular vestibule) at the root apex (apices) of the tooth (teeth) to be anesthetized (41). Reported success rates (no patient response to two consecutive 80 readings with EPT) for profound anesthesia have reported mandibular primary buccal infiltration injections of 4% articaine HCl with 1:100,000 epinephrine as superior when compared with mandibular primary buccal infiltrations with 2% lidocaine with 1:100,000 epinephrine. Though superior, the defined success rates ranged from 54% - 87%. The duration of pulpal anesthesia declined over 60 minutes in these reports (1-3, 5, 6, 9).

Kanaa et al (1) demonstrated that administering 1.8 mL of 4% articaine HCl with 1:100,000 epinephrine was superior in anesthetic success rate (no patient response to two consecutive 80 readings with EPT) compared to 2% lidocaine HCl with 1:100,000 epinephrine for a primary buccal infiltration of the mandibular first molar. The success rate for the primary mandibular buccal infiltration was 64.5% using 4% articaine HCl with 1:100,000 epinephrine. Two percent lidocaine HCl with 1:100,000 epinephrine was reported to have a success rate of 38.7%. The duration of anesthesia (maximum of 28 minutes) was not sufficient to warrant use of a primary mandibular buccal infiltration alone for treatment requiring pulpal anesthesia.
Robertson et al (2) showed a success rate (no patient response to two consecutive 80 readings with EPT) of 87% for a primary 4% articaine with 1:100,000 epinephrine buccal infiltration of the mandibular first molar compared with a 57% defined success rate when using 2% lidocaine 1:100,000 epinephrine for the same injection and tooth. The duration of pulpal anesthesia was again not sufficient to warrant use of the mandibular primary buccal infiltration alone for treatment requiring pulpal anesthesia. Anesthesia peaked around 8 minutes and steadily declined over the remaining period of sixty minutes. First molar anesthesia percentages dropped below 75% around 25-30 minutes.

Corbett et al (3) investigated the efficacy of a primary mandibular buccal infiltration of 1.8 mL of 4% articaine HCl with 1:100,000 epinephrine for anesthetizing the first molar compared to primary mandibular buccal and lingual infiltration injections of 0.9 mL of 4% articaine HCl with 1:100,000 epinephrine for the first molar. They reported a success rate (no patient response to two consecutive 80 readings with EPT) of 64.5% for the buccal infiltration alone and 67.7% for buccal plus lingual infiltration injections.

Jung et al (4) reported a success rate (subject did not respond to the maximum output (80) of the electric pulp tester at two or more consecutive time points) for the mandibular first molar using a primary mandibular buccal infiltration with 1.7 mL of 4% articaine HCl with 1:100,000 at 54%.

Abdulwahab et al (5) reported that primary mandibular buccal infiltration of the first molar with 4% articaine HCl 1:100,000 and 1:200,000 epinephrine formulations, demonstrated higher success rates than formulations of lidocaine, prilocaine, and
bupivacaine. However, the articaine formulation success rates were below 40%. At this percentage of success, predictable pulpal anesthesia for clinical treatment is inadequate to recommend the primary mandibular buccal infiltration for routine use.

Pabst et al (6) demonstrated that repeating a mandibular primary buccal infiltration with 4% articaine HCl with 1:100,000 epinephrine (1.8 mL) twenty-five minutes after the primary mandibular buccal infiltration (same formulation and volume), prolonged the duration (25 minutes to 109 minutes) of pulpal anesthesia in the first molar even though initial success rates (no patient response to two consecutive 80 readings with EPT) were below 70%. By repeating the injection at 25 minutes (a time determined from Robertson et al’s (2) data when pulpal anesthesia following a primary mandibular buccal infiltration with 4% articaine HCl with 1:100,000 epinephrine began to diminish), authors were able to show a new modality to prolong anesthesia by using only mandibular buccal infiltration injections.

Nuzum et al (7) reported the success rate (no patient response to two consecutive 80 readings with EPT) increased for anesthetizing the mandibular incisors with 1.8 mL of 4% articaine HCl with 1:100,000 epinephrine with primary mandibular labial infiltration injections (76% to 98%) when a lingual infiltration injection of the same articaine formulation was added as a treatment modality.

Jaber et al (75) demonstrated an increased success rate (no patient response to two consecutive 80 readings with EPT within the first 15 minutes and sustained for 45 minutes) for mandibular incisor pulpal anesthesia using 1.8 mL of 4% articaine HCl with 1:100,000 epinephrine versus 1.8 mL of 2% lidocaine HCl with 1:100,000 epinephrine for labial (3% vs. 45% success rate) or labial plus lingual (10% vs. 65%) infiltration
injections. Lingual infiltration injections were with a 0.9 mL lidocaine or articaine formulation. The articaine formulation for both labial alone and labial plus lingual infiltration had higher sustained anesthesia (45 minutes) than the lidocaine formulations (45% to 65% versus 3% and 10%, respectively). This study indicates that the use of articaine is superior to lidocaine for labial and labial plus lingual infiltrations, and the lingual infiltration addition increases anesthetic success. Both Nuzum et al (7) and Jaber et al (75) show that the addition of a lingual infiltration will increase the anesthetic success, thus providing another primary or supplemental injection technique to use for patient treatment.

Martin et al (8) demonstrated an improved success rate (no patient response to two consecutive 80 readings with EPT) for the mandibular first molar using 3.6 mL of 4% articaine HCl with 1:100,000 epinephrine (70%) versus 1.8 mL of 4% articaine HCl with 1:100,000 epinephrine (50%). Onset of anesthesia peaked around 10 minutes with a slow decline thereafter. Duration of anesthesia was not reported. Anesthesia plateaued up to 20 minutes. The success rate for the 3.6 mL (70%) was still not high enough to routinely use this injection as a primary injection and expect all patients to achieve adequate pulpal anesthesia.

McEntire et al (9) demonstrated a success rate (no patient response to two consecutive 80 readings with EPT) of 59% and 67% for primary mandibular buccal infiltration injections using 4% articaine HCl with 1:100,000 and 1:200,000 epinephrine formulations, respectively. The reported success rates indicate inadequate predictability for use of a primary mandibular buccal infiltration as a stand-alone modality for pulpal anesthesia. The duration of anesthesia was not specifically calculated or reported. Both
anesthetic groups peaked around 7 minutes and maintained a plateau of anesthesia until around the 20-minute mark. The graph has similar lines of data for each group. There was no difference between formulations for anesthesia duration. The reported success rates were not significantly different for either formulation indicating that the epinephrine concentration does not provide any advantage or disadvantage in terms of anesthetic effect.

Meechan et al (76) reported a higher success rate for the first molar (no patient response to two consecutive 80 readings with EPT) using a primary mandibular buccal infiltration injection using 4% articaine HCl with 1:100,000 (65%). This was compared to the success rate (10%) of the first molar using a primary mandibular lingual infiltration injection with 4% articaine HCl with 1:100,000 epinephrine. The primary mandibular buccal infiltration was shown to be superior in providing pulpal anesthesia then the primary mandibular lingual infiltration when using an articaine formulation.

Currie et al (77) reported a success rate (no patient response to two consecutive 80 readings with EPT) of 72.7% for the mandibular first molar using 1.8 mL of 4% articaine HCl with 1:100,00 epinephrine given as a primary mandibular buccal infiltration at the first molar. This was compared to the anesthetic success rates of 40.9% and 31.8% for the first molar when given at the mandibular canine (ipsalateral) and the second molar using the same injection technique, respectively. The injection administered at the first molar reported the highest anesthetic success rates for the second molar, first molar and first premolar. This group’s work confirmed Robertson et al’s (2) findings of a greater than 70% success rates for pulpal anesthesia using a primary mandibular buccal infiltration. Other studies (1, 6-11, 75, 76) have not reported these high success rates.
The authors also concluded that the injection was not considered a mental nerve block, but an infiltration. The reported success also confirms that a primary buccal infiltration was inadequate in providing adequate and predictable pulpal anesthesia for the entire treatment period of 50 minutes. The authors did not report a specific duration of anesthesia.

Dressman et al (10) demonstrated an increase in success rate (no patient response to two consecutive 80 readings with EPT) for the mandibular first molar by giving a repeat mandibular buccal infiltration (4% articaine with 1:100,000 epinephrine) twenty minutes after the initial primary mandibular buccal infiltration injection (79% compared with 54-59% respectively). Anesthesia declined after 20-25 minutes from the initial injection. For the first molar, anesthesia plateaued until the 40th minute with a steady decline for the remaining test period time of 120 minutes. Pabst et al (6) reported an increased duration (25 minutes to 109 minutes) and increased pulpal anesthesia success after administering another infiltration (25 minutes after initial injection) before the initial anesthesia diminished. The authors concluded that giving a repeat injection improved anesthetic success and augmented anesthetic duration. However, when comparing the reported results to Pabst et al (6) giving the injection earlier (at the 20th minute versus the 25th minutes) did not improve anesthetic success and prolong duration.

Dou et al (78) conducted a review of the literature on the efficacy of lingual infiltrations with 4% articaine and 2% lidocaine (1:100,000 epinephrine) for mandibular local anesthesia. Studies from Corbett et al (3), Nuzum et al (7), and Jaber et al (75) were included as part of the review. The review concluded no significant difference between the primary mandibular infiltrations (buccal alone versus buccal plus lingual). However,
the articles with articaine HCl as one of the study anesthetic formulations did
demonstrate improved anesthetic success for primary buccal and buccal plus lingual
mandibular infiltrations when compared to a lidocaine formulation primary buccal
infiltrations.

Nydegger (11) showed a higher success rate (55%)(no patient response to two
consecutive 80 readings with EPT) for a primary mandibular buccal infiltration with 1.8
mL of 4% articaine HCl with 1:100,000 epinephrine compared with 1.8 mL of 4%
prilocaine with 1:200,000 epinephrine (32%), and 4% lidocaine with 1:100,000
epinephrine (33%). The results indicate that the concentration of the anesthetic seems not
to be the deciding factor for increased efficacy for this injection type. Rather, the
molecular hydrogen bonding and folding capability of articaine, which allows for greater
penetration within the nerve increases its efficacy (49, 50).

Kwon et al (79) reported a total participant success rate (no patient response to
two consecutive 80 readings with EPT) for a primary mandibular buccal infiltration with
1.7 mL of 4% articaine HCl at 51.7% for the mandibular first molar. There were
significant gender differences in success reported. Female participants reported a success
of 76.9% for the mandibular first molar compared with the 31.3% success rate of the
male participants (P<0.05). Other studies have not reported a gender difference in
anesthetic success with primary mandibular buccal infiltrations using articaine
formulations. The duration of the anesthesia was not reported in discrete numbers, but
the teeth were tested for thirty minutes.

Pulpal anesthesia diminished rather quickly after plateauing, following the buccal
infiltration over the course of testing for all the studies cited in this section (1-11, 75-79).
Few studies reported discreet times for duration. Most duration of pulpal anesthesia data were reported graphically with peak success around 7-11 minutes following injection. The duration generally lasted around 20-30 minutes. The studies tested pulpal anesthesia for 30 to 120 minutes with an EPT. Pabst et al (6) and Dressman et al (10) reported an increased duration with the addition of supplemental buccal infiltrations at 25 and 20 minutes, respectively. The majority of studies reported that pulpal anesthesia was unable to be sustained for the full experiment time with predictable anesthetic success rate using primary mandibular buccal or labial infiltrations. This injection technique with articaine formulations was unable to provide 100% predictable anesthesia.

In summary, these aforementioned studies were all modeled in asymptomatic patients as a primary mandibular buccal infiltration injection. Success was defined as no patient response to two consecutive 80 readings with EPT. Articaine HCl with 1:100,000 epinephrine was reported to have a higher success rate than 2% lidocaine with 1:100,000 epinephrine, 4% lidocaine with 1:100,000 epinephrine, and 4% prilocaine with 1:200,000 epinephrine. Though a higher success was reported, duration (peak was around 7-10 minutes with a duration of 20-30 minutes) for most of the studies conducted diminished over the course of the study time (usually 60 minutes). A primary mandibular buccal infiltration injection with 4% articaine HCl with 1:100,000 epinephrine has not been predictable for pulpal anesthesia (1-11, 75-79).
Primary Mandibular Buccal Infiltration Injections with Articaine HCl –

Symptomatic Patients

Recently, several studies have reported research evaluating the primary mandibular buccal infiltration against the IANB for first and second molars with patients diagnosed with symptomatic irreversible pulpitis.

Aggarwal et al (80) reported on primary mandibular buccal infiltration plus lingual infiltration success (patient recorded ‘none or ‘mild’ on a Heft-Parker visual analog scale (VAS) for first and second mandibular molars for patients presenting with a symptomatic irreversible pulpitis at 27%. A 4% articaine with 1:100,000-epinephrine formulation was used. They analyzed various injections (Gow-Gates, Vazirani-Akinosi, and conventional IANB) along with the buccal plus lingual infiltration. The authors concluded that for teeth diagnosed with symptomatic irreversible pulpitis, no injection technique was adequate in acceptable pulpal anesthesia and success rates.

Poorni et al (81) evaluated success (no pain or weak/mild pain) during endodontic access preparation and pulp extirpation for the treatment of symptomatic irreversible pulpitis (SIP). The reported success rate for both second and first molars with a primary mandibular buccal infiltration with 1.8 mL of 4% articaine with 1:100,000 epinephrine was 69.2% for access preparation and 65.2% for pulp extirpation. The success rates do not warrant use of the primary mandibular buccal infiltration injection for predictable pain relief and pulpal anesthesia when patients with mandibular molars have been diagnosed with symptomatic irreversible pulpitis. However, the reported success rates are higher than the counterpart studies which reported success rates by 30-50% (80, 82). The authors included only patients in active moderate-to-severe pain with a prolonged
cold response; a diagnosis of symptomatic irreversible pulpitis. The success rates are unusually high for symptomatic teeth.

Monteiro et al (82) reported a 12% success rate (defined as no pain during emergency treatment) for a primary mandibular buccal infiltration using 1.8 mL of 4% articaine HCl with 1:100,000 epinephrine for mandibular second and first molars diagnosed with symptomatic irreversible pulpitis. The authors did not include mild pain scores using the Heft-Parker VAS as part of the definition of success. The success rate compared well with Aggarwal et al’s (80) reported 27% success rate. Poorni et al’s (81) reposted success rates similar to asymptomatic primary mandibular buccal infiltration studies’ success rates. Generally, symptomatic models report lower anesthetic success.

Success rates for pulpal anesthesia employing a primary buccal infiltration are lower in teeth diagnosed with SIP than asymptomatic teeth (80-82). The results of these studies conclude that attempts to anesthetize a mandibular molar diagnosed with SIP utilizing articaine with a buccal infiltration will provide few patients with acceptable anesthesia for endodontic therapy. Block injections, supplemental and other anesthetic modalities must be used in conjunction to provide better anesthetic success.

**Supplemental Mandibular Buccal Infiltration Injection with Articaine HCl after an Inferior Alveolar Nerve Block Injection – Asymptomatic Patients**

The IANB injection has been shown to confer inconsistent success with first molar pulpal anesthesia to perform restorative or endodontic procedures in asymptomatic patients. Several authors (83-91) reported a success (no patient response to two consecutive 80 readings with EPT) rate for the IANB injection to anesthetize the
mandibular first molar in asymptomatic models of 32% - 93%, evaluating several different anesthetic formulations and concentrations.

Further research has been conducted to determine if the success rate of first molar anesthesia could be increased by adding a supplemental mandibular buccal infiltration with 4% articaine HCl with 1:100,000 epinephrine to the IANB injection.

Haase et al (92) demonstrated that by adding a supplemental mandibular buccal infiltration of 1.8 mL 4% articaine HCl with 1:100,000 epinephrine formulation following an IANB injection (1.8 mL of the same formulation) increased the success (no patient response to two consecutive 80 readings with EPT) to 88% versus 71% for the supplemental mandibular buccal infiltration using 2% lidocaine with 1:100,000 epinephrine.

Kanaa et al (93) reported that supplementing an IANB injection of 2.0 mL of 2% lidocaine HCl with 1:100,000 epinephrine with a mandibular buccal infiltration of 2.0 mL of 4% articaine HCl 1:100,000 epinephrine increased pulpal anesthesia success (no patient response to two consecutive 80 readings with EPT) to 92% when compared to administering an IANB and dummy injection (56% success).

In summary, adding a supplemental mandibular buccal infiltration with 4% articaine HCl with 1:100,000 epinephrine after administering an IANB injection in asymptomatic patients, improved success in anesthetizing the mandibular first molar. However, anesthetic success was not 100% predictable.
Epinephrine Concentration

McEntire et al (9) reported that using an epinephrine concentration of 1:100,000 or 1:200,000 in a 1.8 mL 4% articaine formulation did not show a significant difference in their reported success rates (2 consecutive 80 readings with the pulp tester were obtained within 10 minutes of the initial injection). The success rates were 67% for the articaine formulation containing 1:100,000 epinephrine and 59% for the articaine formulation containing 1:200,000 epinephrine.

Kämmerer et al (94) investigated 4% articaine plain and with epinephrine at four different concentrations, (1) 1:100,000, (2) 1:200,000, (3) 1:300,000, (4) 1:400,000. They administered all anesthetic formulations as primary maxillary buccal infiltrations over an asymptomatic maxillary right central incisor. The authors reported no significant difference in onset time and duration of the different local anesthetic agents with epinephrine. The agent without epinephrine showed a statistically significant difference in the duration compared with all other anesthetic agents (23.5 minutes versus 55-62 minutes). The authors concluded that the use of epinephrine demonstrated benefits over the epinephrine-free agent.

Daubländer et al (95) reported 88% complete anesthesia (assessed by patient and provider using a verbal scale) for a variety of performed dental treatments using 1.3 mL of 4% articaine with 1:400,000 epinephrine as a primary mandibular buccal infiltration. The authors reported on anesthetic success, but never indicated how this was evaluated. The authors did not report the specific jaw location and numbers of the teeth receiving the reported treatment. Though the epinephrine concentration was reduced, the authors reported no decrease in efficacy with the lower concentration in regard to performing
dental treatment. They reported an average 7.3 minutes to anesthetic onset for all injections administered (IANB, IANB plus BI, and BI alone). Kämmerer et al (94) also reported that a 1:400,000 epinephrine concentration provided adequate anesthesia to perform the dental procedures.

In summary, epinephrine increases the duration of the anesthesia when using articaine formulations. The concentration of the epinephrine does not increase or decrease anesthetic success.

**Local Anesthetic Buffering**

A possible modality to improve local anesthetic efficacy has been proposed within medicine and dentistry - buffering local anesthetics. A common buffering agent is sodium bicarbonate. Sodium bicarbonate (NaHCO₃) is an alkalinizing agent used to treat various medical conditions such as metabolic acidosis, intoxications, urinary pH imbalances, hemolytic reactions, severe diarrhea, esophageal reflux, heartburn and indigestion. It is also part of the body’s natural buffering systems.

When sodium bicarbonate is added to a local anesthetic it will increase the formulation’s pH. As pH increases towards the anesthetic’s pKa, the amount of deionized, uncharged base molecules also increases. Theoretically, increasing the base molecule concentration by shifting the Henderson-Hasselbach equation (\( \text{pH} = \text{pK}_a + \log_{10}\left(\frac{[A^-]}{[HA]}\right) \)) to favor the base form of the anesthetic (higher physiologic pH closer to anesthetic pKa) will render greater amounts of anesthetic (base form) crossing the neuronal membrane and potentially providing anesthesia more effectively.
Several authors (13, 21, 26, 27, 41, 96, 97) have reported that buffering local anesthetics increases efficacy by increasing anesthesia success rates, decreasing onset time to anesthesia, and providing less painful injections. Research has been conducted in both medicine and dentistry to evaluate the potential benefit of anesthetic buffering.

**Buffering of Local Anesthetics in Medicine**

The medical literature is vast on the topic of buffering local anesthetics and opinions to its efficacy are varied. However, three recent literature reviews and meta-analysis (96-98) have compiled a comprehensive recommendation in regard to buffering local anesthetics for treatment and for injection pain reduction.

Davies et al (96) conducted a review of the literature in regard to the efficacy of buffering local anesthetics to reduce pain of infiltration injections. Of the 63 articles initially selected, 22 were included in the review. Only three (99-101) of the 22 included articles reported results that buffering local anesthetics had no effect upon pain of infiltration injection. Buffering the local anesthetic formulations did not decrease the pain reported by patients when buffered and non-buffered formulations were compared. Interestingly, the included study by Primosch and Robinson (99) was a dental model, which reported no difference in pain of injection when maxillary labial and palatal infiltration injections with lidocaine formulations were administered. The remaining articles provided impressive evidence for buffering local anesthetics before infiltration injections for procedures on the forearm, finger, hand, wrist, face, ears, skin, and toe. Buffered local anesthetics reduced pain of injection. The authors also concluded that buffering a local anesthetic did not adversely affect the onset, duration or quality of the
anesthetic block. In other words, injection pain was reduced while maintaining adequate onset and duration times, and the quality of the anesthesia remained at acceptable levels compared to a non-buffered local anesthetic (i.e. lidocaine, mepivacaine, etidocaine, bupivacaine). These three factors (onset time, duration time and quality) were not reported to have improved with the use of a buffered local anesthetic for infiltration.

Hanna et al (98) conducted a meta-analysis of the literature contained within the National Library of Medicine Pubmed’s database on intradermal infiltration anesthesia with buffered local anesthetics. Twelve articles met the inclusion criteria: double-blind, randomized controlled trials; use of a visual analog scale (VAS) to measure pain on infiltration of local anesthetics; and local anesthetics were buffered with sodium bicarbonate and compared with that of an unbuffered local anesthetic formulation. Lidocaine HCl was the most used anesthetic within the studies (11/12). When compared, the addition of sodium bicarbonate resulted in a statistically significant decrease in pain of injection with a lower weighted mean difference on the VAS. This suggests that the buffering of local anesthetics is associated with a decrease in pain of injection when compared with a nonbuffered local anesthetic.

Cepeda et al (97) conducted a systematic review of medical literature to determine the efficacy of buffering lidocaine anesthetic formulations to reduce pain of injection. The authors state that the review did not evaluate the quality of sensory blockade in relation to buffering the lidocaine formulations. Twenty-three studies met their review criteria: double-blinded, randomized controlled trials that compared pH-adjusted lidocaine with unadjusted lidocaine; evaluation of pain at the injection site, satisfaction and adverse events; and studies that enrolled healthy volunteers as patients were
excluded. The twenty-three studies involved 1,067 patients. The authors determined that by increasing the pH of lidocaine there was reduced pain and improved patient comfort and satisfaction, leading to a patient preference for buffered lidocaine. The authors recommended buffering the lidocaine formulation immediately before use.

Siler et al (102) and Gaggero et al (103) have described the effect of buffered local anesthetics upon the quality of anesthesia. Siler et al (102) investigated epidural anesthesia for arthroscopic surgery using a buffered and non-buffered 2% lidocaine HCl formulation. The 2% lidocaine was buffered with NaHCO₃ at a 10:1 ratio. Motor blockade and function were measured using the Bromage scale. Sensory analgesia was measured with sensation to pinpricks at 2-minute intervals for the first 30 minutes, then every 15 minutes thereafter. The authors reported that sensory analgesia, motor blockade, duration of procedures, time to anesthetic regression and actual lidocaine dosage was not statistically different for the two groups.

Gaggero et al (103) conducted a double-blind, randomized study to compare the effects of epidural anesthesia using 2% lidocaine HCl with and without buffering the formulation with sodium bicarbonate (NaHCO₃) at a 10:1 concentration. Grade of motor blockade, time to blockade, sensory level and time to regain sensory levels were recorded for both groups. There was no reported statistical difference between the buffered and non-buffered epidural anesthesia formulations for these metrics. Several other studies (104-108) also reported no difference on the quality of anesthesia when comparing local anesthetics administered as buffered and nonbuffered formulations.

Though these previous described studies showed no difference in buffering local anesthetics on the quality of epidural anesthesia, Capogna et al (109) reported an
enhanced effect upon the quality of anesthesia when a buffered anesthetic formulation was administered. The group reported that patients receiving 5 mL of 2% lidocaine with 1:200,000 epinephrine buffered with NaHCO₃ experienced less pain and required less intravenous analgesics during surgery when compared to a group receiving the same anesthetic without buffering with NaHCO₃.

**Buffering of Local Anesthetics in Dentistry**

The research in medicine demonstrated that pain of injection was reduced when buffered local anesthetics were used for infiltration anesthesia. The evidence for the quality of anesthesia being improved when using a buffered local anesthetic is still debated. Research within dentistry is also controversial as to its efficacy to modify pain of injection and quality of anesthesia in symptomatic and asymptomatic patient models.

Rood et al (110) investigated the anesthetic efficacy of buffering a 2% lidocaine with 1:80,000 epinephrine formulation to the same non-buffered lidocaine formulation for the extraction of maxillary teeth using labial and palatal infiltration injections. Patients (34 with inflammation) were included if they presented for the “extraction of periodontitic maxillary teeth associated with soft tissue inflammation.” Patients without inflammation were also included (40 without inflammation). Each patient received a labial infiltration of 1.0 mL of lidocaine formulation, and 0.5 mL of lidocaine formulation on the palate. The anesthetic formulation was either buffered or non-buffered. The buffered anesthetic had a final pH reported at 6.5. The method for buffering the anesthetic formulations was not reported, nor was the concentration of the final buffered anesthetic. Success was defined as absolute analgesia resulting in a completely painless
extraction, as assessed by provider and patient. Success for inflamed teeth, overall, was reported at 13% for the buffered formulation and 22% for the non-buffered formulation. The non-inflammation group had 100% success for both buffered and non-buffered groups. A significant difference for anesthetic success between inflamed and non-inflamed teeth was reported (P<0.0005). However, no significant difference for anesthetic success was reported between the buffered and non-buffered groups for inflamed or non-inflamed teeth (P>0.2).

Primosch and Robinson (99) evaluated pain of injection for primary maxillary labial and palatal infiltrations using buffered and non-buffered 2% lidocaine with 1:100,000 epinephrine. The buffered lidocaine formulation was composed of a 1:10 dilution of the 2% lidocaine with 1:100,000 with 1 mEq/mL of 8.4% sodium bicarbonate. Both buffered and non-buffered lidocaine formulations were tested for appropriate pH before administering the injections. Non-buffered lidocaine pH was acceptable between 3.3-5.5. The buffered lidocaine pH was acceptable between 7.2-7.4. The participants rated pain intensity on a 0 to 10 scale after receiving a series of four injections. The score of 0 represented no pain. The score of 10 represented the worst pain. The authors distinguished pain from needle penetration and formulation infiltration (deposition). Labial infiltrations were administered with 1.2 mL of lidocaine formulation for 20 seconds over the maxillary canine. Palatal infiltrations were administered with 0.3 mL of lidocaine formulation over 10 seconds. The mean pain intensity rating for non-buffered and buffered infiltrations was 2.6 and 1.6 out of 10, respectively. No significant difference was found between formulation type (P=0.365), and injection side (P=0.424). There was a significant difference between pain intensity for site of infiltration only, the
palatal injection being more painful (1.8 of 10) than the labial injection (3.1 of 10) (P=0.002). Buffering the anesthetic formulation did not affect pain of injection for primary maxillary labial and palatal infiltrations.

Bowles and coauthors (111) investigated three aspects of dental anesthetic buffering: (1) to determine the mean pH of 2% lidocaine with 1:100,000 epinephrine, (2) to determine the average volume to titrate a lidocaine formulation to a pH of 7, and (3) determine the pain of injection difference between regular versus buffered lidocaine formulations. The authors buffered the lidocaine formulation to pH = 7 through titration by adding 10 µL volumes of 1.0 N (8.4%) NaHCO₃. There were 38 participants in the study. Each participant received 1.0 mL of 2% lidocaine with 1:100,000 epinephrine as primary maxillary buccal infiltrations over teeth number 3 and 14. They received a different formulation at each tooth. The study was double-blinded and the patients informed the provider on which side, right or left, they experienced the more uncomfortable injection. The injections were repeated at a second appointment at least ten days from the previous appointment. The mean pH of non-buffered lidocaine was 4.5. The titration method used 100 µL of 1.0 N (8.4%) NaHCO₃ to reach pH 7. Forty-seven of the 73 respondents (64.4%) rated regular lidocaine as more painful than the buffered lidocaine (P<0.001). There was a significant difference for the reported pain of injection between the anesthetic formulations. The buffered lidocaine was reported as being less painful than the regular lidocaine.

Kashyap et al (112) investigated pain of injection and onset of anesthesia for buffered 2% lignocaine HCl with 1:80,000 epinephrine in a double-blind study. One hundred patients were admitted into the study and all received three standard nerve
blocks: IANB, lingual, and long buccal nerve injections. The patients were divided into non-buffered and buffered anesthetic groups, 50 patients per group. The lignocaine formulation was buffered using 3 mL of 8.4% NaHCO₃ formulation added to 30 mL of 2% lidocaine 1:100,000 resulting in a 1:10 dilution for the sodium bicarbonate. Injections were given using a 1½ inch 25-gauge needle. Pain of injection was assessed using a four-point visual analog scale (VAS): 0 = no pain, 1 = mild pain (pain reported only in response to questioning and without any behavioral signs), 2 = moderate pain (pain reported in response to questioning and accompanied by signs, or pain reported spontaneously without questioning), and 3 = severe pain (strong vocal response or response accompanied by grimaces, withdrawal of the arm, or tears). The authors did not report when pain of injection assessments were made. The patients described the pain of injection from the formulation deposition and not the needle insertion/penetration. Time of anesthesia onset was defined as the first sensation of tingling or numbness in the region being anesthetized. The time was calculated from needle withdrawal. Anesthesia was assessed with a straight probe inserted into the gingival sulcus of the anesthetized region. The time intervals at which the probe was used to assess anesthesia were not reported. The authors also did not report the definition of anesthetic success. The non-buffered lignocaine formulation pH was 3.05. The buffered lignocaine formulation pH was 7.38. The non-buffered lignocaine injection group reported pain upon injection for 78% (39/50) of injections. Eleven participants reported no pain, 31 mild pain, 8 moderate pain and 0 severe pain. The buffered lignocaine group all reported no pain (50/50 = 100%). There was a significant difference between the non-buffered and buffered lignocaine groups for pain of injection (P<0.0001). The mean time for onset of
anesthesia for the non-buffered and buffered lignocaine groups was 109.8 seconds and 34.4 seconds, respectively. Time to onset of anesthesia was significantly different between the non-buffered and buffered lignocaine groups (P<0.001). The onset of anesthesia in this study was fairly subjective. The methodology for collecting time interval data was not addressed by the authors. No pulpal anesthesia assessments were determined. Reader et al (73) concluded that soft tissue anesthesia is not a reliable assessment for pulpal anesthesia as patients with profound soft tissue and lip numbness have not achieved pulpal anesthesia (29, 83-86, 91, 92, 113, 114). Therefore this study can only be looked at for the success/efficacy of the anesthetic formulations for achieving soft tissue anesthesia, not pulpal anesthesia.

Al-Sultan et al (115) investigated the effect of buffered 2% lidocaine with 1:80,000 epinephrine for periapical surgery of maxillary teeth. Eighty patients were divided into two groups, buffered and non-buffered lidocaine formulations. A buccal and palatal infiltration of the pre-determined formulation was deposited slowly (no described time) over the root apices of the tooth to be surgically treated. Removing 0.1 mL of lidocaine from the anesthetic cartridge and replacing it with 0.1 mL of 8.4% sodium bicarbonate formulation into the cartridge prepared the buffered lidocaine before injection administration. The final formulation had a 18:1 NaHCO₃ dilution (5.5%). Pain of injection was evaluated by the patient using ‘no pain’, ‘mild’, ‘moderate’, or ‘severe intolerable’ pain as descriptors. The pain of operation was assessed using the Dobb and Devier System: Grade A – no pain, Grade B – mild to moderate pain, and Grade C – severe pain that was intolerable. The injection was assessed as a whole and not in phases. Onset of anesthesia was assessed with probing of the gingiva over the anesthetized area.
until patient reported elimination of the pain sensation. Frequency of gingival probing was not reported. The pH of the non-buffered lidocaine was 3.5. The pH of the buffered lidocaine was 7.2. The buffered lidocaine formulation was reported to have a lower pain rating for pain of injection (P=0.001). The non-buffered lidocaine group reported 5 patients experiencing no pain (12.5%), 12 patients experiencing mild pain (30%), 8 patients experiencing moderate pain (20%), and 15 patients experiencing severe pain (37.5%) during surgical treatment. The buffered lidocaine group reported 12 patients experiencing no pain (30%), 18 patients experiencing mild pain (45%), 8 patients experiencing moderate pain (20%), and 2 patients experiencing severe pain (5%) during treatment. The pain of operation was significantly different between the non-buffered and buffered lidocaine groups (P=0.001). A significant difference for onset of anesthesia was reported between the non-buffered and buffered lidocaine groups (no P-value recorded; t-test = 5.9). The mean onset of anesthesia for non-buffered and buffered lidocaine groups was 215 seconds and 33 seconds, respectively. The reported onset relied on patient responses and did not quantitatively report the interval for testing the soft tissue. Soft tissue anesthesia does not correspond to pulpal or periapical anesthesia, as 46 of the 80 patients in both anesthetic groups for operation pain reported mild-to-severe pain. This indicates that the surgical area for 57.5% of patient was not adequately anesthetized for the surgery.

In another study, Al-Sultan et al (116) investigated the pain of injection, onset of anesthesia and depth of anesthesia for buffered 2% lidocaine with 1:80,000 epinephrine for maxillary tooth extraction versus the same non-buffered formulation. Two hundred patients were enrolled in the study. Injections were administered as a posterior superior
alveolar (PSA) nerve block, labial infiltration, buccal infiltration and palatal infiltration depending upon the location of the maxillary tooth to be extracted. Removing 0.1 mL of lidocaine from the anesthetic cartridge and replacing it with 0.1 mL of 8.4% sodium bicarbonate formulation into the cartridge freshly prepared the buffered lidocaine formulation before injection administration. The final formulation had a 18:1 NaHCO₃ dilution (5.5%). Pain of injection was evaluated by the patient using ‘no pain’, ‘mild’, ‘moderate’, or ‘severe intolerable’ pain as descriptors. The pain during extraction was recorded by dentist observation as ‘no pain’, ‘mild pain’ and ‘moderate-to-severe pain’. The injection was assessed as a whole and not in phases. Onset of anesthesia was assessed with probing of the gingiva over the anesthetized area until patient reported elimination of the pain sensation. Frequency of gingival probing was not reported. The pH of the non-buffered lidocaine was 3.5. The pH of the buffered lidocaine was 7.2. Pain was assessed and recorded by asking the patient about pain following the injection. The pain of injection for the buffered lidocaine group was reported to be significantly different when compared with the non-buffered lidocaine group (P=0.002). They reported no significant difference for pain of extraction between the lidocaine formulation groups (P=0.64). The mean onset of anesthesia time for the non-buffered and buffered lidocaine groups was 182 seconds and 93 seconds, respectively. There was a significant difference between these mean onset times for the anesthetic formulation groups (no p-value reported; t-test = 5.62). The authors concluded that pain of injection decreased with the use of buffered lidocaine formulation for infiltration anesthesia. The reported onset was subjective to the patients’ responses and did not quantitatively report the interval for testing the soft tissue. Soft tissue anesthesia does not correspond to pulpal
anesthesia (29, 83-86, 91, 92, 113, 114). The dentist, via observations of the patient, recorded pain during extraction of the teeth. This method is very subjective and may not represent the pain experienced by the patient, as they did not participate in the assessment.

Gupta et al (28) investigated the effect of buffered 2% lignocaine with 1:80,000 epinephrine for extraction of maxillary teeth with periapical infections. Specifically, the authors were interested in the pH increase of a buffered formulation that potentially could increase the anesthetic effectiveness in localized dental infection. They compared a buffered formulation to same non-buffered anesthetic: 2% lignocaine with 1:80,000 epinephrine. Two hundred subjects enrolled in the study and were divided into two groups: non-buffered lignocaine group and the buffered lignocaine group. The non-buffered lignocaine formulation’s pH was 3.91. The buffered lignocaine formulation’s pH was 7.51. The buffered formulation was prepared fresh before each injection by mixing 1.3 mL of 7.4% sodium bicarbonate with 3.7 mL of the 2% lignocaine with 1:80,000 epinephrine formulation. Before extraction, a buccal infiltration of 1.0 mL of anesthetic formulation and a palatal infiltration of 0.5 mL was administered. Pain of injection was assessed using the Wong-Baker FACES VAS with markings from 0 to 5. Zero indicated ‘no pain’, while 5 indicated ‘hurts worst’. Onset of anesthesia was determined by probing the marginal gingiva 1 minutes after needle retrieval for the tooth anesthetized. The probing was repeated every 20 seconds until gingival anesthesia occurred. The extraction was rated by verbal response scale (VRS) for procedure acceptability and pain. ‘Acceptable’ and ‘unacceptable’ were the choices after the extraction for rating satisfaction. For pain, ‘less than expected’, ‘as expected as’, and
greater than expected’ were used to describe the extraction pain. This was determined by the patient. The mean onset time for the non-buffered and buffered lignocaine groups was 144 seconds and 72 seconds, respectively. The authors did not report if this difference was significant. The authors did not report the location, number, and diagnosis of teeth extracted in the study or what the pain ratings were associated with the teeth. They reported the average pain levels recorded and the sum of ranks for the VAS and visual response scale (VRS). No other statistical analysis was reported. These were not indicated as being significantly different between the non-buffered and buffered lignocaine groups. The significantly different statistic was the proportion of repeated injections for the non-buffered formulation (12) and buffered formulation (4). The authors concluded that the study confirmed the enhancement of buffered local anesthetics by decreasing time to onset of anesthesia (soft tissue), reduction of pain intensity during extractions, and decreasing total amount of anesthetic injections required for the procedure. This statement is speculative, as neither the average onset time (144 sec versus 72 sec) or the VAS pain ratings were found to be significantly different.

Whitcomb et al (29) evaluated buffered and non-buffered 2% lidocaine HCl with 1:100,000 epinephrine IANB injections for anesthetic success rate, pain of injection and onset of anesthesia. Forty adult subjects received both IANB injections with 2% lidocaine formulations with 1:100,000 epinephrine at separate appointments spaced at least one week apart. The lidocaine formulation was buffered using sodium bicarbonate to a final 1.0 mEq/mL concentration (0.17 mEq) of NaHCO₃ or a 10:1 dilution. A volume of 0.6 mL of 8.4% NaHCO₃ was added to a 3.0 mL of 2% lidocaine HCl with 1:100,000 epinephrine before injection. Pain of injection was assessed at three phases – needle
insertion, needle placement and formulation deposition. Pain of injection was assessed using a pain scale of 0 to 3. Zero equaled no pain; 1 indicated mild pain; 2 indicated moderate pain; and 3 equaled severe pain. Successful anesthesia was defined as two consecutive 80 reading with the EPT within 15 minutes of injection and sustained for 60 minutes. Onset of anesthesia was determined by testing the experimental teeth in 4-minute cycles with an EPT. Success for the first molar was reported as 58% for the non-buffered lidocaine formulation and 48% for the buffered lidocaine formulation. There was no significant difference between the anesthetic success between groups (P>0.05). No significant difference between the lidocaine formulations for pain of injection was reported for any phase of the injection.

Formulation deposition pain for non-buffered lidocaine was reported as 58% none, 35% mild and 8% moderate pain. Formulation deposition pain for buffered lidocaine was reported as 72% none, 25% mild, and 2% moderate pain. No severe pain ratings were reported for formulation deposition for either anesthetic group. No significant difference was reported for formulation deposition pain between the anesthetic groups. No significant differences were noted in onset times between the anesthetic groups (P>0.05). Mean onset times for the mandibular first molar for the non-buffered and buffered lidocaine groups were 5 minutes and 10 minutes, respectively. The authors concluded that a buffered 2% lidocaine HCl with 1:100,000 epinephrine did not significantly increase anesthetic success, decrease time of onset to anesthesia, and decrease injection pain for an IANB.
Recently a system for buffering commercially manufactured dental anesthetic cartridges was developed by Onpharma®, Inc., called Onset®. It has been commercially available since 2010. The company heralds the product to provide faster onset of anesthesia and a less painful injection through buffering the local anesthetic immediately before its use for a dental injection. The system provides a compact, portable way to buffer the commercially manufactured local anesthetic cartridges in dental offices and clinics. The system comes with a cartridge connector, a mixing pen, and a sodium carbonate formulation cartridge (Photo of system in Appendix A). The method for mixing is described in detail in Chapter 3: Methods and Materials of this thesis. As a simple overview, the dental cartridge connector is attached to the mixing pen. A sodium bicarbonate cartridge is inserted into the housing chamber of the mixing pen. The dial is attached to the other end of the mixing pen. A dental local anesthetic cartridge is attached to the cartridge connector. A specified volume of sodium bicarbonate to be injected into the dental cartridge is set with the dial. The local anesthetic formulation is buffered by adding sodium bicarbonate into the anesthetic cartridge with the push of the button on the end of the dial. The sodium bicarbonate volume added is 0.18 mL to a 1.8 mL cartridge. As the sodium bicarbonate enters the dental cartridge, the same volume of anesthetic is removed from the cartridge, resulting in the recommended 10:1 dilution of NaHCO₃. The anesthetic cartridge is removed from the connector and is ready for immediate use. The manufacturer recommends buffering the local anesthetic immediately before the injection is administered. With each sodium bicarbonate cartridge, 5-6 local anesthetic cartridges may be buffered. The sodium bicarbonate is replaced each day with a new
cartridge per manufacturer’s instruction for best results. The dental cartridge connector is disposable. The other components are disinfected between patients with a disposable disinfectant wipe. The pen may not be sterilized via autoclave (117).

Several peer-reviewed studies have investigated the Onset® system (27, 30, 31). Malamed et al (27) investigated the onset time to anesthesia and pain of injection using an IANB injection of 1.8 mL 2% lidocaine with 1:100,000 epinephrine buffered with NaHCO₃ to a 9:1 ratio. Part of their evaluation included the “alkalinization armamentarium” used for buffering the lidocaine formulations, and was their main stated purpose of the experiment. Using the Onset® buffering system, all buffered lidocaine formulations had 0.20 mL of 8.4% bicarbonate mixed into the 1.8 mL cartridge of lidocaine formulation. Simultaneously, 0.20 mL of lidocaine formulation was removed into a reservoir within the dental cartridge connector. The manufacturer’s recommended ratio of NaHCO₃ to local anesthetic was 10:1. This would indicate using a 0.18 mL volume for a 1.8 mL cartridge of local anesthetic formulation (117). It is unclear why the authors chose a 9:1 ratio. A trained person not participation in the testing appointment mixed the anesthetic cartridge. Twenty participants were enrolled in the study with a crossover design, each person serving as their own control. Each person sat for two appointments, each three weeks apart. The different lidocaine formulations were used at different appointments, but injections were given on the same side for each appointment. Injection pain was measured with a 100-mm VAS. The patient was informed when the formulation deposition phase of the injection started and was calibrated not to record pain of injection for needle penetration or insertion. Patients assessed pain after the injection was given (needle retrieval from tissue) by marking ‘X’
at the level of pain along the VAS. Onset to anesthesia was determined by testing the tooth with a cotton pellet sprayed with refrigerant. Cold testing began when the patient raised their hand indicating that they felt tingling or a numb sensation in their lower lip. Cold testing was repeated every 15 seconds until the patient had a loss of sensation. Loss of sensation was confirmed by EPT (80/80 reading). If confirmed with EPT, the time noted for loss of sensation to the cold test was recorded as the onset for pulpal anesthesia. If not confirmed with EPT, the EPT testing continued every 30 seconds until loss of sensation occurred. The time of loss of sensation to EPT was then used for time to pulpal anesthesia. Failure of anesthesia was determined if the patients had no loss of sensation to cold or EPT within 15 minutes of the patient raising their hand. The authors reported not using these patient data, and deemed them anatomical misses, even though lip tingling or numbness was achieved. One injection was deemed an anatomical miss. The duration of anesthesia was not measured. Anesthetic success for IANB for either lidocaine formulation was never defined or reported. The authors reported that 72% (13/18) of the participants rated the buffered lidocaine IANB injection as a more comfortable injection while 11% (2/18) rated the non-buffered lidocaine IANB injection as the more comfortable injection. The remaining 17% (3/18) of patients reported no preference to either formulation. The authors reported the difference between patient preferences for buffered or non-buffered lidocaine formulation was statistically significant (P=0.013). This was determined using a repeated measures test. Forty-four percent of the patients receiving the buffered lidocaine IANB injection rated the injection pain as zero ("no pain") on the 100 mm VAS. This was compared to 6% of the patients who received the non-buffered lidocaine IANB injection. They also reported 71% of
patients receiving the buffered lidocaine formulation achieved pulpal anesthesia in less than two minutes following the patient indicated onset of lip tingling or numbness. The mean time from needle retrieval to the patient indicating their onset of lip tingling or numbness was not reported. The non-buffered lidocaine injection group achieving pulpal anesthesia in less than two minutes was only 12%. A repeated measures test determined this difference to be significant (P<0.001). The mean onset to anesthesia for non-buffered and buffered lidocaine groups were 6 minutes and 37 seconds and 1 minute and 51 seconds, respectively. The mean onset time was significantly different using the paired Wilcoxon ranked-sign test (P<0.001). The determination of onset time by the authors was fairly subjective. Patient variation for lip anesthesia onset exists (83-91). The time between the end of the injection and the beginning of alteration to lip sensation was not recorded or factored into the time to anesthesia onset calculations for the buffered or non-buffered formulations. The authors concluded that by precisely buffering the lidocaine formulation before an IANB injection, onset of analgesia and pain of injection were significantly faster and less painful when compared to a non-buffered formulation. They concluded that patients are seven times more likely to report a pain free injection with a buffered formulation than with non-buffered formulations.

Balasco et al (31) reported on a buffered 2% lidocaine with 1:100,000 epinephrine for a primary maxillary or mandibular labial or buccal infiltration injection, given prior to an incision and drainage procedure in patients with a diagnosis of pulpal necrosis and acute apical abscess. Eighty (80) patients were enrolled in the study that had a tooth diagnosed as pulpal necrosis with acute apical abscess. Patients rated their current pain on a 170 mm Heft-Parker VAS. Using the Onset® buffering system, all buffered
lidocaine formulations had 0.18 mL of 8.4% bicarbonate mixed into the 1.8 mL cartridge of lidocaine formulation. Simultaneously, 0.18 mL of lidocaine formulation was removed into a reservoir within the dental cartridge connector. The final NaHCO₃ dilution to lidocaine formulation was 10:1. Each patient received two labial or buccal infiltration injections mesial and distal to the swelling with the same lidocaine formulation, either buffered or non-buffered. Pain of injection was assessed upon needle insertion, placement and formulation deposition using the Heft-Parker VAS at each phase. After ten minutes post-injection, the incision and drainage procedure was performed and pain of the procedure was also assessed via a Heft-Parker VAS for the incision, drainage and dissection phases of the procedure. Success for the procedure was defined as the patient pain rating of no pain to mild pain (0 to less than or equal to 54 mm on the VAS). There was no reported significant difference between the non-buffered and buffered lidocaine formulations for all three phases of the injection and all three phases of the incision and drainage procedure (P>0.05). The mean pain ratings for mesial and distal non-buffered lidocaine formulation deposition pain were 58 mm and 54 mm, respectively. The mean pain ratings for mesial and distal buffered lidocaine formulation deposition pain were 65 mm and 53 mm, respectively. The mean pain rating for non-buffered lidocaine incision pain was 104 mm. The mean pain rating for buffered lidocaine incision pain was 80 mm. The mean pain rating for non-buffered lidocaine drainage pain was 103 mm. The mean pain rating for buffered lidocaine drainage pain was 86 mm. The mean pain rating for non-buffered lidocaine dissection pain was 113 mm. The mean pain rating for buffered lidocaine dissection pain was 97 mm. Patients experienced moderate-to-severe pain for the injection and the incision and drainage procedure. The pH was measured for the non-
buffered and buffered lidocaine formulations. The average pH for each formulation was 6.97 (buffered lidocaine) and 4.6 (non-buffered lidocaine). The authors concluded that there was no difference between the lidocaine formulations for the injection pain and incision and drainage procedure. Buffering the local anesthetic did not decrease injection pain or procedural pain reported by patients.

Hobeich et al (30) investigated the efficacy of buffering a 2% lidocaine with 1:100,000 epinephrine formulation with different sodium bicarbonate concentrations. Thirty subjects participated in the study. All injections given were primary maxillary labial infiltrations over the canine. Each subject received three injections at three different appointments on the same side (same canine infiltration injection) with three different lidocaine formulations. Each appointment was at least one week apart. The three formulations were 1.8 mL 2% lidocaine with 1:100,000 epinephrine, 1.8 mL 2% lidocaine with 1:100,000 epinephrine buffered at 5% NaHCO₃, and 1.8 mL 2% lidocaine with 1:100,000 epinephrine buffered at 10% NaHCO₃. Both buffered lidocaine formulations were mixed with the Onset® system just prior to the infiltration of the formulation. The 5% sodium bicarbonate buffered lidocaine formulation was prepared with 0.9 mL of 8.4% bicarbonate mixed into the 1.8 ml cartridge of lidocaine formulation. The 10% sodium bicarbonate lidocaine formulation was prepared with 0.18 mL of 8.4% bicarbonate mixed into the 1.8 mL cartridge of lidocaine formulation. A 1¼” 30-gauge needle was used for all injections. The anesthetic was delivered over one minute (1.8 mL/min). Injection pain was rated using a Heft-Parker VAS (no length specified) for both needle penetration and formulation deposition. Patients rated the injection pain immediately after receiving the injection. Onset of anesthesia was defined
by testing the study tooth (canine) with an EPT every 30 seconds until pulpal anesthesia was achieved (80 reading). No measure of the duration of anesthesia was reported or discussed. Pulpal anesthesia success was defined by 2 consecutive maximum readings (80) within ten minutes of the infiltration injection. The authors reported 100% of study participants achieved pulpal anesthesia. The authors did not specify which anesthetic formulation this success was reporting upon. The assumption is that all anesthetic formulations produced pulpal anesthesia (according to their definition) due the authors not distinguishing between the groups investigated. The average time to pulpal anesthesia onset was 119 seconds for the non-buffered group, 116 seconds for the 5% NaHCO₃ group, and 121 seconds for the 10% NaHCO₃ group. No significant difference was reported between any of the groups for onset of anesthesia (P>0.05). The authors also reported no significant difference between any of the three anesthetic groups for pain of needle penetration or formulation deposition (P>0.05). The mean needle penetration rating for each lidocaine formulation was: non-buffered – 34 mm; 5% buffered – 40 mm; 10% buffered – 40 mm. The mean formulation deposition pain rating for each lidocaine formulation was: non-buffered – 39 mm; 5% buffered – 45 mm; 10% buffered – 42 mm. The authors concluded that neither a 5% or 10% NaHCO₃ buffered lidocaine formulation decreased pain of injection (needle penetration or formulation deposition) and onset to pulpal anesthesia when compared to a non-buffered lidocaine formulation.

**Purpose**

Research on mandibular buccal infiltration injections has demonstrated limited success (1-4, 6-11, 75-77, 79, 81, 92, 93, 118-127). Both in medicine and dentistry, the
buffering of local anesthetic formulations have been shown to improve anesthetic success (27, 90, 96, 97). Nydegger (11) showed that articaine and its specific properties are the key to the mandibular infiltration injection’s success using articaine and not the concentration of this specific local anesthetic. Thus by buffering a 4% articaine HCl with 1:100,000 epinephrine formulation with sodium bicarbonate, we may be able to demonstrate an increased success rate, a decrease in pain of injection and a faster onset of anesthesia when compared to the same non-buffered formulation.

No objective study has addressed the success rate of buffering articaine in a mandibular primary buccal infiltration of the first molar. Therefore, the purpose of this prospective randomized, double-blind, crossover study was to compare the degree of pulpal anesthesia obtained with a buffered 4% articaine with 1:100,000 epinephrine formulation versus a non-buffered 4% articaine with 1:100,000 epinephrine formulation as a primary infiltration in the mandibular first molar. We also recorded the pain of injection and postoperative pain to determine similarity or difference in comparison to past research.
Chapter 3

Materials and Methods

Eighty adult subjects participated in this study. A clinical examination of each subject showed that all study teeth, mandibular first molars and canines, were free of caries, large restorations, root canal therapy and periodontal disease. All teeth had no histories of trauma or dental sensitivity. The subjects were 18 - 65 years of age and medical history was evaluated. All subjects were normal healthy patients with no systemic diseases. Study subjects were excluded if pregnant, nursing, currently using pain altering medications (opioid analgesics, NSAID analgesics, tricyclic antidepressants, dopamine or serotonin, migraine medications, etc.) and/or reported an allergy to local anesthetics. The principal investigator periodically monitored the progress of the study to ensure proper protection of the subjects. The status of actively participating study subjects was assessed to ensure that treatment protocols and privacy policies were being provided (Appendix A - Research protocol and HIPAA Form). Study medications were kept in a locked cabinet accessible by the supervising investigator. The Ohio State University Human Subjects Review Committee approved the study. Written and verbal informed consent was obtained from each study participant (Appendix B).

The eighty (80) blinded subjects received two mandibular buccal infiltration injections of the first molar with either a cartridge of 64.8 mg articaine with 16.2 µg
epinephrine (Septocaine, Dentsply Pharmaceutical, York, PA) buffered with 0.18 mEq sodium bicarbonate or a cartridge of unaltered 72 mg articaine with 18 µg epinephrine at two separate appointments spaced at least two weeks apart, in a crossover design. With the crossover design, there were a total of 160 infiltration injections administered. Each subject served as his or her own control. An equal number of infiltration injections were administered on the right side and the left side. The same side randomly chosen for the first infiltration injection was used again for the second injection. An equal number of patients were male and female; 40 for each sex. The mandibular first molar was chosen as the test tooth for this study. The contralateral canine was used as the un-anesthetized control to ensure that the electric pulp tester (EPT) (Kerr, Analytic Technology Corp., Redmond, WA) was operating properly. The contralateral canine was also used to ensure that the subject was responding appropriately to EPT testing.

Before the experiment, six-digit numbers were acquired using a random number generator (Random Integer Generator, Random.org). Each number was randomly assigned sex, injection side and type of formulation for the first infiltration injection. A trained dental assistant loaded the appropriate cartridge for each appointment therefore blinding the anesthetic formulations administered. The expiration dates on the cartridges were checked before use to ensure they were not expired. The random numbers, date, injection side, appointment number and research assistant name were recorded on the data collection sheets to blind the experiment and ensure privacy policy adherence.

At the beginning of each appointment and before any injections were given, the experimental tooth and control contralateral canine were tested three times with the EPT to record baseline vitality. The experimental tooth (first molar) and contralateral canine
were isolated and dried with cotton rolls. The study subject was given the lip clip to hold to complete the testing circuit. After applying toothpaste (Crest, Proctor & Gamble, Cincinnati, OH) as a conduction medium, the EPT probe tip was placed midway between the gingival margin and the occlusal or incisal edge of the tooth. The current rate was set to increase from no output (0) to the maximum output (80) in 25 seconds. The subject indicated sensation in the tooth from the EPT by raising their hand or releasing the hand clip. The number associated with the initial sensation was recorded. Trained research personnel performed all pre-injection and post-injection tests. The trained research assistants were dental or hygiene students specifically trained in conducting this clinical trial.

A Heft-Parker 170-mm visual analog scale (VAS) was used in this study (Appendix B). The subjects placed a mark on the scale, which best described their pain level during the injection. To analyze and interpret the data, the VAS was divided into four categories. No pain corresponded to 0 mm on the scale. Mild pain was defined as greater than 0 mm and less than or equal to 54 mm. Mild pain includes the descriptors of “faint”, “weak”, and “mild” pain. Moderate pain was defined as greater than 54 mm and less than 114 mm with the descriptor of “moderate”. Severe pain was defined as equal to or greater than 114 mm. Severe pain includes the descriptors of “strong”, “intense” and “maximum possible”. Before each injection, subjects were shown the VAS used to rate the three stages of the infiltration injection. The subjects were told to mark the form using a vertical line anywhere on the VAS (not only on the descriptor tags). The subjects were also instructed to remember their pain assessment after each injection phase and to place the rating marks after the injection was completed.
For the buffered articaine formulation, each local anesthetic cartridge was buffered with an 8.4% sodium bicarbonate formulation to produce a final amount of 0.18 mEq of sodium bicarbonate. The buffered anesthetic formulation was prepared by a trained dental assistant not involved in pulp testing or administration of the anesthetic formulations.

Buffered local anesthetic formulation preparation was accomplished using the Onpharma® Onset® system (Onpharma Inc., Los Gatos, CA). The system is comprised of a mixing pen, an anesthetic cartridge connector and a sodium bicarbonate cartridge (Appendix C – System photo and part labeling). The mixing pen has two ends – the sodium bicarbonate chamber and volume dial with a rod piston. When indicated, the trained dental assistant buffered the anesthetic using the following protocol. The mixing pen was oriented with the sodium bicarbonate chamber to the left and the black volume dial to the right. The local anesthetic connector was removed from its packaging and inserted into the mixing pen on the left end of the sodium bicarbonate chamber. The black volume dial was unscrewed from the mixing pen. A sodium bicarbonate cartridge was inserted into the sodium bicarbonate chamber. Before replacing the volume dial the rod piston was reset by manually twisting the red reset mechanism counter-clockwise until it was flush with the volume dial. The volume dial was screwed back onto the pen. The rod piston was primed by repeatedly twisting the volume dial and pushing the dispensing button until the rod piston contacted the sodium bicarbonate cartridge stopper. The local anesthetic cartridge was then loaded into the anesthetic connector. The volume dial was turned to number 18 which dispensed 0.18 mL of 8.4% sodium bicarbonate. This followed the manufacturer’s recommended 10:1 anesthetic-to-bicarbonate
formulation ratio. The dispensing button was pushed gently, injecting the sodium bicarbonate into the local anesthetic cartridge. When the dispensing button is pushed the sodium bicarbonate influx pressure pushes the equivalent 0.18 mL of local anesthetic from the anesthetic cartridge into a receiving chamber in the anesthetic connector. The anesthetic cartridge was then removed from the connector and loaded into a standard aspirating syringe with a 27 gauge, 1¼ inch needle (Monoject; Sherwood Medical, St. Louis, MO). The buffered anesthetic formulation was administered immediately after mixing.

A volume of approximately 0.1 mL of 20% benzocaine topical anesthetic gel (Patterson Dental Supply, Inc., St. Paul, MN) was placed at the infiltration injection site of the mandibular first molar for 60 seconds using a cotton tip applicator. A standard buccal mandibular infiltration injection was administered, the target site for the injection being the level of the mandibular first molar root apices. The 27-gauge needle was placed into the alveolar mucosa (needle insertion phase) and advanced until the needle was estimated to be at or just superior to the apices of the tooth (needle placement phase). Needle placement phase occurred over two to three seconds. The anesthetic formulation was then deposited over a one-minute period (formulation deposition phase). One research investigator gave all injections. The needle bevel was not placed in any particular direction.

At 30 seconds after the infiltration, the first mandibular molar was tested using the EPT as described previously. The numeric reading on the EPT was recorded by the study subject on an EPT values form (Appendix D). At 60 seconds, the first mandibular molar was again tested in the same manner. This cycle of testing was repeated every 30
seconds for 5 minutes. After 5 minutes, testing was changed to 1-minute intervals for a total testing time of 60 minutes. At every fifth-minute cycle, the control tooth (the contralateral canine) was tested using the EPT. After every 4th cycle of pulp testing the contralateral canine was tested with the EPT tip disconnected to test the reliability of the subject.

No response from the subject at the maximum output (80 reading) of the electric pulp tester was used as the criterion for pulpal anesthesia. Anesthesia was considered successful when two consecutive 80 readings were obtained within the 60 minutes following injection. Anesthesia was considered a failure if the subject never achieved two consecutive 80 readings during the 60 minutes. Onset of pulpal anesthesia was recorded as the first of two consecutive 80 readings. Duration of pulpal anesthesia was recorded from the first of the two consecutive 80 readings until the last reading of the final two consecutive 80 readings.

Comparisons between the two anesthetic formulations for anesthetic success, failure, and incidence of pulpal anesthesia (percentage of 80 readings across time) was analyzed non-parametrically using Exact McNemar tests with P-values adjusted using the Step-down Bonferroni method of Holm. Between anesthetic formulation differences in pain ratings for needle insertion, needle placement, formulation deposition, and onset times were analyzed using repeated measures analysis of variance. Comparisons were considered significant at P<0.05.

With a non-directional alpha risk of 0.05 and assuming a total proportion of discordant pairs of 0.5, a sample size of 75 subjects was required to demonstrate a difference of ±20 percentage points in anesthetic success with a power of 0.82. With a
non-directional alpha risk of 0.05 and assuming a standard deviation of 27.4, a sample size of 75 subjects provided a power of 0.82 to demonstrate a difference ± 10 points on the visual analogue scale. However, because of potential withdrawal by some subjects, we set the number of participants to 80. The power analysis was determined before the clinical data collection began to ensure appropriate sample size.
Chapter 4

Results

Eighty subjects participated in this study ranging in age from 21 to 33 years. There were 42 males and 38 females. The average age of the participants was 25.3 years (Table 1).

The mean VAS pain ratings for needle insertion for buffered articaine and non-buffered articaine formulations by gender were 34.6±27.1 mm (female buffered), 36.3±26.9 mm (female non-buffered), 27.0±18.8 mm (male buffered), and 27.7±20.8 mm (male non-buffered) (Table 2). There was no significant difference between anesthetic formulation groups for needle insertion pain by gender (P=1.000). The means for both anesthetic groups were within the ‘mild’ category range. For the female buffered articaine group, 24 participants (63.2%) reported ‘none’ to ‘mild’ pain, and 14 participants (36.8%) reported ‘moderate’ to ‘severe’ pain. For the female non-buffered articaine group, 29 participants (76.3%) reported ‘none’ to ‘mild’ pain, and 9 participants (23.7%) reported ‘moderate’ to ‘severe’ pain. For the male buffered articaine group, 36 participants (85.7%) reported ‘none’ to ‘mild’ pain, and 6 participants (14.3%) reported ‘moderate’ to ‘severe’ pain. For the male non-buffered articaine group, 35 participants (83.3%) reported ‘none’ to ‘mild’ pain, and 7 participants (16.7%) reported ‘moderate’ to ‘severe’ pain. There were no participants who reported ‘severe’ pain for needle insertion.
for either gender or anesthetic group (Table 3). The mean VAS pain ratings for needle placement for buffered articaine and non-buffered articaine formulations by gender were 47.5±30.4 mm (female buffered), 50.4±33.2 mm (female non-buffered), 31.2±24.0 mm (male buffered), and 33.1±23.2 mm (male non-buffered (Table 2). There was no significant difference between anesthetic formulation groups for needle placement pain by gender (P=1.000). The means for both anesthetic groups were within the ‘mild’ category range. For the female buffered articaine group, 24 participants (63.2%) reported ‘none’ to ‘mild’ pain, and 14 participants (36.8%) reported ‘moderate’ to ‘severe’ pain. For the female non-buffered articaine group, 23 participants (60.5%) reported ‘none’ to ‘mild’ pain, and 15 participants (39.5%) reported ‘moderate’ to ‘severe’ pain. For the male buffered articaine group, 31 participants (73.8%) reported ‘none’ to ‘mild’ pain, and 11 participants (26.2%) reported ‘moderate’ to ‘severe’ pain. For the male non-buffered articaine group, 32 participants (76.2%) reported ‘none’ to ‘mild’ pain, and 10 participants (23.8%) reported ‘moderate’ to ‘severe’ pain. There were no participants who reported ‘severe’ pain for needle insertion for either male anesthetic group. One participant for each anesthetic group reported ‘severe’ pain for needle placement (1.3%), both were female (Table 3).

The mean VAS pain ratings for formulation deposition for buffered articaine and non-buffered articaine formulations by gender were 49.6±26.4 mm (female buffered), 58.2±32.9 mm (female non-buffered), 40.6±26.6 mm (male buffered), and 39.9±25.9 mm (male non-buffered (Table 2). There was no significant difference between anesthetic formulation groups for formulation deposition pain by gender (P=1.000). The means for both anesthetic groups were within the ‘mild’ category range. For the female buffered
articaine group, 22 participants (57.9%) reported ‘none’ to ‘mild’ pain, and 16 participants (42.1%) reported ‘moderate’ to ‘severe’ pain. For the female non-buffered articaine group, 19 participants (50.0%) reported ‘none’ to ‘mild’ pain, and 19 participants (50.0%) reported ‘moderate’ to ‘severe’ pain. For the male buffered articaine group, 30 participants (71.4%) reported ‘none’ to ‘mild’ pain, and 12 participants (28.6%) reported ‘moderate’ to ‘severe’ pain. For the male non-buffered articaine group, 31 participants (73.8%) reported ‘none’ to ‘mild’ pain, and 11 participants (26.2%) reported ‘moderate’ to ‘severe’ pain. There were no participants who reported ‘severe’ pain for needle insertion from either male anesthetic group. Two participants in the female non-buffered articaine group reported ‘severe’ pain for formulation deposition (Table 3).

Female participants reported more pain for both anesthetic formulations at each phase of the injection. Female participants rated their formulation deposition pain in the ‘moderate’ category (>54 mm and <114 mm) for non-buffered articaine.

Anesthetic success was defined as two consecutive maximum readings (80/80) during the 60 minute testing period using an electric pulp tester (EPT) on the test tooth (mandibular first molar). The mandibular first molar success rates were 65.0% for non-buffered articaine, and 71.2% for buffered articaine. There was no significant difference between non-buffered articaine and buffered articaine for anesthetic success (P=0.3018) (Table 6).

Mean onset times for both anesthetic formulations can be seen on Table 7. The mean onset time (minutes) for the mandibular first molar was 5.4±5.9 for non-buffered articaine, and 5.9±5.9 for buffered articaine. There was no significant difference between
mean onset times (minutes) for non-buffered articaine and buffered articaine anesthetic formulation groups (P=1.000). Mean duration times for both anesthetic formulations can be seen in Table 7. The mean duration time (minutes) for the mandibular first molar was 41.7±13.4 for non-buffered articaine, and 42.4±16.8 for buffered articaine. There was no significant difference between mean duration times (minutes) for non-buffered articaine and buffered articaine anesthetic formulation groups (P=1.000).

The mean postoperative VAS pain ratings for Day 0, Day 1, Day 2 and Day 3 are reported in Table 8. There were no significant differences between either anesthetic formulation by gender for Day 0. The mean postoperative VAS pain ratings for female buffered and non-buffered groups for Day 1, Day 2, and Day 3 were: Day 1 - 55.4±32.1 mm (buffered articaine), and 30.0±26.9 mm (non-buffered articaine); Day 2 - 46.0±30.7 mm (buffered articaine), and 24.1±26.5 mm (non-buffered articaine); and Day 3 - 33.1±26.9 mm (buffered articaine), and 12.9±17.9 mm (non-buffered articaine). The female buffered articaine formulation had the most painful rating on postoperative Day 1. There was a significant difference between female buffered and non-buffered articaine groups for Day 1, Day 2, and Day 3 (0.0079, 0.0038, 0.0000, respectively). The buffered articaine formulation had more painful ratings than the non-buffered formulation for these time periods. There were no significant differences between mean postoperative VAS pain ratings for male articaine groups by gender for Day 1, Day 2, and Day 3. The mean postoperative VAS pain ratings for both each anesthetic groups by day were within the ‘mild’ category range, except for the female buffered articaine for Day 1 (moderate category). Pain generally decreased from Day 0 through Day 3 for both anesthetic formulation groups and for gender (Table 8).
A summary of VAS pain ratings for female buffered articaine for each postoperative day can be found on Table 8. The mean pain ratings were 51.0±31.6 mm (Day 0), 55.4±32.1 mm (Day 1), 46.0±30.7 mm (Day 2), and 33.1±26.9 mm. For Day 0, 23 participants (58.3%) reported ‘none’ to ‘mild’ pain and 15 participants (41.7%) reported ‘moderate’ to ‘severe’ pain. For Day 1, 19 participants (52.8%) reported ‘none’ to ‘mild’ pain and 17 participants (47.2%) reported ‘moderate’ to ‘severe’ pain. For Day 2, 21 participants (58.3%) reported ‘none’ to ‘mild’ pain and 15 participants (41.7%) reported ‘moderate’ to ‘severe’ pain. For Day 3, 24 participants (66.7%) reported ‘none’ to ‘mild’ pain and 12 participants (33.3%) reported ‘moderate’ to ‘severe’ pain. There were 2 participants who reported ‘severe’ pain for Day 0/1 for the female buffered articaine group (Table 9).

A summary of VAS pain ratings for female non-buffered articaine for each postoperative day can be found on Table 8. The mean pain ratings were 34.0±25.2 mm (Day 0), 30.0±26.9 mm (Day 1), 24.1±26.5 mm (Day 2), and 12.9±17.9 mm. For Day 0, 25 participants (69.4%) reported ‘none’ to ‘mild’ pain and 11 participants (30.6%) reported ‘moderate’ to ‘severe’ pain. For Day 1, 27 participants (75%) reported ‘none’ to ‘mild’ pain and 9 participants (25%) reported ‘moderate’ to ‘severe’ pain. For Day 2, 31 participants (86.1%) reported ‘none’ to ‘mild’ pain and 5 participants (13.9%) reported ‘moderate’ to ‘severe’ pain. For Day 3, 34 participants (94.4%) reported ‘none’ to ‘mild’ pain and 2 participants (5.6%) reported ‘moderate’ to ‘severe’ pain. There were no participants who reported ‘severe’ pain for any postoperative day for the female non-buffered articaine group (Table 9).
There was a significant difference between female buffered and non-buffered articaine groups for the mean VAS postoperative pain ratings for Day 1, Day 2, and Day 3 (P=.0079, P=0.0038, and P=0.0000, respectively) (Table 8).

A summary of VAS pain ratings for male buffered articaine for each postoperative day can be found on Table 8. The mean pain ratings were within the ‘mild’ category for postoperative pain for all day categories. There were no male participants who reported ‘severe’ pain for any postoperative day for buffered articaine (Table 9).

A summary of VAS pain ratings for male non-buffered articaine for each postoperative day can be found on Table 8. The mean pain ratings were within the ‘mild’ category for postoperative pain for all day categories. There were no male participants who reported ‘severe’ pain for any postoperative day for non-buffered articaine (Table 9). There was no significant difference between male buffered and non-buffered articaine groups for mean VAS postoperative pain ratings for any postoperative day (P>0.05).

A summary of postoperative complications by articaine formulation for each postoperative day can be seen in Table 10. Soreness at the injection site and surrounding tissue (i.e. muscles, mucosa, gingiva, etc.) were the most common reported postoperative complications for each anesthetic formulation. Subjective swelling at the injection site was the second most common reported postoperative complication for each anesthetic formulation. Prolonged numbness and tingling, headache, light-headedness and dizziness, nausea, bruising, and akinesia were also reported as complications. Generally, both buffered and non-buffered articaine formulations had equal amount of postoperative complications. The incidence of subjective swelling was slightly higher for the buffered articaine formulation for all postoperative time periods (Day 0 – Day 3).
significant difference between buffered and non-buffered articaine formulations for tenderness and subjective swelling on Day 1, Day 2, and Day 3 (Table 11).

A summary of the measured pH values by articaine formulation is presented in Table 12 and Table 13. The mean pH for buffered articaine over a fifteen-minute period was 7.59 (N=5). The mean pH for buffered articaine at the initial time period was 7.54 (N=5). The mean pH for non-buffered articaine was 4.76 (N=10). The difference in pH were significantly different (P=0.0000).
Chapter 5

Discussion

Eighty adult subjects participated in this study, ranging in age from 20 to 33 years. There were 42 males and 38 female. The average age of all participants was 25.3 years, with an average female participant age of 25.2 years and an average male participant age of 25.5 years (Table 1).

Participants older than 65 years of age were excluded from this study due to shorter anesthetic onset time compared to a younger patient group for infiltration anesthesia, as reported by Nordenram et al (128). Only patients under 65 years of age were admitted to eliminate this possible confounder and its effects on the results of the study. Participants under the age of 18 were also excluded from this study. By law, minors (any person younger than 18 years old) are not able to give their own informed consent (Appendix E). By excluding these two groups (persons younger than 18 years old or older than 65 years old), the results cannot be extrapolated with certainty to these populations.

Similar numbers of men and women were admitted to this study. The study sample was designed to mimic the general population as far as general gender percentages. Men and women also tend to report pain differently. Several investigations have documented this tendency (129-131). Liddell et al (129) demonstrated that women
reported that they would try to avoid pain more than men, accept pain less than men, and fear pain more than men. Keogh et al (130) reported that males were more tolerant to cold pressor pain than females and reported less sensory pain. In a study investigating thermal pain thresholds between males and females, Fillingim et al (131) showed that females reported a significantly greater sensitivity to thermal stimuli than males. They also concluded that evaluating pain clinically might only be relevant for female participants. Thus if a disproportionate number of females to males were admitted to the study it may have affected the reporting and analysis for pain of injection and postoperative pain with a bias to either gender. By using relatively equal numbers of male to female participants the sample population resembles the general U.S. populous for gender (U.S. population by percentage: Female – 50.8%, Male – 49.2% (132).

Participants who enrolled in this study were required to complete a written health history (Appendix D) followed by verbal questioning about their current health status. Participants were excluded from the study if they had any known allergy to local anesthetics, had a significant medical history (ASA Class II or higher), were currently taking any medications that may alter anesthetic assessment (over-the-counter (OTC) or prescriptions analgesics, pain relieving, or pain altering medications – NSAIDs, narcotics; sedatives, anti-anxiety, or anti-depressant medications), had active sites of pathosis in the study tooth or injection site, had large restorations, crowns or previous root canal therapy on the test tooth, had an inability to give informed consent, and were pregnant or nursing. Participants were excluded if they met one or more of the previous list. Exclusion criteria existed to eliminate or reduce any factors that might have changed the metabolism or ability of the experimental and control local anesthetic to exert an
effect. Alteration of the perception and degree of pain experienced during the test procedure could be effected by analgesic and anxiolytic medications. Participants taking analgesic and/or anxiolytic medications may experience an altered perception to the pain of the infiltration injection and thereby affect the results of the study (133).

Pregnant and nursing participants were excluded because articaine is classified by the Food and Drug Administration (FDA) as a pregnancy category C medication. As described previously in the Literature Review, drugs classified as pregnancy category C are defined as medications in which “no adequate and well-controlled studies have been performed in pregnant women, but animal reproduction studies are lacking or have shown an adverse effect on the fetus” (54).

**Pain of Injection**

Before the infiltration injection was administered, participants were given instructions on how to rate their pain for each phase of the infiltration injection (needle insertion, needle placement, and anesthetic formulation deposition) using a 170-mm Heft-Parker visual analog scale (VAS)(Appendix G). The VAS was divided into four categories - no pain, mild pain, moderate pain and severe pain. Research on measuring pain perception has demonstrated that a 4- or 5-point category rating scales did not accurately assess the associated categorical descriptors with the pain level patients experienced (134, 135). The category rating scales may require minimal instructions due to ease of use; however, this tool lacks the sensitivity to measure pain accurately. Historically, visual analog scales were developed to overcome the low sensitivity of
category rating scales by providing an infinite number of points within the ends of the scale to rate pain. However, these visual analogs scales lacked descriptors to guide patients in assessing pain other than the end-point descriptors (i.e., ‘no pain’ and worst pain I can imagine’). With no descriptors, accurate pain assessment was variable between patients assessing pain. Heft and Parker (134) proposed that by using a graphic rating scale it would combine the category ratings and visual analog scales to provide a inhomogeneous spacing with categorical descriptors (‘faint’, ‘weak’, ‘mild’, ‘moderate’, ‘strong’, and ‘intense’) on a visual analog scale, that had a quantified length, and therefore produced a more accurate scale for rating pain. As stated, this study employed a Heft-Parker VAS to allow for accurate pain assessment for pain of injection and postoperative pain.

Prior to each injection, 0.2 mL of 20% benzocaine topical anesthetic gel was placed next to the test mandibular first molar with a cotton tip applicator for 60 seconds at the intended site of injection. Robertson et al (2), Pabst et al (6), Nuzum et al (7), McEntire et al (9), Martin et al (8), Dressman et al (10), and Nydegger (11) reported using topical anesthetic at the injection site for mandibular buccal or labial infiltration injections. In order to compare the results of the current study with the previous mandibular buccal infiltration injection studies, similar methods from these experiments were used. When comparing 20% benzocaine topical anesthetic gel (0.2 mL) with no topical anesthetic gel, used prior to a primary maxillary buccal infiltration injection, Nusstein et al (136) reported no significant difference between the two techniques for needle insertion pain.
Martin et al (8) reported that application of topical anesthetic significantly reduced the amount of anticipated pain for needle insertion of maxillary buccal infiltration injection, even though participants reported their pain level the same. No anesthetic formulation was deposited during needle insertion and the needle was inserted to a depth of 3 mm. Nusstein et al (137) reported no significant difference for the needle insertion pain between application of 0.2 mL of 20% benzocaine topical anesthetic gel and a placebo gel to the injection site prior to the administration of a palatal anterior superior alveolar nerve block injection using either 2% lidocaine with 1:100,000 epinephrine or 3% mepivacaine plain.

Gill and Orr (138) investigated the effect of three separate topical anesthetic agents and a placebo. Each topical anesthetic or placebo was applied for 1 minute before assessing degree of anesthesia with palatal needle insertion. The authors reported no significant difference between any topical anesthetic and placebo.

A survey of 3,051 pediatric dentists investigated their use of local and topical anesthetics. The survey had a 55% response rate and revealed that most pediatric dentists used a 20% benzocaine topical anesthetic gel (HurriCaine®) prior to local anesthetic injection. The dentists’ perception varied as to its effectiveness.

No studies have investigated the effect of 20% benzocaine topical anesthetic gel versus a placebo prior to administration of a mandibular buccal infiltration injection. Further research within this particular scope is needed.
Needle Insertion Pain

The summary for pain ratings of needle insertion using a Heft-Parker VAS can be seen in Table 2. There was no significant difference between non-buffered and buffered articaine, by gender, for needle insertion pain (P=1.000). The mean needle insertion pain ratings for non-buffered articaine were 27.7 mm and 36.3 mm (male and female, respectively). The mean needle insertion pain ratings for buffered articaine were 27.0 mm and 34.6 mm (male and female, respectively). The mean insertion pain ratings were in the mild category for both anesthetic formulations and genders.

Robertson et al (2) Pabst et al (6), McEntire et al (9), Martin et al (8), Dressman et al (10), and Nydegger (11) reported a mean VAS needle insertion pain for articaine within the ‘mild’ category, ranging from 20 mm to 37 mm. All the reported mean VAS ratings for needle insertion pain were similar to the current study’s mean VAS ratings, which were also in the mild category. The rationale for similarities was that no anesthetic formulation was deposited during needle insertion in any of the reported studies, each study used a 27-gauge needle, and each study used the same type and concentration of topical anesthetic. As discussed earlier in the section, topical anesthetic may have little to no effect on the reported needle insertion pain for historical studies.

Other studies using articaine HCl as a mandibular buccal infiltration injection have also reported their participants’ pain of injection ratings. Many of the studies followed a different protocol for rating pain and cannot be compared directly to the current study. However, the reported information warrants discussion as it presents more information pertaining to mandibular buccal infiltration injections with articaine formulations. Kanaa et al (1) used a 100 mm VAS to rate participant injection pain. No
topical anesthetic was applied prior to anesthetic formulation administration. They administered 1.8 mL of 4% articaine with 1:100,000 epinephrine as a primary buccal infiltration injection using a standard syringe with a 30-gauge needle. The mean pain rating for articaine HCl was 20.9 mm. When proportionally compared to a 170-mm VAS this mean corresponds to a 35.5 mm rating and would be within the ‘mild’ category. The injection was unfortunately reported as a whole and not delineated into separate phases. Therefore, the reported injection pain ratings cannot be compared to the current study’s reported needle insertion pain.

Corbett et al (3) reported a mean injection pain of 22.4 mm for a primary buccal infiltration injection with 1.8 mL of 4% articaine with 1:100,000 epinephrine using a 100 mm VAS. No topical anesthetic was applied prior to injection administration with a 27-gauge needle. Their mean score corresponds to a mean of 38.1 mm on the 170-mm Heft-Parker VAS for injection pain and was within the ‘mild’ category. The injection was separated into penetration and deposition phases in the methods descriptions. However, the injection pain was reported for the entire injection and not delineated into phases. Therefore, the reported injection pain ratings cannot be compared to the current study’s reported insertion pain.

Abdulwahab et al (5) reported a mean injection pain rating of 26.2 mm for a primary buccal infiltration injection with 0.9 mL of 4% articaine with 1:100,000 epinephrine, using a 100-mm VAS. Topical anesthetic gel was not used prior to injection administration. All injections were given using a 30-gauge “short” needle. Pain of injection ratings were reported in a whole stage fashion and not delineated into phases.
When proportionally compared to a 170-mm Heft-Parker VAS the mean was 44.5 mm. This mean is considered ‘mild’ on a 170-mm VAS.

Kanaa et al (1), Abdulwahab et al (5) and Corbett et al (3) did not report possible differences between males and females for pain of injection. Each study reported ‘mild’ pain for pain of injection. Again, the studies did not delineate the phases of the injection, as the current study did when rating injection pain. Without this delineation it is impossible to know the level of pain that could be attributed to the specific phases of injection (needle insertion, needle placement, and formulation deposition). Research (2, 6, 8-11) has demonstrated anesthetic formulation deposition as being the most painful phase of a primary mandibular buccal infiltration injection. This information may be extrapolated to assume that the greatest amount of pain reported during the injections by Kanaa et al (1), Abdulwahab et al (5) and Corbett et al (3) was from the deposition phase of the injection and not needle insertion.

The aforementioned studies (1-3, 5, 6, 8, 10, 11) did not investigate a buffered anesthetic formulation. Currently there are no studies that have investigated a primary mandibular buccal infiltration injection with a NaHCO₃-buffered 4% articaine HCl with 1:100,000 epinephrine formulation. However, several studies investigating buffered local anesthetics reported on needle insertion pain. The terminology differed, but their injection phase definition was analogous. Hobeich et al (30) investigated buffered 5% and 10% sodium bicarbonate 2% lidocaine HCl with 1:100,000 epinephrine formulations compared to the same non-buffered lidocaine formulation. The authors injected the anesthetic formulations as primary maxillary labial infiltrations over the canine. The authors used a VAS for rating injection/placement pain. The injection was delineated into
2 phases – needle penetration and formulation deposition. The length of the VAS was not specified. The mean for needle insertion/placement pain ratings were 34 mm (non-buffered lidocaine), 40 mm (5% buffered lidocaine) and 40 mm (10% buffered lidocaine). There was no significant difference between any of the anesthetic formulations’ mean VAS pain ratings for needle penetration (i.e. insertion and placement). This was similar to the current study’s needle insertion pain – no difference between buffered and non-buffered anesthetic formulations.

Balasco et al (31) investigated the use of a buffered lidocaine formulation when performing incision and drainage procedures. Infiltration injections were given on either side of the swelling. The reported mean needle insertion pain was 58 mm (mesial insertion) and 55 mm (distal insertion). These values were within the ‘moderate’ category. The higher pain ratings were attributed to the pathologic condition (symptomatic necrotic teeth with acute apical abscess) and the inflammation present. The current study enrolled asymptomatic patients and direct comparisons cannot be made.

**Needle Placement Pain**

The mean 170-mm Heft-Parker VAS pain ratings for needle placement for female and male non-buffered and buffered articaine anesthetic formulations are presented in Table 2. There was no significant difference in needle placement pain between either of the anesthetic formulations by gender (P=1.000). The mean needle placement pain ratings for non-buffered articaine were 33.3 mm and 50.4 mm (male and female, respectively). The mean needle placement pain ratings for buffered articaine were 31.2 mm and 47.5
mm (male and female, respectively). Female needle placement pain ratings were higher for both anesthetics as compared to males. As discussed previously, females tend to report pain higher than males (130, 131). The mean needle placement pain for both genders and anesthetic groups were within the ‘mild’ category. The summary of pain ratings for needle placement for each anesthetic is shown in Table 4.

The mean needle placement pain ratings for the non-buffered articaine formulation was comparable to previous research conducted using non-buffered 4% articaine HCl with 1:100,000 epinephrine given as a primary mandibular buccal infiltration injection adjacent to the mandibular first molar with a 27-gauge needle. Pain from needle placement was rated using a 170-mm Heft-Parker VAS in the following comparison studies and the current study. Robertson et al (2), Pabst et al (6), McEntire et al (9), Martin et al (8), Dressman et al (10), and Nydegger (11) reported mean needle placement pain ranging from 26 mm to 39 mm which was within the ‘mild’ pain category. The current study reported the mean needle placement pain ratings between 31 mm and 50 mm, which also were within the ‘mild’ pain category. Similar results between the current study and comparison studies are most likely due to methodological similarities. The same topical anesthetic was used prior to needle insertion. All needle placement occurred within the buccal mucosa of the posterior mandible. Each study used a 27-gauge needle and directed it to a depth of the root apices. Needle placement also occurred over a two to three second period. There was also no anesthetic formulation deposited within the tissues during needle placement. A balanced number of men and women participated. The slight differences in pain ratings may be attributed to operator variation with the injection technique.
Other research (1, 3, 5) has investigated 4% articaine HCl with 1:100,000 epinephrine administered as a primary mandibular buccal infiltration injection adjacent to the mandibular first molar. These studies differ from the previously cited (2, 6, 8-11) articles due to a lack of topical anesthetic application, injection phase delineation and use of a 100-mm VAS instead of a 170-mm Heft-Parker VAS with inhomogeneous descriptors. Gender of the study groups were also not reported. Kanaa et al (1), Corbett et al (3), and Abdulwahab et al (5) each investigated a primary mandibular buccal infiltration injection with 1.8 mL of 4% articaine with 1:100,000 epinephrine using a 30-gauge needle. The proportionally converted mean injection pain ratings were 35 mm, 38 mm and 44 mm, respectively, and fell within the ‘mild’ pain category. Again, there were overall injection pain ratings, not ratings specific to needle placement. These results were similar to the current study’s mean needle placement pain ratings of 31 mm and 50 mm.

There was no significant difference between the buffered and non-buffered articaine formulations for mean needle placement pain. No anesthetic was delivered during the needle placement phase and did not contribute to the pain experienced. Pain felt during needle placement was completely due to the needle traversing the tissue and the resultant trauma incurred.

McCartney et al (139) investigated the deposition of local anesthetic formulations during the needle placement phase of an injection. In their study the needle traversed the tissue to the target site for an IANB injection and approximately 0.4 mL of 2% lidocaine with 1:100,000 epinephrine was deposited over the 10 seconds of needle placement. No significant difference was reported for needle placement pain between anesthetic
formulation deposition and no anesthetic formulation deposition for both genders (P>0.753).

Nusstein et al (140) investigated the injection pain of a 1-stage versus 2-stage IANB injection. A 1-stage technique was a conventional IANB injection with 0.4 mL of anesthetic formulation deposited during the needle placement phase. During the 2-stage injection technique, the needle was inserted 2-3 mm into the tissue and 0.4 mL was administered over one minute then withdrawn. After five minutes the needle was reinserted and advanced to the injection target site without any anesthetic formulation deposition. No significant reduction in needle placement pain between 1-stage compared to the 2-stage technique was reported for men. There was a significant decrease in needle placement pain for women in favor of the 2-stage technique (P=0.0015). The current study utilized a different injection technique where no anesthetic was deposited at any time until the target was reached. Future research could look at the potential benefit of a 2-stage injection in reducing injection pain for the mandibular buccal infiltration.

Previous research (2, 6, 8-11) has been conducted and reported needle placement pain using a non-buffered articaine formulation, and similar injection technique and injection location. Each has similar results to the current study. The type of anesthetic formulation used and gender was reported to have no significant difference for needle placement pain.

As previously stated, there are no studies that have investigated a primary mandibular buccal infiltration injection with a NaHCO₃-buffered 4% articaine HCl with 1:100,000 epinephrine formulation. However several studies investigating buffered local anesthetics reported on needle placement pain. Hobeich et al (30) investigated buffered
5% and 10% sodium bicarbonate 2% lidocaine HCl with 1:100,000 epinephrine formulations compared to the same non-buffered lidocaine formulation. The injection was delineated into 2 phases – needle penetration and formulation deposition. The mean for needle insertion/placement pain ratings were 34 mm (non-buffered lidocaine), 40 mm (5% buffered lidocaine) and 40 mm (10% buffered lidocaine). The VAS quantified length was not reported. The authors reported no difference for the mean needle penetration pain (needle insertion and placement pain) between the buffered formulations and the non-buffered formulation. These results were similar to the current study.

As previously reported, Balasco et al (31) investigated buffered lidocaine formulations when performing incision and drainage procedures. They anesthetized on either side of a facial swelling using a 27-gauge needle after placing topical (0.2 mL of 20% benzocaine) for 60 seconds. The reported mean needle placement pain ratings were 56 mm (mesial placement), and 50 mm (distal placement). The mesial placement value was within the ‘moderate’ pain category. The distal placement value was within the ‘mild’ pain category. No formulation was deposited during needle placement. The higher pain ratings were attributed to the pathologic condition (symptomatic necrotic teeth with acute apical abscess) and the inflammation present. The current study enrolled asymptomatic patients and direct comparisons cannot be made.

The current study’s participants rated the needle placement pain as ‘none’ to ‘mild’ 68.7% of the time, with a mean VAS rating ranging from 31.2 mm to 50.4 mm. This finding is comparable to the needle placement pain reported by other research (2, 6, 8-11) using the same anesthetic formulation, injection, and experiment methodology. The needle placement pain was not significantly different between buffered and non-
buffered articaine formulations by gender. Needle placement pain was rated slightly higher than needle insertion by anesthetic formulation and gender (Table 2). However, all reported mean needle insertion and placement pain ratings were within the ‘mild’ pain category.

Solution Deposition Pain

The summary for pain ratings of solution deposition using a Heft-Parker VAS can be seen in Table 2. There was no significant difference between the mean solution deposition pain ratings for the non-buffered and buffered articaine groups by gender (P=1.000). The mean solution deposition pain ratings for non-buffered articaine were 39.9 mm and 58.2 mm (male and female, respectively). The mean solution deposition pain ratings for buffered articaine were 40.6 mm and 49.6 mm (male and female, respectively). The mean pain ratings for solution deposition were within the ‘mild’ category for the male groups and ‘mild’ and ‘moderate’ categories for the female groups. Table 5 summarizes the pain ratings via a descriptive scale. Approximately 64% of solution deposition pain ratings were in the ‘none’ to ‘mild’ pain category. Female participants rated their pain slightly higher than the male participants. No major differences were seen between the non-buffered and buffered articaine formulations by gender. In other words, the female and male participants did not rate the solution deposition pain any lower for the buffered articaine when compared to the non-buffered articaine. However, two female participants (1.3%) rated the non-buffered articaine solution deposition as ‘severe’. As discussed previously, several studies have investigated the differences between male and female pain responses. Keogh et al (130)
and Fillingim et al (131) demonstrated a female predilection for lower pain thresholds and pain tolerance when compared to male participants. For both thermal and cold pressor stimuli female participants reported a greater number of sites, greater sensitivity, and experienced lower thresholds to experimental pain. These studies also concluded that experimental pain might be reliable for investigating female participants only.

Solution deposition pain ratings for the non-buffered articaine formulation were comparable to previous research (2, 6, 8-11) conducted using 1.8 mL of non-buffered 4% articaine HCl with 1:100,000 epinephrine given as a primary mandibular buccal infiltration injection adjacent to the mandibular first molar and with a 27-gauge needle. The anesthetic formulation was deposited at a rate of 1.8 mL/min in all the listed studies (same as this one). Pain from solution deposition was rated using a 170-mm Heft-Parker VAS in the comparison studies and the current study. Robertson et al (2), Pabst et al (6), McEntire et al (9), Martin et al (8), Dressman et al (10), and Nydegger (11) reported mean solution deposition pain ratings ranging from 30 mm to 37 mm. These reported means were all within the ‘mild’ pain category. The current study reported the mean formulation deposition pain rating for non-buffered articaine as 39.9 mm and 58.2 mm (male and female, respectively). The male mean pain rating was within the ‘mild’ category. The female mean pain rating was within the ‘moderate’ pain category. The male rating was slightly higher than the comparison studies; however it is close in range. The female ratings are higher by 20 mm. This higher rating may be partially due to the comparison studies’ mean pain ratings including both male and female ratings, where as the current study separated male and female participants. If combined, the means for non-buffered articaine and buffered articaine would be 48.6 mm and 44.9 mm.
respectively. Both mean ratings would fall within the ‘mild’ pain category. Unless a study delineates between male and female formulation deposition pain ratings, a comparison to the current study has limitations.

As previously stated, Kanaa et al (1), Corbett et al (3), and Abdulwahab et al (5) investigated 4% articaine HCl with 1:100,000 epinephrine administered as a primary mandibular buccal infiltration injection adjacent to the mandibular first molar using a 30-gauge needle. Injection phases were not reported separately. The proportionally converted mean injection pain ratings were 35 mm, 38 mm and 44 mm, respectively, and were within the ‘mild’ category. These results compare to the current study’s mean solution deposition pain ratings, which for male participants were also in the ‘mild’ pain category. The female participants’ mean solution deposition pain rating was in the ‘moderate’ pain category. Abdulwahab (5) used an injection rate of 0.9 mL/30 sec, which is the same as the current study. Kanaa et al (1) and Corbett et al (3) used an anesthetic formulation injection rate of 0.9 mL/15 sec. Corbett et al (3) and Abdulwahab et al (5) reported injection pain ratings that were slightly higher than the previously cited mandibular infiltration studies (2, 6, 8-11), which used an injection rate of 1.8 mL/60 sec. However, Corbett et al (3) used a slightly faster rate of deposition, which has been shown to produce more pain upon solution delivery (141-144). The current study employed an injection rate of 1.8 mL/60 sec. However, none of the three listed studies (1, 3, 5) separated pain ratings by gender. The mean injection pain ratings were combined and could not be reliably compared to the current study’s mean pain ratings, as gender differences do exist. The current study found no significant difference between mean solution deposition pain ratings for the anesthetic formulations by gender.
Another infiltration study investigated buffered anesthetics and their effect on solution deposition pain. Hobeich et al (30) reported on pain of injection with 2% lidocaine with 1:100,000 epinephrine formulation buffered with different sodium bicarbonate concentrations and plain. All injections given were primary maxillary labial infiltrations over the canine. Solution deposition pain was rated using a Heft-Parker VAS (no length specified). Patients rated the solution deposition pain immediately after receiving the injection. The mean formulation deposition pain ratings were 39 mm (plain lidocaine), 45 mm (5% buffered lidocaine) and 42 mm (10% buffered lidocaine). The authors reported no significant difference between any of the three anesthetic groups for formulation deposition pain (P>0.05). The authors concluded that neither a 5% or 10% NaHCO₃ buffered lidocaine formulation decreased pain of injection (solution deposition) when compared to a non-buffered lidocaine formulation.

Solution deposition was reported as the most painful phase of injection for the current study for both anesthetic formulations and genders (Table 2). Several studies (2, 10, 11, 30) also reported solution deposition as the most painful phase of the injection when administering a primary infiltration. Solution deposition is generally the only phase of the infiltration injection when local anesthetic formulations are deposited in the tissue. The pH of most local anesthetic formulations is below physiologic pH (7.2-7.4). This relative acidity may contribute to the injection pain during solution deposition as the formulation’s acidity can cause tissue damage (145). Articaine HCl with 1:100,000 epinephrine is adjusted to a pH of 5.0 with sodium hydroxide by the manufacturer (46). The current study reported the mean pH for the non-buffered articaine formulation as 4.76 (Table 12). The mean pH for the buffered articaine formulation was 7.59.
There are several theories to explain why formulation deposition is the more painful stage of the infiltration injection. The speed of local anesthetic administration has been proposed as contributory to formulation deposition pain (141-144). A rate of 1.8 mL/min of formulation was instituted in the current study for comparison to other studies, which used this rate. Robertson et al (2), Abdulwahab et al (5), Pabst et al (6), McEntire et al (9), Martin et al (8) Dressman (10) and Nydegger (11) employed the same formulation deposition rate Kudo et al (143) reported a significant correlation between injection pain and injection pressure (P=0.0012), when a slower injection speed (0.006 mL/sec or 0.375 mL/min) was used versus a faster speed (0.033 mL/sec or 2 mL/min) for a primary buccal mandibular infiltration injection with 0.5 mL of 2% lidocaine HCl with 1:100,000 epinephrine. Lower pressure during injection was correlated with a slower injection and less pain. Primosch and Brooks (142) reported a significantly lower pain for slower injections (0.006 mL/sec) versus the faster injection (0.033 mL/sec)(P=0.006) when given as palatal infiltrations. Kanaa et al (144) showed that when a slow IANB injection (2.0 mL/60 seconds) was compared to a fast IANB injection (2.0 mL/15 seconds) there was a significant decrease in injection pain (P<0.001).

Therefore a slower injection was used for the current study. However, Kanaa et al (1) and Corbett et al (3) used a faster formulation deposition rate, 1.8 mL/30 seconds, and they reported ‘mild’ pain ratings, which was similar to the other mandibular infiltration studies and the current study. Therefore, primary mandibular buccal infiltrations given at a slower injection rate (1.8 mL/60 sec) resulted in no difference when compared to the faster rate (1.8 mL/30 sec) for formulation deposition pain.
Kudo et al (143) reported a significant correlation between injection pain and injection pressure (P=0.0012), when a slower injection speed (0.006 mL/sec or 0.375 mL/min) was used versus a faster speed (0.033 mL/sec or 2 mL/min) for a primary buccal mandibular infiltration injection with 0.5 mL of 2% lidocaine HCl with 1:100,000 epinephrine. Lower pressure during injection was correlated with a slower injection and less pain. Primosch and Brooks (142) reported a significantly lower pain for slower injections (0.006 mL/sec) versus the faster injection (0.033 mL/sec)(P=0.006) when given as palatal infiltrations. Kanaa et al (144) showed that when a slow IANB injection (2.0 mL/60 seconds) was compared to a fast IANB injection (2.0 mL/15 seconds) there was a significant decrease in injection pain (P<0.001).

The buffered articaine mean solution deposition pain ratings for both genders were not significantly different than the non-buffered articaine formulation deposition pain ratings (Table 2). No other study has investigated a buffered 4% articaine HCl with 1:100,000 epinephrine formulation administered as a primary mandibular buccal infiltration. Thus there are no direct comparison studies to evaluate the pain of a buffered formulation for this infiltration technique. However, several studies have investigated the pain of injection for buffered anesthetic formulations.

Primosch and Robinson (99) evaluated pain of injection for primary maxillary labial and palatal infiltrations using buffered and non-buffered 2% lidocaine with 1:100,000 epinephrine. The injection was separated into two phases – needle penetration and solution infiltration (deposition). Only the solution deposition was reported. The mean pain intensity rating for non-buffered and buffered solution deposition was 2.6 and 1.6 out of 10, respectively. No significant difference was found between formulation
type \((P=0.365)\). Buffering the anesthetic formulation did not affect solution deposition pain of primary maxillary labial and palatal infiltrations.

Bowles and coauthors’ (111) investigated differences of the pain of injection between regular and buffered lidocaine formulations. Forty-seven of the 73 subjects \((64.4\%)\) rated a regular lidocaine injection as more painful than the buffered lidocaine \((P<0.001)\).

Kashyap et al (112) investigated pain of injection for buffered 2\% lignocaine HCl with 1:80,000 epinephrine in a double-blind study. The patient described the pain of injection after the solution deposition and not the needle insertion/placement. The non-buffered lignocaine injection group reported pain upon injection for 78\% \((39/50)\) of the study participants. Eleven participants reported no pain, 31 mild pain, 8 moderate pain and 0 severe pain. The buffered lignocaine group all reported no pain \((50/50 = 100\%)\) to formulation injection. There was a significant difference between the non-buffered and buffered lignocaine groups for pain of injection \((P<0.0001)\).

Al-Sultan et al (115) investigated the effect of buffered 2\% lidocaine with 1:80,000 epinephrine for periapical surgery of maxillary teeth. The injection pain was assessed as a whole and not in phases. The buffered lidocaine formulation was reported to have a lower pain rating for the pain of injection \((P=0.001)\) compared with the non-buffered lidocaine formulation.

In another study, Al-Sultan et al (116) investigated the pain of injection for buffered 2\% lidocaine with 1:80,000 epinephrine for maxillary tooth extraction versus a non-buffered formulation. Pain was assessed and recorded by asking the patient about pain following the injection. The pain of injection for the buffered lidocaine group was
reported to be significantly lower when compared with the non-buffered lidocaine group (P=0.002). The authors concluded that pain of injection decreases with the use of buffered lidocaine formulation for infiltration anesthesia.

Gupta et al (28) investigated the effect of buffered 2% lignocaine with 1:80,000 epinephrine for extraction of maxillary teeth with periapical infections. Pain of injection was assessed using the Wong-Baker FACES VAS with markings from 0 to 5. Zero indicated ‘no pain’, while 5 indicated ‘hurts worst’. The reported mean value of the sum ranks test was 14,008.5 (non-buffered anesthetic) and 6,091.5 (buffered anesthetic). Even though the sum ranks test values are different, there was no reported statistical analysis between these two groups and no reported significant difference between the non-buffered and buffered lignocaine groups concerning injection pain. The entire injection was rated for pain with no phase delineation.

Whitcomb et al (29) evaluated buffered and non-buffered 2% lidocaine HCl with 1:100,000 epinephrine IANB injections for pain of injection. Pain of injection was assessed at three phases – needle insertion, needle placement and solution deposition. No significant difference between the lidocaine formulations for solution deposition was reported (P>0.05). The authors conclude that a buffered 2% lidocaine HCl with 1:100,000 epinephrine did not significantly decrease solution deposition pain for an IANB.

Malamed et al (27) investigated the pain of injection using an IANB injection of 1.8 mL 2% lidocaine with 1:100,000 epinephrine buffered with NaHCO₃ to a 9:1 ratio for the mandibular first molar. The patient was informed when the solution deposition phase of the injection started and was calibrated not to record pain of injection for needle
penetration or insertion. Patients assessed pain after the injection was given (needle retrieval from tissue). The authors reported that 72% (13/18) of the participants rated the buffered lidocaine IANB injection as a more comfortable injection while 11% (2/18) rated the non-buffered lidocaine IANB injection as the more comfortable injection. The remaining 17% (3/18) of patients reported no preference to either formulation. The authors reported the difference between patient preferences for buffered or non-buffered lidocaine formulation was statistically significant (P=0.013). This was determined using a repeated-measures test. Forty-four percent of the patients receiving the buffered lidocaine IANB injection rated the injection pain as zero ("no pain") on a 100-mm VAS. This was compared to 6% of the patients who received the non-buffered lidocaine IANB injection. The authors concluded that buffering the lidocaine formulation decreased the pain of injection and patients preferred the buffered lidocaine formulation to the plain lidocaine formulation.

Balasco et al (31) reported on a buffered 2% lidocaine with 1:100,000 epinephrine for a primary maxillary or mandibular labial or buccal infiltration injection, given prior to an incision and drainage procedure in patients with a diagnosis of pulpal necrosis and acute apical abscess. Patients rated their pain on a 170-mm Heft-Parker VAS. Formulation deposition pain was assessed. There was no reported significant difference between the non-buffered and buffered lidocaine formulations for formulation deposition (P>0.05). Buffering the local anesthetic did not decrease formulation deposition pain reported by patients.

The current study’s data showed that buffering articaine provided no benefit in significantly reducing formulation deposition pain. Buffering the formulation increased
the pH of the anesthetic formulation (4.76 to 7.59). Changing the pH to be closer to physiologic pH did not result in less pain from formulation deposition. As stated previously, intrinsic physiologic buffering capabilities convert the pH of acidic and basic formulation to tissue pH (7.4). Though the pH of buffered articaine was more basic and slightly more buffered than tissue pH, this conversion made any improvement negligible. The increased buffering may have caused similar discomfort to the tissue upon solution deposition as an acidic solution (non-buffered articaine with a pH of 4.76).

This study showed that for pain of injection, buffering a local anesthetic (4% articaine with 1:100,000 epinephrine) did not significantly decrease the pain of injection for all three phases (needle insertion and placement, and formulation deposition) of a primary mandibular buccal infiltration. Female participants rated the three phases of the injection higher than the male participants during each phase and both anesthetic formulations. As previously discussed, female participants tend to rate their pain higher in experimental clinical trials.

**Anesthetic Success**

Several studies have reported 4% articaine with 1:100,000 epinephrine as a superior local anesthetic when compared to 2% lidocaine with 1:100,000 epinephrine as a primary buccal infiltration of the mandibular first molar (1-6, 9, 11) and as a supplemental buccal infiltration of the mandibular first molar following an inferior alveolar nerve block (92, 93). Skjevik et al (49) suggested that articaine’s favorable molecular properties are due to the intramolecular hydrogen bond formation. The authors
demonstrated that when articaine is exposed to a lipid membrane an internal hydrogen bond forms between the amine nitrogen and ester carbonyl oxygen groups within the molecule, causing the molecule to fold over onto itself. Kuhn et al (50) reported that the intramolecular hydrogen bond leads to increased lipophilicity. Nydegger (11) showed that articaine’s superior efficacy compared to lidocaine and prilocaine was not due to anesthetic formulation concentration. Articaine had a superior success rate (55.0%) when compared to 4% lidocaine (33.3%) and 4% prilocaine (31.7%).

The current study defined pulpal anesthetic success as achieving 2 consecutive 80/80 or maximum EPT output readings at any time during the testing period (60 minutes). The definition of anesthetic success ensured that pulpal anesthesia was actually achieved and was not just an artifact or periodic false response with the EPT. A limitation of this definition is that the minimum of two consecutive readings, which could be a duration of just one minute (within the first 5 minutes of testing) or 2 minutes for the remaining portion of testing would not be sufficient time to complete any procedures in dentistry. There was also no defined time when these two consecutive readings needed to occur. Therefore the two consecutive readings could occur immediately after the injection or at minute 59 and 60. Clinically, this makes treatment difficult for the dentist due to an unpredictable onset and duration time. However, there has been no other superior clinical definition proposed.

To determine pulpal anesthesia, the experimental tooth (mandibular first molar) was tested every thirty seconds for the first 5 minutes of the 60 minute test period. Testing began approximately thirty seconds after the anesthetic deposition phase of the primary mandibular infiltration injection was administered. At the fifth minute the
experimental tooth was assessed for pulpal anesthesia every minute for the remaining fifty-five minutes of the test period. The control tooth (contralateral canine) was tested every five minutes to assure participant reliability and EPT functionality. One hour was chosen as the test period because pulpal anesthesia was reported (2, 6, 8-10, 92) to peak around 20 to 30 minutes after anesthetic solution deposition for a primary mandibular buccal infiltration.

A summary of anesthetic success by formulation is reported in Table 6. The buffered articaine anesthetic success rate was 71.2%. The non-buffered articaine anesthetic success rate was 65.0%. There was no significant difference for anesthetic success between buffered articaine and non-buffered articaine for the mandibular first molar after a primary mandibular buccal infiltration (P=0.3018).

When comparing the non-buffered articaine anesthetic success rate (65.0%) with several primary mandibular buccal infiltration studies, the success rate was within a similar range previously reported, 51.7% - 87.0% (1-4, 6, 8-11, 75-77). Each of the following comparison studies used a standard cartridge of 4% articaine HCl with 1:100,000 epinephrine as a primary mandibular buccal infiltration.

Kanaa et al (1), Jung et al (4), and Corbett et al (3) reported a 64.5%, 54.0%, 64.5% anesthetic success rate for the mandibular first molar, respectively. The test period was only thirty minutes, however Robertson et al (2) reported an 87.0% anesthetic success rate for the mandibular first molar. The sample size was 60 with a sixty-minute test period. This study had the highest reported anesthetic success of any published studies. Pabst et al (6) reported a 69.8% anesthetic success rate for the mandibular first molar. The sample size was 86 with a 112 min test period. Meechan et al (76) and Currie
et al (77) reported a 65.0% and 51.7% anesthetic success rate for the mandibular first molar, respectively. The test period was for 47 minutes. McEntire et al (9), Martin et al (8), Kwon et al (79), and Nydegger (11) reported a reported a 67.0%, 52.3%, 51.7%, and 55.0% anesthetic success rate for the mandibular first molar, respectively. The test periods were for 60 minutes.

Figure 3 presents the pulpal anesthesia (percent of 80/80 readings) by time period for the mandibular molar for both formulations. The buffered articaine formulation’s peak anesthetic success was around eight minutes and was sustained until twenty minutes before a slow decline over the remaining test time period. The non-buffered articaine formulation’s peak anesthetic success was also around eight minutes and was sustained until seventeen minutes before a slow decline over the remaining test time period. Clinically, these results indicate that this injection technique may be used for shorter (25-30 minute) appointments for over half of patients within the study sample’s demographics. However, for longer clinical time and more predictable anesthesia, different anesthetic injection techniques should be employed.

Robertson et al (2), Pabst et al (6), McEntire et al (9), Martin et al (8), and Nydegger (11) reported that pulpal anesthesia peaked from 20 to 30 minutes after administration of a primary mandibular buccal infiltration over the first molar with 1 cartridge of 4% articaine with 1:100,000 epinephrine (same as current study). Pulpal anesthesia declined incrementally for next 20 to 30 minutes. Kanaa et al (1) reported similar results with a study test period of 30 minutes. Abdulwahab et al (5) reported a test period for 20 minutes with peak onset of anesthesia at 14 minutes. Little to no decline of pulpal anesthesia was reported, most likely due to the short test period.
The buffered articaine anesthetic success rate for the current study was 71.2%.

As mentioned previously, within the available literature, there was no other study that has investigated a buffered 4% articaine HCl with 1:100,000 epinephrine as a primary mandibular buccal infiltration. Direct comparison of the anesthetic success rate to another study was not possible.

However, there have been several recent studies, which have used the same buffering system (Onset®) to evaluate the effect of buffering on dental local anesthesia (27, 30, 31). Malamed et al (27) investigated a buffered lidocaine formulation with an IANB injection. The authors did not report their IANB success rates for the experimental teeth (mandibular first molar). Only the results of the onset of anesthesia and injection pain were reported. However, from the study description it can be determined that the anesthetic failures (response to cold or EPT after 15 minutes) were removed from the study. Therefore 18 of the 20 patients enrolled in the study experienced pulpal anesthesia and their data were included in the statistical analysis. The extrapolated success rate was 18/20 or 90%. The authors did not report any comparison of anesthesia success rate between the buffered and a non-buffered lidocaine formulation.

Hobeich et al (30) investigated primary maxillary labial infiltrations over the canine with a non-buffered, and 5% and 10% sodium bicarbonate buffered 2% lidocaine HCl with 1:100,000 epinephrine formulations. The reported anesthetic success rate was 100% for all study participants. If all the test anesthetic formulations (plain lidocaine, 5% buffered lidocaine, and 10% buffered lidocaine) produced 100% anesthetic success, there was no difference between the formulations for anesthetic success. Buffering an
anesthetic within this model for maxillary labial infiltration over the maxillary canine did not provide additional information for improving anesthetic success.

Balasco et al (31) investigated buffered lidocaine formulations in symptomatic patients with facial swelling for performing an incision and drainage procedure. Success for the procedure was defined as the ability to incise and drain the swelling with no pain or mild pain. The reported anesthetic success rates for the buffered lidocaine were 44% (incision), 37% (drainage), and 32% (dissection). These rates were not significantly different than the non-buffered lidocaine formulation (25% -incision, 27% - drainage, 32% - dissection)(P>0.05). Buffering the lidocaine formulation did not improve the studies defined procedural success.

With no direct comparisons for anesthetic success, it was speculated that the use of buffered articaine as a primary mandibular buccal infiltration would result in an increased anesthetic success rate for the mandibular first molar. Buffering an anesthetic, in theory, should increase anesthetic success by providing a greater number of deionized, uncharged base anesthetic molecules. With a greater number of base molecules, more anesthetic should be able to penetrate the nerve sheath and block the sodium ion channels to disrupt the impulse conduction in an activated sensory nerve. In this study the pH was 7.59 for the buffered articaine formulation and 4.76 for the non-buffered articaine formulation (Table 12). The buffered formulation was closer to the articaine’s pKa (7.8) and tissue pH (7.4) than previously reported by other studies (11, 27, 31). The higher pH should have resulted in more deionized uncharged base molecules available for adequate anesthesia. Increased success was not noted. The body intrinsically has an efficient buffering system that maintains tissues at physiologic pH (~7.4) for optimal physiologic
functions. When encountering pH variations, the body converts basic or acidic environments to minimize tissue and physiologic damage. The pH conversion process, as reported by Wennberg et al (146), could occur within several minutes. The authors investigated various anesthetic formulations, 2% lidocaine with 1:100,000 epinephrine – commercially produced (pH 3.5-4.0) and freshly formulated (pH 6.5), injected within normal and inflamed tissues. After three minutes, pH values following the anesthetic formulation injections were generally equal to the more acidic anesthetic formulation (commercially manufactures 2% lidocaine). Punnia-Moorthy et al (147) reported a freshly prepared 2% lignocaine with adrenaline formulation (pH 5.25) being converted to a pH of 7.17 following an intradermal injection. This conversion occurred by the third minute following the injection. This phenomenon may explain why buffering an anesthetic to a pH closer to physiologic pH did not demonstrate any benefit in increasing anesthetic success. It appears that the acidic anesthetic formulations are buffered within the tissues relatively quickly (by 3 minutes). Therefore the body is buffering the anesthetics to a level, and with significant enough speed, to render a buffered anesthetic and non-buffered anesthetic formulation relatively equal and no significant advantage is noted.

Due to the current study’s novelty (no previous investigation using buffered articaine formulations), it was important to first test the efficacy of a buffered 4% articaine HCl with 1:100,000 epinephrine formulation for a primary mandibular buccal infiltration in subjects with normal pulp tissue. If it had clinical application and relevance in normal teeth, then the buffered formulation may be applicable to use for treatment of symptomatic teeth (symptomatic irreversible pulpitis). With no increase in
efficacy demonstrated from the current study, the application in patients with symptomatic irreversible pulpitis would need further study.

**Onset of Anesthesia**

Pulpal anesthesia was determined through the use of an electric pulp tester (EPT). All participants presented for both appointments with an asymptomatic test tooth (mandibular first molar) and control tooth (contralateral mandibular canine). Certosimo et al (148) reported that the EPT is a valuable instrument due to its accuracy and reliability for assessing pulpal anesthesia. Dreven et al (149) reported that using an EPT for determining pulpal anesthesia in normal and/or asymptomatic teeth was very reliable and effective. Jespersen et al (150) also concluded that an EPT was accurate and reliable for determining pulpal vitality.

The definition for the onset of pulpal anesthesia was the first of two consecutive maximum readings (80/80) with an EPT. The time this value was recorded, served as the onset time for the individual. EPT values for the test tooth (first molar) were recorded every 30 seconds for the first five minutes, then starting at the sixth minute of testing the values were recorded every minute for the remainder of the test period (60 minutes). The control tooth (contralateral canine) was tested every five minutes for the duration test period. This study monitored the first molar in shorter intervals (30 seconds) than other studies. Other studies looking at anesthesia onset (2, 6, 8-11, 29) utilized a 3-4 minute test cycle. The results for the onset of anesthesia for the first molar in these studies were at best accurate to 3 minutes in either time direction (low sensitivity). In other words, it is possible for any test tooth to become anesthetized ten seconds after the initial testing
interval, but not be recorded for success until the next cycle, a possible 3-4 minute interval. In the current study the interval accuracy was shortened to 30 seconds in either direction within the first five minutes following injection, and one minute in either direction for the remainder of the test period. Onset of pulpal anesthesia was only calculated from study subjects who achieved pulpal anesthesia for both anesthetic groups - buffered and non-buffered articaine. The sample size decreased to 47 participants due to this requirement. Thus, 33 participants either never achieved pulpal anesthesia for both appointments or only at one appointment.

The mean times of onset of pulpal anesthesia for buffered articaine and non-buffered articaine groups were 5.9±5.9 minutes and 5.4±5.9, respectively (Table 7). There was no significant difference between onset of pulpal anesthesia for the buffered versus non-buffered articaine groups (P=1.000).

Several studies reported onset of pulpal anesthesia for primary mandibular buccal infiltration with articaine formulations. Generally, the measured onset of pulpal anesthesia was determined as the time from the end of the injection to the first of two consecutive maximum output readings using an EPT. Robertson et al (2), Corbett at el (3), Jung et al (4), Pabst et al (6), McEntire et al (9), Martin et al (8), Meechan et al (76), and Currie et al (77) reported an onset of anesthesia ranging from 4.2±3.1 minutes to 9 minutes for the mandibular first molar. Nydegger (11) reported an onset of anesthesia of 11.6±11.4 minutes for the mandibular first molar. The current study’s mean onset of pulpal anesthesia was comparable to most of these studies using a non-buffered 4% articaine HCl with 1:100,000 epinephrine formulation. Nydegger (11) was longer by almost double the time of the reported studies (2-4, 6, 8, 9, 76, 77) and the current study.
Nydegger (11) did not articulate the reason for having a higher mean onset time of anesthesia than the other studies investigating articaine given as a mandibular buccal infiltration injection. A possible cause may be the time intervals of the testing technique used. Testing periods were every 4 minutes for 4 posterior teeth, which would not allow for a more precise measurement.

Research on the impact buffering has on anesthesia onset has been conducted with other types of dental injections. Kashyap et al (112) investigated onset of anesthesia for buffered 2% lignocaine HCl with 1:80,000 epinephrine in various nerve blocks (inferior alveolar, lingual and long buccal). Anesthesia onset was assessed with a straight probe inserted into the gingival sulcus of the anesthetized region. This assessed soft tissue anesthesia and not pulpal anesthesia. The mean time for onset of anesthesia for the non-buffered and buffered lignocaine groups was 109.8 seconds and 34.4 seconds, respectively. Time to onset of anesthesia was significantly different between the non-buffered and buffered lignocaine groups (P<0.001). The onset of anesthesia in that study was fairly subjective. The methodology for collecting time interval data was not addressed by the authors. No pulpal anesthesia assessments were determined. As mentioned previously, the authors only assessed soft tissue anesthesia. Reader et al (73) concluded that soft tissue anesthesia is not a reliable assessment for pulpal anesthesia as patients with profound soft tissue and lip numbness may not have achieved pulpal anesthesia (29, 83-86, 91, 92, 113, 114).

Al-Sultan et al (115) investigated the effect of buffered 2% lidocaine with 1:80,000 epinephrine for periapical surgery of maxillary teeth. Onset of anesthesia was assessed by probing of the gingiva over the anesthetized area until the patient reported
elimination of the pain sensation. The mean onset of anesthesia for non-buffered and buffered lidocaine groups was 215 seconds and 33 seconds, respectively. The reported onset was subjective to the patients’ responses and did not quantitatively report the interval for testing the soft tissue nor did it address that soft tissue is a poor predictor of pulpal anesthesia.

Al-Sultan et al (116) also investigated onset of anesthesia for buffered 2% lidocaine with 1:80,000 epinephrine for maxillary tooth extraction versus the same non-buffered formulation. Onset of anesthesia was assessed by probing of the gingiva over the anesthetized area until the patient reported elimination of the pain sensation. Frequency of gingival probing was not reported. The anesthesia measured was for soft tissue and not pulpal anesthesia. The mean onset of anesthesia time for the non-buffered and buffered lidocaine groups was 182 seconds and 93 seconds, respectively. The authors reported a significant difference between these mean onset times for the anesthetic formulation groups (no p-value reported; t-test=5.62). The reported onset was subjective to the patients’ responses and, again, did not quantitatively report the interval for testing the soft tissue.

Gupta et al (28) investigated the effect of buffered 2% lignocaine with 1:80,000 epinephrine for extraction of maxillary teeth with periapical infections. The mean onset time for the non-buffered and buffered lignocaine groups was 144 seconds and 72 seconds, respectively. The authors did not report if this difference was significant. The authors concluded that the study confirmed the enhancement of buffered local anesthetics due to the increased pH of the formulation. This statement was speculative with minimal significant differences to be shown within their research.
Whitcomb et al (29) evaluated buffered and non-buffered 2% lidocaine HCl with 1:100,000 epinephrine IANB injections for onset of anesthesia. Onset of anesthesia was determined by testing the experimental teeth in 4-minute cycles with an EPT. Mean onset times for the mandibular first molar for the non-buffered and buffered lidocaine groups were 5 minutes and 10 minutes, respectively. No significant differences were noted in onset times between the anesthetic groups (P>0.05). The authors concluded that a buffered 2% lidocaine HCl with 1:100,000 epinephrine did not significantly decrease time of onset to anesthesia for an IANB.

Malamed et al (27) investigated the onset time to anesthesia using an IANB injection of 1.8 mL 2% lidocaine with 1:100,000 epinephrine buffered with NaHCO₃ to a 9:1 ratio for the mandibular first molar. Onset to anesthesia was determined by testing the tooth with a cotton pellet sprayed with refrigerant. Cold testing began when the patient raised their hand indicating that they felt tingling or a numb sensation in their lower lip. Cold testing was repeated every 15 seconds until the patient had a loss of sensation. Loss of sensation was confirmed by EPT (80/80 reading). If confirmed with EPT, the time noted for loss of sensation to the cold test was recorded as the onset for pulpal anesthesia. If not confirmed with EPT, the EPT testing continued every 30 seconds until loss of sensation occurred. The time to loss of sensation to EPT was then used for time to pulpal anesthesia. The authors reported 71% of patients receiving the buffered lidocaine formulation achieved pulpal anesthesia in less than two minutes following when the patient indicated onset of lip tingling or numbness. The mean time from needle retrieval to the patient indicating their onset of lip tingling or numbness was not reported. The non-buffered lidocaine injection group achieving pulpal anesthesia in less than two
minutes was only 12%. A repeated-measures test determined this difference to be significant (P<0.001). The mean onset to anesthesia for non-buffered and buffered lidocaine groups were 6 minutes and 37 seconds and 1 minute and 51 seconds, respectively. The mean onset time was significantly different using the paired Wilcoxon ranked-sign test (P<0.001). The determination of anesthetic onset time by the authors was fairly subjective. Patient variation for lip anesthesia onset exists (83-91). The time between the end of the injection and the beginning of alteration to lip sensation was not recorded or factored into the time to anesthesia onset calculations for the buffered or non-buffered formulations. The authors concluded that the study demonstrates that a buffered lidocaine formulation decreased the onset time of pulpal anesthesia.

Hobeich et al (30) investigated the efficacy of buffering a 2% lidocaine with 1:100,000 epinephrine formulation with different sodium bicarbonate concentrations. Onset of anesthesia success was defined by testing with an EPT the study tooth (canine) every 30 seconds until pulpal anesthesia was achieved (80 reading). The average time to pulpal anesthesia onset was 119 seconds for the non-buffered group, 116 seconds for the 5% NaHCO$_3$ group, and 121 seconds for the 10% NaHCO$_3$ group. No significant difference was reported between any of the groups for onset of anesthesia (P>0.05). The authors concluded that neither a 5% or 10% NaHCO$_3$ buffered lidocaine formulation decreased onset time of pulpal anesthesia when compared to a non-buffered lidocaine formulation.

As stated previously, there was no significant difference between the onset time of pulpal anesthesia for the buffered (5.9±5.9) and non-buffered (5.4±5.9) articaine formulations. The current study shows that the buffered articaine formulation did not
decrease the onset time of pulpal anesthesia. The pH adjustment using the Onset® system did not decrease onset time of pulpal anesthesia. A pH closer to the pKa of articaine (7.8) should have theoretically increased the deionized base anesthetic molecules. The pH of the anesthetic formulation may not be a contributing factor to decreasing onset time due to the body’s buffering capabilities, which may shift the pH to 7.4 quickly enough to render the buffered anesthetic with no added effect.

**Duration of Anesthesia**

The definition for the duration of pulpal anesthesia was the time period between the first of two consecutive 80/80 readings until the last of the final two consecutive 80/80 readings as measured with the EPT. The mean duration, in minutes, for buffered and non-buffered articaine was 42.4±16.8 min and 41.7±13.4 minutes, respectively (P=1.000)(Table 7). This is a calculated duration time due to fact that 8.8% of subject appointments resulted in an anesthetic duration up to the 60th minute.

Other comparison studies did not report the mean duration of pulpal anesthesia for the mandibular first molar due to the fact that not all participants had a returned of pulpal sensation (as tested with an EPT) at the end of their testing period (60 minutes). However, two investigations (6, 151) did report portions of data for the duration of pulpal anesthesia with a mandibular buccal infiltration of 4% articaine formulation.

Pabst et al. (6) reported the duration of pulpal anesthesia for the mandibular first molar after giving a primary mandibular buccal infiltration with 1.8 mL of 4% articaine with 1:100,000 epinephrine. The initial plus mock injection group showed a shorter duration, with pulpal anesthesia beginning to decline around minute 20. The authors did
not report a specific calculated duration of anesthesia due to the fact that 100% of participants not having pulpal sensation return by the end of the test period (similar to the current study). However, in their study the experimental group received a repeated injection 25 minutes after the initial injection using the same articaine formulation at the same injection site. The authors reported a significant increase in duration of pulpal anesthesia from the 28th min to the 109th minute after the second injection. The initial plus mock injection group showed a shorter duration, beginning to decline around minute 20.

Smoth (151) reported the duration of pulpal anesthesia for the mandibular first molar after a primary mandibular buccal infiltration of 1.8 mL of 4% articaine with 1:100,000 epinephrine given over the second premolar. The same injection was repeated 20 minutes later or a mock infiltration was administered. The authors did not report mean duration of anesthesia for the initial articaine infiltration plus repeat injection group for the same reason the current study did not report the mean duration of pulpal anesthesia. The infiltration plus mock group had a reported mean duration of pulpal anesthesia for the mandibular first molar of 36.7 minutes. This is fairly similar to the current study’s calculated duration for the non-buffered articaine formulation (42 minutes). However, the infiltration technique and site of injection were different. The infiltration plus mock group showed a decline in pulpal anesthesia around the 24th minute for the mandibular first molar. The authors reported that the repeat injection of articaine increased the duration of pulpal anesthesia of the mandibular first molar and premolars through the 116-7 minutes.
In the published literature, there are no studies that have accurately measured the duration of pulpal anesthesia for primary mandibular buccal infiltration. The values presented in the current study and other studies only represent potential anesthesia duration since the test periods ended before 100% of participants, who achieved pulpal anesthesia, regained pulpal sensation. In Figure 3, the percentage of reported 80/80 readings with an EPT are depicted for the current study’s pulpal anesthesia. Onset of pulpal anesthesia peaked around 8 minutes with a plateau of anesthesia until the 20\textsuperscript{th} minute before a steady decline began over the remaining test period (60 minutes total). As reported previously, 8.8% of participants experienced pulpal anesthesia up to the 60\textsuperscript{th} minute of testing. The time at which this group regained pulpal sensation was not measured. Therefore, the true duration of anesthesia for the buffered and non-buffered articaine formulations is an unknown.

**Solution pH**

The Onset\textsuperscript{®} buffering system by Onpharma\textsuperscript{®} (Onpharma Inc., Los Gatos, CA) manufacturer instructions recommend immediate use of the buffered local anesthetic to minimize the loss of carbon dioxide and change in pH over time. Investigations (34, 103) have reported that these changes might occur slowly (30 minutes to an hour), if at all. Ackerman et al (34) showed that the pH and carbon dioxide concentration of lidocaine formulations buffered with sodium bicarbonate are stable for at least 30 minutes before changes occur, regardless of the volume of formulation, the container used, or whether it was exposed to ambient air. When studied in containers with no air-liquid interface (as would be found in a prepared anesthetic cartridge), no changes in pH or carbon dioxide
were reported over 60 minutes. Additionally, the stability of buffered lidocaine in glass vials (152) has also been evaluated. Donnelly (152) reported that a 1% lidocaine formulation buffered with 8.4% sodium bicarbonate to a final 10:1 concentration was successfully stored in glass vials at 23°C (exposed to light) and 5°C (no light exposure) with minimal sodium bicarbonate concentration reduction. The author tested the formulations after preparation and storage at Day 7, 14, 28, 56 and 91. The percent of initial concentrations were recorded as 99.8±0.9 (Day 7) to 96.7±0.6 (Day 91). The mean pH of the formulations rose from 7.89 to 8.01. The reason for the increase in pH was not reported. However, it was similar to the increase seen in the current study and will be addressed later. The authors concluded that the buffered lidocaine formulation concentration was stable for up to 91 days after preparation and storage. Gaggero et al (103) found that there were no significant differences between quality and onset of anesthesia for a buffered 2% lidocaine formulation injected immediately after preparation versus the same formulation injected one hour after preparation for epidural anesthesia. A plain lidocaine formulation was tested along with buffered lidocaine formulations. Epidural anesthesia formulations for elective Caesarean section were mixed one hour and immediately prior to injection. The pH of the formulations were measured immediately prior to injection (plain lidocaine – pH 6.77, buffered lidocaine mixed immediately – pH 7.34, buffered lidocaine mixed one hour before – pH 7.35). Onset of tissue anesthesia was assessed with pinpricks every two minutes for the first 20 minutes and every five minutes for the following 10 minutes. Quality of anesthesia using the Bromage scale was assessed every two minutes for the first 20 minutes and every five minutes for the following 10 minutes.
The current study prepared the anesthetic formulations immediately prior to administration. The findings of this investigation would not be affected by a loss of carbon dioxide or a change in pH. Balasco et al (31) reported minimal pH changes of a buffered lidocaine formulation tested over a period of 60 minutes. When initially measured, the pH averaged 6.97±0.20, and then slowly increased over a 60 minute test period to 7.2±0.08. Similar changes with a buffered articaine formulation could be expected. The current study’s mean pH values are reported in Table 12. The mean buffered articaine formulation pH for the initial time period was 7.54. The pH increased slightly over the fifteen minutes pH test period from 7.54 to 7.63 (Figure 4). Murakami et al (153) reported that the pH increase overtime is due to the CO₂ diffusing out of a solution. When CO₂ reacts with water, carbonic acid is formed. As CO₂ diffuses out of solution, the solution becomes more basic. In the current study, the containers used to measure solution pH were not left open to ambient air. Septodont Inc. (46) does not report the pH of the non-buffered articaine formulation on the product insert. It only reports that sodium hydroxide is used to adjust the pH. The mean non-buffered articaine formulation pH was 4.76 (Table 12). Nydegger (11) reported the pH of the same anesthetic formulation and from the same manufacturer as 3.3. Both investigations used the same pH meter and probe for measurements calibrated per manufacturer’s instructions. Thus, the experimentally determined pH range for a non-buffered 4% articaine HCl with 1:100,000 epinephrine is 3.3 – 4.76. Though not previously stated, but rather implied, the target pH for the buffered articaine formulation was physiologic pH (7.4). The buffered articaine formulation was buffered to a mean pH of 7.54. This was likely because the starting pH of articaine (5.0) is higher than lidocaine (3.5-4.0),
which was used to calculate the amount of bicarbonate to be injected into the anesthetic cartridge. Despite the pH value differences between the articaine formulations, anesthetic success, pain of injection and onset time were not significantly different.

Postoperative Pain

Postoperative pain ratings were analyzed from 75 study participants. Five patients did not return the postoperative survey and were excluded from the postoperative analysis (Tables 8, 9, & 10, Appendix I). Postoperative pain was rated using a 170-mm Heft-Parker VAS (Appendix H). Participants rated their initial postoperative pain after the anesthetic effects wore off (Day 0). The next three consecutive mornings after the study appointment, the participants rated their pain and noted any complications (Day 1, Day 2, and Day 3, respectively). Postoperative pain ratings by gender and day are reported in Table 8.

The mean Heft-Parker VAS pain ratings for each anesthetic group were not significantly different for Day 0 for both males and females. For Day 1, Day 2, and Day 3, the males did not have significant differences between the anesthetic groups. For Day 1, Day 2, and Day 3, the females demonstrated a significant difference between the buffered and non-buffered articaine groups (P=0.0079, P=0.0038, P=0.0000, respectively), with Day 1 reporting the greatest postoperative pain (55 mm)(female buffered articaine). Day 1 mean postoperative pain rating for the female buffered articaine was on the border of ‘mild’ and ‘moderate’ pain categories (55 mm). The Day 2 and Day 3 mean postoperative pain ratings were within the ‘mild’ pain category. The
summary of postoperative pain by day and anesthetic using a descriptive scale is presented in Table 9. Most of the postoperative pain ratings were in the ‘mild’ range (except for the female buffered articaine formulation on postoperative Day 1 - 55.4 mm which was in the ‘moderate’ pain range) and would not be of great clinical significance.

Though not statistically analyzed, the pain ratings for females were higher than the males pain ratings. As previously discussed, Liddell et al (129) reported that women said they would try to avoid pain more than men, accept pain less than men, and fear pain more than men. Keogh et al (130) and Fillingim et al (131) reported a female predilection for lower pain thresholds and pain tolerance when compared to male participants. In general, this may explain why females had more postoperative pain.

Nydegger (11) reported that a non-buffered 4% articaine formulation caused more postoperative pain at the time anesthesia wore off (Day 0) than 4% lidocaine or 4% prilocaine for female participants. There were no significant differences among the anesthetic formulations on Day 1, Day 2, and Day 3. Robertson et al (2), Pabst et al (6), McEntire et al (9), and Martin et al (8) reported the mean postoperative pain ratings following a primary mandibular buccal infiltration with 1.8 mL of 4% articaine with 1:100,000 epinephrine for Day 0, Day 1, Day 2 and Day 3 averaged 23 mm; 16 mm; 11 mm; and 7 mm, respectively. They did not report on gender differences. Nydegger (11) reported mean postoperative pain ratings for the four days using a non-buffered 4% articaine formulation were 37 mm, 27 mm, 18 mm, and 10 mm. The current study reported mean postoperative pain ratings for the four days using the non-buffered articaine formulation were 27-34 mm, 20-30 mm, 15-24 mm, and 6-13 mm. These values were very similar to the results reported by the other studies (2, 6, 8-11). The
mean postoperative pain ratings revealed a pattern of decreasing pain over the three days for both articaine formulations (Table 8). Similar results were reported in previous studies (2, 6, 8, 9, 11). All mean postoperative pain ratings were in the range of mild pain (except for females at postoperative Day 1) and demonstrated no tissue damage from the anesthetic formulations administered.

In summary, postoperative pain was generally in the ‘mild’ pain range. Pain decreased over the three day period. The mean postoperative pain ratings reported for the female buffered articaine group were significantly higher for Day 1, Day 2 and Day 3 when compared to the female non-buffered postoperative pain ratings. The increased pain ratings may be due to the pH. The increased pH, above physiologic pH, and the hyperosmolar formulation may have induced tissue inflammation and damage at the injection site. Several case reports and studies (145, 154, 155) have reported tissue damage from noncytotoxic formulations such as sodium bicarbonate. It is possible that the pH of the buffered formulation given in the submucosal tissue could produce a mild inflammatory reaction that would elevate the pain ratings in the buffered articaine group.

**Postoperative Complications**

The majority of postoperative complications were reported as injection site tenderness and subjective swelling at the injection site. A full list of complications for each day and anesthetic formulation is reported in Table 10. The major postoperative complications reported for the buffered and non-buffered articaine formulation were initial tenderness (18%) and subjective swelling (11%) around the injection site (Table 10). Nydegger (11) used an identical methodology as the current study for reporting
postoperative complications. Initial tenderness was reported 17% of the time and subjective swelling 10% of the time in his study. The current study’s results were very similar. Using 1.8 mL of 4% articaine with 1:100,000 epinephrine for a primary mandibular buccal first molar infiltration, Pabst et al (6), McEntire et al (9), and Martin et al (8) reported postoperative averages of 14% injection site tenderness, and 7% subjective swelling at the injection site. These results are similar to the current study. Robertson et al (2) reported postoperative complications for subjective swelling at 4% with the mandibular first molar primary mandibular buccal infiltration using 1.8 mL of 4% articaine with 1:100,000 epinephrine.

Subjective swelling was reported as resolved by postoperative Day 3. In the current study, most complications resolved within 3 days except for 8 participants who reported injection site tenderness on Day 3 and one participant who reported subjective swelling on Day 3 (Table 10). Pabst et al (6), McEntire et al (9), Martin et al (8), and Nydegger (11) also reported a small number of participants had tenderness at the injection site on postoperative Day 3 for both lidocaine and prilocaine formulations. Nydegger (11) also reported that articaine had the highest number of postoperative complications for Day 0 and Day 1 time periods.

Several authors investigated reports of paresthesia associated with articaine use (66, 71, 72). Articaine was reported to have a higher incidence of paresthesia than lidocaine (i.e., 1:4,159,848 injections versus 1:181,076,673 injections). The incidences were reported from nonsurgical dental treatment following local anesthesia administration. Of the reported incidences indicating the type of injection technique used, 94.5% of paresthesia cases involved a mandibular nerve block (IANB and lingual).
Only 4.6% involved an infiltration injection. The mandibular arch was effected most (95.5%). Though statistically significant, paresthesia from nonsurgical dental treatment after local anesthetic administration was still a rare event for any anesthetic. The current study reported one participant experiencing numbness (corner of the mouth) for the survey-reporting period following both formulation injection appointments (Table 10). Numbness was confirmed clinically. The time period for the duration of numbness, which lasted past the survey reporting period, was not recorded. The patient was contacted and reported that the numbness resolved.

The participants reported a higher incidence of postoperative complications for the buffered articaine formulation for initial tenderness and subjective swelling than the non-buffered articaine formulation (Table 10). Buffered articaine initial tenderness reported an incidence of 25%, 27% and 20% (Day 1, Day 2, Day 3, respectively) versus non-buffered articaine with an incidence of 19%, 15% and 11% (Day 1, Day 2, Day 3, respectively). Subjective swellings were reported for buffered articaine of 27%, 21% and 21% (Day 1, Day 2, Day 3, respectively) versus non-buffered articaine of 11%, 5%, and 1% (Day 1, Day 2, Day 3, respectively). The associated postoperative pain ratings for Day 1, Day 2 and Day 3 were generally mild. Clinically, this may not be of great concern. The initial tenderness and subjective swellings were reported in a higher number of participants at postoperative Days 1 – Day 3 for the buffered formulation (Table 10). It is difficult to explain why the participants with the buffered 4% articaine formulation experienced more postoperative complications. A possible theory may be due to the hyperosmolarity and pH of the buffered formulation. Several case reports have discussed extravasation injuries due to hyperosmolar formulations. Gaze (155) reported
eight cases of tissue necrosis due to extravasation of 4.2% or 8.4% sodium bicarbonate formulations (100-200 mL) administered for various medical procedures. The only intravenous formulation used was sodium bicarbonate. The reported sodium bicarbonate pH was 8.15. Schummer et al (154) reported an injury due to a 8.4% sodium bicarbonate formulation (100 mL) administered to achieve circulatory stabilization after a cardiopulmonary bypass. The NaHCO₃ was administered via a cannula placed in the dorsum of the left hand. Extravasation was identified and measures to eliminate the fluid were conducted. Severe soft tissue necrosis resulted with surgical debridement of the area. The pH of the NaHCO₃ was reported as 7.0-8.5. Le and Patel (145), in a review of extravasation injuries from intravenous therapy administration, reported sodium bicarbonate as one of the medications with vesicant properties, capable of causing severe tissue necrosis and permanent complications. The buccal infiltration injection was administered as a supraperiosteal injection into the submucosal tissues. The extent of subjective swelling and tenderness was minimal and does not compare to the tissue necrosis observed in the case reports and review. Also, the volume of sodium bicarbonate administered in the extravasation investigations was usually 100-200 mL. They did not indicate the amount expected to have entered the tissue. The administered volume of sodium bicarbonate in the current study was 0.18 mL; a 550-1100 times difference in administered volume. This may have been the why the tissue's inflammatory response to the buffered formulation was milder. Whitcomb et al (29) performed a pilot study to determined the ideal concentration of sodium bicarbonate to use when investigating buffered lidocaine formulation given as a IANB. When administering a 1:1 concentration of freshly prepared 2% lidocaine: 8.4% sodium
bicarbonate formulation with a final 0.5 mEq/mL NaHCO₃ as an infiltration over the maxillary lateral incisor. The patients (N=2) experienced profound numbness at the site of injection for the remainder of the day of the infiltration. For several days following the injection pain and a small knot was present at the site of injection. One subject was unable to move their nostril on the side of the injection. This study provides relevant evidence of a 8.4% sodium bicarbonate causing irritation after a dental infiltration.

This is the first clinical study to investigate the use of buffered articaine for infiltration. The postoperative complications appear to be related to the higher mean postoperative pain ratings for the 4% buffered articaine formulation. Essentially, the majority of postoperative complications would be of little clinical significance due to the subjective nature of the complications and the overall pain reported within the mild category. There may have been annoyance to the patient (tenderness and/or swelling), but reported symptoms did not get worse over the three days. However, the current study only measured postoperative pain and complications for 3 days. It is not known when all of the postoperative pain and complications completely resolved.

In conclusion, a buffered 4% articaine formulation was not statistically or clinically different than a non-buffered 4% articaine formulation for a primary buccal infiltration of the mandibular first molar in asymptomatic subjects. The success rate of 65% to 71% is not high enough to support its use as a primary buccal infiltration technique in the mandibular first molar. The pain of injection, specifically the pain of formulation deposition was not significantly different between either articaine formulation. The buffering system manufacturer (Onset®) reported that buffered formulations (lidocaine) would cause less pain of injection. This study did not find such
results. The onset time for pulpal anesthesia was also not significantly different between either articaine formulation. Again, the buffering system manufacturer (Onset®) indicated that the onset time for pulpal anesthesia would be quicker. This study did not come to that conclusion.
Chapter 6

Summary and Conclusions

The purpose of this prospective randomized, double-blind, crossover study was to compare the degree of pulpal anesthesia obtained with a buffered 64.8 mg articaine with 16.2 µg epinephrine formulation versus a non-buffered 72 mg articaine with 18 µg epinephrine formulation as a primary infiltration at the mandibular first molar.

Eighty adult participants enrolled in this study (38 female, 42 male). Every participant presented for the study with asymptomatic test teeth. Topical anesthetic (0.2 mL of 20 % benzocaine) was applied for 60 seconds at the injection site prior to administering the primary mandibular buccal infiltration. All participants received each anesthetic formulation (buffered 64.8 mg articaine with 16.2 µg epinephrine formulation; non-buffered 72 mg articaine with 18 µg epinephrine formulation) at two appointments spaced at least two weeks apart. The mandibular first molar was tested every 30 seconds for the first 5 minutes, then every minute for the remaining 55 minutes of the test period with an electric pulp tester (EPT). The control tooth (contralateral canine) was tested every 5 minutes. Each participant rated the three phases (needle insertion, needle placement, and formulation deposition) of the injection for experienced pain. Postoperative pain was also recorded at four time periods: immediately after numbness
subsided, and the mornings of the next three days. Participants were also asked to record any associated postoperative complications for each time period. There were no significant differences in the mean pain ratings for needle insertion, needle placement and formulation deposition for the buffered and non-buffered articaine by gender. All mean pain ratings for needle insertion, needle placement, and formulation deposition were within the ‘mild’ pain category except for the female non-buffered articaine formulation deposition, which was in the ‘moderate’ pain category. Formulation deposition was rated as the most painful phase of the injection for both articaine formulations and gender when compared to the other phases (needle insertion and placement). The female participants experienced more pain than the male participants during each stage of the infiltration injection for the buffered and non-buffered articaine formulations.

Successful pulpal anesthesia was defined as two consecutive 80/80 readings with an EPT within the test period (60 minutes). The buffered articaine formulation anesthetic success rate was 71%. The non-buffered articaine formulation anesthetic success rate was 65%. There was no significant difference for anesthetic success between buffered articaine and non-buffered articaine formulations (P>0.05).

The definition for the onset of pulpal anesthesia was the first of two consecutive maximum readings (80/80) with an EPT for the mandibular first molar. The time of onset to pulpal anesthesia for the buffered articaine and non-buffered articaine formulations were 5.9±5.9 minutes and 5.4±5.9, respectively. There was no significant difference between the onset of pulpal anesthesia by formulation for the mandibular first molar.

There was a significant difference between the buffered and non-buffered
formulations for female participant postoperative pain on Day 1, 2, and 3 (P=0.0079, P=0.0038, and P=0.000, respectively). All mean pain ratings were within the ‘mild’ pain category except for the female subjects who received buffered articaine for postoperative Day 1, which was in the ‘moderate’ pain category. There was no significant difference for the postoperative male participants’ mean pain ratings for either anesthetic during any time period. All male mean pain ratings were within the ‘mild’ pain category.

We concluded that a buffered articaine formulation was not significantly better than a non-buffered articain formulation for buccal infiltration of the mandibular first molar in asymptomatic mandibular first molars. The success rate of 65% to 71% (plain versus buffered) is not high enough to support its use as a primary buccal infiltration technique in the mandibular first molar.
References


11. Nydegger B. Anesthetic efficacy of 4% articaine with 1:100,000 epinephrine, 4% prilocaine with 1:200,000 epinephrine, and 4% lidocaine with 1:100,000 epinephrine as a primary buccal infiltration of the mandibular first molar. Master's Thesis, The Ohio State University, 2013.


61. Simon MA, Gielen MJ, Alberink N, Vree TB, van Egmond J. Intravenous regional anesthesia with 0.5% articaine, 0.5% lidocaine, or 0.5% prilocaine. A double-blind randomized clinical study. Reg Anesth. 1997;22(1):29-34.


<table>
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<th># of Subjects</th>
<th>Age Range (years)</th>
<th>Mean Age (years)</th>
<th>Standard Deviation</th>
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<td>22-30</td>
<td>25.5</td>
<td>±2.7</td>
</tr>
<tr>
<td>Females</td>
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<td>21-33</td>
<td>25.2</td>
<td>±2.3</td>
</tr>
<tr>
<td>Totals</td>
<td>80</td>
<td>21-33</td>
<td>25.3</td>
<td>±2.5</td>
</tr>
</tbody>
</table>

Table 1. Biographical data for all subjects.
Table 2. Mean VAS Values (mm) of Injection Pain Ratings for the Primary Mandibular Buccal Infiltration of Anesthetic Formulations by Gender.

<table>
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<tr>
<th>Injection Phase</th>
<th>Anesthetic</th>
<th>Males (N=42)</th>
<th>Females (N=38)</th>
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<tr>
<td>Insertion</td>
<td>Buffered Arti</td>
<td>27.0±18.8</td>
<td>34.6±27.1</td>
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<tr>
<td></td>
<td>Non-Buffered Arti</td>
<td>27.7±20.8</td>
<td>36.3±26.9</td>
</tr>
<tr>
<td></td>
<td>P-value</td>
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<td>1.000</td>
</tr>
<tr>
<td>Placement</td>
<td>Buffered Arti</td>
<td>31.2±24.0</td>
<td>47.5±30.4</td>
</tr>
<tr>
<td></td>
<td>Non-Buffered Arti</td>
<td>33.1±23.2</td>
<td>50.4±33.2</td>
</tr>
<tr>
<td></td>
<td>P-value</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Deposition</td>
<td>Buffered Arti</td>
<td>40.6±26.6</td>
<td>49.6±26.4</td>
</tr>
<tr>
<td></td>
<td>Non-Buffered Arti</td>
<td>39.9±25.9</td>
<td>58.2±32.9</td>
</tr>
<tr>
<td></td>
<td>P-value</td>
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<td>1.000</td>
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</table>
Table 3. Summary of Pain Ratings for Needle Insertion Using a Descriptive Scale.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
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<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<td><strong>Total</strong></td>
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<td>16 (10%)</td>
<td>108 (67.5%)</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>38</td>
<td>6 (15.8%)</td>
<td>18 (47.4%)</td>
<td>14 (36.8%)</td>
<td>0 (0%)</td>
</tr>
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<td>Male</td>
<td>42</td>
<td>3 (7.1%)</td>
<td>33 (78.6%)</td>
<td>6 (14.3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Non-Buffered Arti</strong></td>
<td>80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>38</td>
<td>4 (10.5%)</td>
<td>25 (65.8%)</td>
<td>9 (23.7%)</td>
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</tr>
<tr>
<td>Male</td>
<td>42</td>
<td>3 (7.1%)</td>
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<td>7 (16.7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>84</td>
<td>6 (7.1%)</td>
<td>65 (77.4%)</td>
<td>13 (15.5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>76</td>
<td>10 (13.2%)</td>
<td>43 (56.6%)</td>
<td>23 (30.3%)</td>
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Table 4. Summary of Pain Ratings for Needle Placement Using a Descriptive Scale.

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<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<tr>
<td><strong>Total</strong></td>
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<td>11 (6.8%)</td>
<td>99 (61.9%)</td>
<td>48 (30%)</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td><strong>Buffered Arti</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>38</td>
<td>1 (2.6%)</td>
<td>23 (60.5%)</td>
<td>13 (34.2%)</td>
<td>1 (2.6%)</td>
</tr>
<tr>
<td>Male</td>
<td>42</td>
<td>5 (11.9%)</td>
<td>26 (61.9%)</td>
<td>11 (26.2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Non-Buffered Arti</strong></td>
<td>80</td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>38</td>
<td>2 (5.3%)</td>
<td>21 (55.3%)</td>
<td>14 (36.8%)</td>
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<tr>
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<td>42</td>
<td>3 (7.1%)</td>
<td>29 (69.0%)</td>
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<tr>
<td><strong>Male</strong></td>
<td>84</td>
<td>8 (9.5%)</td>
<td>55 (65.5%)</td>
<td>21 (25.0%)</td>
<td>0 (0%)</td>
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<tr>
<td><strong>Female</strong></td>
<td>76</td>
<td>3 (3.9%)</td>
<td>44 (57.9%)</td>
<td>27 (35.5%)</td>
<td>2 (2.6%)</td>
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Table 5. Summary of Pain Ratings for Formulation Deposition Using a Descriptive Scale.

<table>
<thead>
<tr>
<th>Variable</th>
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<th>None (%)</th>
<th>Mild (%)</th>
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<tr>
<td>Total</td>
<td>160</td>
<td>6 (3.8%)</td>
<td>96 (60.0%)</td>
<td>56 (35.0%)</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Buffered Arti</td>
<td>80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>38</td>
<td>1 (2.6%)</td>
<td>21 (55.3%)</td>
<td>16 (42.1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Male</td>
<td>42</td>
<td>2 (4.8%)</td>
<td>28 (66.7%)</td>
<td>12 (28.6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Non-Buffered Arti</td>
<td>80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>38</td>
<td>0 (0%)</td>
<td>19 (50.0%)</td>
<td>17 (44.7%)</td>
<td>2 (5.3%)</td>
</tr>
<tr>
<td>Male</td>
<td>42</td>
<td>3 (7.1%)</td>
<td>28 (66.7%)</td>
<td>11 (26.2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Male</td>
<td>84</td>
<td>5 (5.9%)</td>
<td>56 (66.6%)</td>
<td>23 (27.4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Female</td>
<td>76</td>
<td>1 (1.3%)</td>
<td>40 (52.6%)</td>
<td>33 (43.4%)</td>
<td>2 (2.6%)</td>
</tr>
</tbody>
</table>
Anesthetic success was defined as two consecutive maximum EPT (80/80) readings during the testing period of 60 minutes.

* McNemar tests.

**Table 6: Anesthetic Success.**

<table>
<thead>
<tr>
<th>Tooth</th>
<th>Buffered Articaine</th>
<th>Non-Buffered Articaine</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Molar</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=80</td>
<td>57 (71.2%)</td>
<td>52 (65.0%)</td>
<td>0.3018*</td>
</tr>
</tbody>
</table>
Anesthesia onset was defined as the time at which the first of two consecutive 80/80 readings were recorded.

Anesthesia duration was defined as the total time between the first of two consecutive 80/80 readings and the last of two consecutive 80/80 readings that were recorded.

* Number of subjects who experienced two consecutive 80/80 readings (anesthetic success) with both formulations.

†Multiple McNemar tests.
‡Adjusted using Step-down Bonferroni method of Holm.

Table 7: Mean Anesthesia Onset and Duration Time for each Anesthetic Group.

<table>
<thead>
<tr>
<th>Solution</th>
<th>N*</th>
<th>Time (Minutes)</th>
<th>S.D. ±</th>
<th>P-value†</th>
<th>Adj. p-value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buffered Arti</td>
<td>47</td>
<td>5.9</td>
<td>±5.9</td>
<td>0.6085</td>
<td>1.000</td>
</tr>
<tr>
<td>Non-Buffered Arti</td>
<td>47</td>
<td>5.4</td>
<td>±5.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buffered Arti</td>
<td>47</td>
<td>42.4</td>
<td>±16.8</td>
<td>0.5046</td>
<td>1.000</td>
</tr>
<tr>
<td>Non-Buffered Arti</td>
<td>47</td>
<td>41.7</td>
<td>±13.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 8. Mean VAS Values (mm) of Postoperative Pain Ratings.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Buffered Articaine</th>
<th>Non-Buffered Articaine</th>
<th>P-value*</th>
<th>Adj. P-value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Post-op Day 0</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>51.0±31.6</td>
<td>34.0±25.2</td>
<td>0.0576</td>
<td>0.1728</td>
</tr>
<tr>
<td>Male</td>
<td>33.5±24.2</td>
<td>27.4±21.6</td>
<td>0.3915</td>
<td>0.3915</td>
</tr>
<tr>
<td><strong>Post-op Day 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>55.4±32.1</td>
<td>30.0±26.9</td>
<td>0.0013</td>
<td><strong>0.0079</strong></td>
</tr>
<tr>
<td>Male</td>
<td>28.2±21.6</td>
<td>20.1±19.1</td>
<td>0.0653</td>
<td>0.1728</td>
</tr>
<tr>
<td><strong>Post-op Day 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>46.0±30.7</td>
<td>24.1±26.5</td>
<td>0.0005</td>
<td><strong>0.0038</strong></td>
</tr>
<tr>
<td>Male</td>
<td>21.6±20.2</td>
<td>14.7±16.6</td>
<td>0.0295</td>
<td>0.1178</td>
</tr>
<tr>
<td><strong>Post-op Day 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>33.1±26.9</td>
<td>12.9±17.9</td>
<td>0.0000</td>
<td><strong>0.0000</strong></td>
</tr>
<tr>
<td>Male</td>
<td>13.8±17.1</td>
<td>5.9±10.4</td>
<td>0.0227</td>
<td>0.1133</td>
</tr>
</tbody>
</table>

N= 75 (Male = 39, Female = 36)

*Wilcoxon matched pairs, signed ranks test.
‡ Adjusted using Step-down Bonferroni method of Holm.
<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Buffered Arti Female</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>36</td>
<td>3 (8.3%)</td>
<td>18 (50.0%)</td>
<td>14 (38.9%)</td>
<td>1 (2.8%)</td>
</tr>
<tr>
<td>Day 1</td>
<td></td>
<td>1 (2.8%)</td>
<td>18 (50.0%)</td>
<td>16 (44.4%)</td>
<td>1 (2.8%)</td>
</tr>
<tr>
<td>Day 2</td>
<td></td>
<td>3 (8.3%)</td>
<td>18 (50.0%)</td>
<td>15 (41.7)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Day 3</td>
<td></td>
<td>6 (16.7%)</td>
<td>18 (50.0%)</td>
<td>12 (33.3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Non-Buffered Arti Female</strong></td>
<td>36</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td></td>
<td>7 (19.4%)</td>
<td>18 (50.0%)</td>
<td>11 (30.6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Day 1</td>
<td></td>
<td>9 (25.0%)</td>
<td>18 (50.0%)</td>
<td>9 (25.0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Day 2</td>
<td></td>
<td>12 (33.3%)</td>
<td>19 (52.8%)</td>
<td>5 (13.9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Day 3</td>
<td></td>
<td>17 (47.2%)</td>
<td>17 (47.2%)</td>
<td>2 (5.6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Buffered Arti Male</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>39</td>
<td>1 (2.6%)</td>
<td>28 (71.76%)</td>
<td>10 (25.6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Day 1</td>
<td></td>
<td>4 (10.3%)</td>
<td>28 (71.76%)</td>
<td>7 (17.9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Day 2</td>
<td></td>
<td>9 (23.1%)</td>
<td>27 (69.2%)</td>
<td>3 (7.7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Day 3</td>
<td></td>
<td>14 (35.9%)</td>
<td>23 (59.0%)</td>
<td>2 (5.1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Non-Buffered Arti Male</strong></td>
<td>39</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td></td>
<td>3 (7.7%)</td>
<td>31 (79.5%)</td>
<td>5 (12.8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Day 1</td>
<td></td>
<td>6 (15.4%)</td>
<td>31 (79.5%)</td>
<td>2 (5.1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Day 2</td>
<td></td>
<td>11 (28.1%)</td>
<td>26 (66.7%)</td>
<td>2 (5.1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Day 3</td>
<td></td>
<td>18 (46.2%)</td>
<td>21 (53.8%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Table 9. Summary of Pain Ratings for Postoperative Pain by Day and Anesthetic Using a Descriptive Scale.
<table>
<thead>
<tr>
<th>Complication</th>
<th>Post-op Day 0 (%)</th>
<th>Post-op Day 1 (%)</th>
<th>Post-op Day 2 (%)</th>
<th>Post-op Day 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tenderness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buffered Articaine</td>
<td>15 (16.7%)</td>
<td>21 (27.6%)</td>
<td>22 (28.9%)</td>
<td>16 (21.1%)</td>
</tr>
<tr>
<td>Non-Buffered Articaine</td>
<td>13 (19.7%)</td>
<td>16 (20.5%)</td>
<td>10 (12.8%)</td>
<td>8 (10.3%)</td>
</tr>
<tr>
<td><strong>Subjective Swelling</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buffered Articaine</td>
<td>10 (13.2%)</td>
<td>22 (28.9%)</td>
<td>16 (21.1%)</td>
<td>16 (21.1%)</td>
</tr>
<tr>
<td>Non-Buffered Articaine</td>
<td>6 (5.3%)</td>
<td>8 (10.3%)</td>
<td>4 (5.1%)</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td><strong>Paresthesia/Tingling</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buffered Articaine</td>
<td>0 (0.0%)</td>
<td>2 (2.6%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Non-Buffered Articaine</td>
<td>2 (2.6%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td><strong>Anesthesia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buffered Articaine</td>
<td>1 (1.3%)</td>
<td>0 (0.0%)</td>
<td>1 (1.3%)</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Non-Buffered Articaine</td>
<td>0 (0.0%)</td>
<td>1 (1.3%)</td>
<td>1 (1.3%)</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td><strong>Prolonged Numbness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buffered Articaine</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Non-Buffered Articaine</td>
<td>2 (2.6%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buffered Articaine</td>
<td>3 (4.0%)</td>
<td>1 (1.3%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Non-Buffered Articaine</td>
<td>1 (1.3%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td><strong>Light-headed/Dizzy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buffered Articaine</td>
<td>2 (2.6%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Non-Buffered Articaine</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buffered Articaine</td>
<td>0 (0.0%)</td>
<td>1 (1.3%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Non-Buffered Articaine</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td><strong>Bruising</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buffered Articaine</td>
<td>1 (1.3%)</td>
<td>1 (1.3%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Non-Buffered Articaine</td>
<td>0 (0.0%)</td>
<td>2 (2.6%)</td>
<td>1 (1.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td><strong>Akenesia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buffered Articaine</td>
<td>2 (2.6%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Non-Buffered Articaine</td>
<td>1 (1.3%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

N=75

Table 10: Frequency of Subject-reported Postoperative Complications by Day.
<table>
<thead>
<tr>
<th>Complication</th>
<th>Post-op Day 0 (%)</th>
<th>Post-op Day 1 (%)</th>
<th>Post-op Day 2 (%)</th>
<th>Post-op Day 3 (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tenderness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buffered Articaine</td>
<td>15 (16.7%)</td>
<td>21 (27.6%)</td>
<td>22 (28.9%)</td>
<td>16 (21.1%)</td>
<td>0.0679</td>
</tr>
<tr>
<td>Non-Buffered Articaine</td>
<td>13 (19.7%)</td>
<td>16 (20.5%)</td>
<td>10 (12.8%)</td>
<td>8 (10.3%)</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.0679</td>
<td><strong>0.0247</strong></td>
<td><strong>0.0016</strong></td>
<td><strong>0.0033</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Subjective Swelling</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buffered Articaine</td>
<td>10 (13.2%)</td>
<td>22 (28.9%)</td>
<td>16 (21.1%)</td>
<td>16 (21.1%)</td>
<td></td>
</tr>
<tr>
<td>Non-Buffered Articaine</td>
<td>6 (5.3%)</td>
<td>8 (10.3%)</td>
<td>4 (5.1%)</td>
<td>1 (1.3%)</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.1573</td>
<td><strong>0.0049</strong></td>
<td><strong>0.0054</strong></td>
<td><strong>0.0004</strong></td>
<td></td>
</tr>
</tbody>
</table>

N=75

Table 11: Frequency of Subject-reported Postoperative Complications by Day.
Table 12: pH of Anesthetic Formulation.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Mean pH</th>
<th>S.D.</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>4% articaine with 1:100,000 epinephrine</td>
<td>4.76</td>
<td>0.085</td>
<td>4.62</td>
<td>4.92</td>
</tr>
<tr>
<td>4% articaine with 1:100,000 epinephrine with 8.4% NaHCO₃</td>
<td>7.54</td>
<td>0.027</td>
<td>7.46</td>
<td>7.67</td>
</tr>
</tbody>
</table>

Table 13: Mean pH Values for Buffered Articaine Over Time.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean pH</td>
<td>7.54</td>
<td>7.56</td>
<td>7.57</td>
<td>7.58</td>
<td>7.58</td>
<td>7.58</td>
<td>7.60</td>
<td>7.59</td>
</tr>
<tr>
<td>Time (min)</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>14</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Mean pH</td>
<td>7.60</td>
<td>7.60</td>
<td>7.61</td>
<td>7.61</td>
<td>7.62</td>
<td>7.63</td>
<td>7.63</td>
<td></td>
</tr>
<tr>
<td>Overall Mean pH</td>
<td>7.59</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIME PERIOD</td>
<td>TIME (MIN)</td>
<td>SOLUTION TYPE</td>
<td>% NUMB</td>
<td>TIME PERIOD</td>
<td>TIME (MIN)</td>
<td>SOLUTION TYPE</td>
<td>% NUMB</td>
<td></td>
</tr>
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Table 15: Percentage of 80/80 Readings by Solution and Time Period.
Appendix B

Figure
Anesthetic success was defined as two consecutive maximum EPT (80/80) readings during the testing period of 60 minutes.

Figure 1. Percentage of 80 Readings for the Mandibular First Molar.
Figure 2. Self-reported Incidence of Postoperative Tenderness by Day.
Figure 3. Self-reported Incidence of Postoperative Swelling by Day.
Figure 4: Buffered Articaine Solution pH Values Over a Recorded Time Period.
Appendix C

Biographical Data
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Appendix D

Medical History
Medical History

1. Do you have or have you had any of the following?
   - a. rheumatic fever or rheumatic heart disease
   - b. heart murmur or mitral valve prolapse
   - c. heart disease or heart attack
   - d. artificial heart valve
   - e. irregular heart beat
   - f. pacemaker
   - g. high blood pressure
   - h. chest pains or angina
   - i. stroke
   - j. artificial joint
   - k. hepatitis/liver disease
   - l. tuberculosis
   - m. thyroid problem
   - n. kidney disease
   - o. diabetes (sugar)
   - p. asthma
   - q. HIV or other immunosuppressive disease
   - r. radiation or cancer therapy

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**

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

______________________________________________________________________________
______________________________________________________________________________

**Medical Risk Assessment**

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

Consent Form
The Ohio State University Consent to Participate in Research

A prospective randomized, double blind study of the anesthetic efficacy of buffered articaine as a primary buccal infiltration of the mandibular first molar.

Study Title: A prospective randomized, double blind study of the anesthetic efficacy of buffered articaine as a primary buccal infiltration of the mandibular first molar.

Principal Investigator: Dr. John M. Nusstein

Sponsor:

- 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?

Articaine is a numbing formulation approved by the FDA for routine use in the dental office. Articaine is given as a shot next to the tooth. The purpose of this study is to see if increased amounts of buffered articaine are better at making your teeth numb for a dental
procedure. Buffering is used to change the pH (acidity) of a drug/formulation to improve patient comfort and/or improve the efficacy (effectiveness) of the drug.

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

Eighty (80) people will take part in this study.

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

You will receive injections (shots) of articaine with epinephrine (a numbing formulation like “novocaine”) and buffered articaine with epinephrine in the back of your lower jaw. The articaine numbing formulation, and the buffering agent (sodium bicarbonate), used is not experimental. It is routinely used in the dental office and has been approved by the FDA for dental use. Prior to the first injection, you will be required to complete a medical history questionnaire. A device called an electric pulp tester will be used to test your teeth for numbness. The electric pulp tester is a battery operated device that delivers a very small amount of current to the tooth resulting in a tingling sensation that might be uncomfortable or cause pain in the tooth being tested and which may last up to one second. It will be used on your teeth before the injections of numbing formulation. One of your lower back teeth as well as a tooth on the opposite side (control tooth) will be tested with the electric pulp tester to be sure that your teeth respond (the nerves are alive and the teeth have not had root canal treatment). This will take about 6 minutes. There will be two appointments spaced at least one week apart. You will receive one injection (shot) at each appointment. After topical numbing anesthetic (20% Benzocaine), a gel that numbs the gum tissue, has been applied to the injection (shot) site for one minute, you will receive 1.8 mL (a little more than one third of a teaspoon) of 4% articaine with 1:100,000 epinephrine or 1.8 mL (a little less than three quarters of a teaspoon) of buffered 4% articaine with 1:100,000 epinephrine (buffering agent is sodium bicarbonate). Whether you receive the buffered or non-buffered articaine formulation will be determined at random (by chance, like flipping a coin). You will not know which injection, either the buffered or non-buffered articaine numbing formulation, you will receive. The doctor will not know which injection you will receive. Your numb tooth will then be tested for numbness every 15 seconds, beginning 30 seconds after the injection (shot) for the first five minutes. After five minutes, your numb tooth will be pulp tested every minute for another 55 minutes to determine how well the injection (shot) gets your tooth numb. In addition, the electric pulp tester will be used on one of your teeth on the opposite side (where you are not numb). Teeth that are not numb or are being used as a control will experience a tingling sensation or discomfort at which time
the device will be removed immediately. You will be asked to rate the amount of pain you feel when the injections are being given. You will do this by marking your pain experience on a line graph with a pen. You will be asked to complete a short survey after each appointment to rate any pain or discomfort you have at the injection site over a three-day period following each appointment. You will also report any other side effects not relating to pain or discomfort. This survey will take about one minute to fill out each morning.

4. How long will I be in the study?

There will be two appointments, each will last approximately 70 minutes - 10 minutes for baseline pulp testing and filling out health information and receiving the initial injection. Your teeth will be pulp tested for a total of 60 minutes. The questionnaires will take about 1 minute to fill out on the day of the appointment and for each morning for 3 days following each appointment. After completing the questionnaires, you will either mail them in a pre-addressed stamped envelope or personally deliver it to the endodontic clinic front office. This will take about five minutes.

5. Can I stop being in the study?

You may leave the study at any time. If you decide to stop participating in the study, there will be no penalty, 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.

If you are a student or staff member at OSU and choose not to participate in this study, your grades and/or employment will not be affected.

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

You may have pain associated with the local anesthetic (numbing formulation) or soreness at the site of the injections (shots) for approximately two days. Where you receive the injection, you may have swelling (hematoma—a collection of blood in my
mouth) or a bruise may develop. You may experience a feeling of anxiety, lightheadedness or fainting, and or a temporary increase in my heart rate. The tingling sensation and/or slight discomfort (pain) produced by the pulp tester may be uncomfortable. 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 requested to take a urine pregnancy test before you can start this study. If you are a woman, you must also be using a reliable method of contraception (oral contraceptives, condoms, diaphragm, or abstinence) during the next 24 hours. 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. There are no adequate and well-controlled studies of articaine in pregnant women. This test will be paid for by the investigator.

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

You will not directly benefit from this study. Society may benefit if the additional infiltration (shot next to the tooth) of buffered articaine demonstrates that your teeth may become anesthetized (numb) sooner, longer and with lower relative discomfort and pain.

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

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

**If you are a student or staff member at OSU and choose not to participate in this study, your grades and/or employment will not be affected.**

There are no other choices other than to participate or not participate in the study.

9. **Will my study-related information be kept confidential?**
Efforts will be made to keep your study-related information confidential. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law. Also, your records may be reviewed by the following groups (as applicable to the research):

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

If 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?

The study will pay for the cost of the study drug (articaine) and urine pregnancy test. The subjects will be responsible for paying for parking.

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

Yes, you will be paid $75 for your participation. You will receive $75.00 for completing all aspects of the study. If you are unable or unwilling to complete both sessions of the study, you will be paid a pro-rated $30.00 per session and an additional pro-rated $5.00 per completed and returned questionnaire form. After completing the questionnaires, you will personally deliver them to the endodontic clinic front office, at which time you will receive payment for the completed parts of the study for which you have not yet received payment. Payment is to compensate you for time and travel expenses. By law, payments to subjects are considered taxable income.

12. What happens if I am injured because I took part in this study?
If you suffer an injury from participating in this study, you should notify the researcher or study doctor immediately, who will determine if you should obtain medical treatment at The Ohio State University Wexner Medical Center.

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

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

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

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

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

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

14. Who can answer my questions about the study?

For questions, concerns, or complaints about the study you may contact Dr. John Nusstein or Dr. Ryan Shurtz 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. John Nusstein or Dr. Ryan Shurtz at 614 – 292-5399.
Signing the consent form

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

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

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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.

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

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Appendix F

HIPAA Forms
Beginning April 14, 2003, the new HIPAA Privacy Rule requires that Ohio State University Principal Investigators (PIs) provide research subjects with greater detail than what is currently included in the IRB-approved consent form concerning how a subject’s past, present and future health-related information (collectively, Protected Health Information or PHI) will be used, shared and protected during the research. Specifically, the Privacy Rule now requires that PIs inform subjects of the following: 1) what specific kinds of information will be used or disclosed to others during the course of the research; 2) the specific identities of collaborating investigators, sponsor companies or sponsor agencies that will potentially receive copies of subjects’ PHI during the research; 3) that subjects have a right to review their research-related PHI; and 4) that subjects have the express right to revoke their authorizations for the release of PHI at any time.

To meet these new requirements, PIs using PHI obtained from medical or research records from the Ohio State University Hospitals, The Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, OSU & Harding Behavioral Health Care & Medicine, the Ohio State University Hospitals East and the Primary Care Network (the University Health System), or other University operated health centers or clinics, must now complete and receive a signed copy of the University’s “Authorization to Use Personal Health Information in Research” form (the Authorization) below from subjects enrolling in research studies on or after April 14th (or be granted a waiver by a HIPAA Privacy Board) in addition to obtaining a signed IRB-approved consent form. The form will need to be carefully prepared by PIs to ensure that the Authorization covers ALL of the necessary uses and disclosures of personal health information used in clinical research. Failure to do so may violate the Privacy Rule and result in penalties against the University as well as individual civil and criminal penalties against the Principal Investigator.

INSTRUCTIONS TO RESEARCHERS
FOR PREPARING THE RESEARCH AUTHORIZATION FORM

1. Complete the first section of the Authorization form with title of the study, the OSU IRB protocol number, and PI name. Add subject name at the time of authorization. Do not include these instructions as part of the completed Authorization form.

2. “Uses and Disclosures Covered by this Authorization” – List every known non-OSU person, class of persons, or organizations (including the sponsor agency or company, known subsidiaries of the sponsor, cooperative data groups, etc.) that may create, disclose, receive, and/or use the information in connection with the study. Fill in the blanks on the form (and
delete the instructions in italics as well as inapplicable bulleted sections) as appropriate. If
information will not be disclosed outside of The Ohio State University, delete all bullets and
insert “None”. Note: if a person(s) or organization is not listed on the form, they may not
create, disclose, receive or use PHI in connection with the study.

3a. “HIPAA Privacy Contact” – If the research involves the use of medical records from the
University Health System, where applicable, insert the contact and address: HIPAA Privacy
Manager, the Ohio State University Medical Center, 140 Doan Hall, 410 W. Tenth Avenue,
Columbus, Ohio 43210.

3b. If the research solely involves the use of personal health records at non-University Health
System clinics or health care facilities (for example, the Dental School, Optometry School,
Nisonger Center, Younkin Center, Psychological Services Center, Anxiety and Stress
Disorder Clinic, Marriage & Family Therapy Clinic, Camera Center or faculty practice group
such as OSU-P) insert the name and address of the appropriate Privacy Contact for the center,
school, clinic or practice group. If unknown, contact the director of the health center, school,
clinic or practice group or the Office of Legal Affairs at (614) 292-0611 for the contact and
address of the applicable Privacy Contact.

4. The Authorization must be presented to all newly enrolled or “re-consented” subjects in IRB-
approved research beginning April 14, 2003 at the time the IRB-approved consent form is
signed. The subject or his/her legally authorized representative must be provided with a copy
of this form after it has been signed. The original, signed copy must be retained in the
research file for a period of six years from the date the Authorization was signed (or longer,
according to sponsor requirements). Prior IRB approval of the Authorization is not required;
however, the Privacy Contact and/or HIPAA Privacy Board may conduct audits of the
Authorization to ensure completeness.

5a. “Notice of Privacy Practices” – Each subject who receives health care services at
the University on or after April 14, 2003 should receive a copy of a Notice of Privacy Practices
(NPP) and sign an acknowledgement (NPP Acknowledgement form) that (s)he obtained the NPP.

5b. If the research involves the use of health and/or medical records from the
University Health System and the subject has not received a copy of the University Health
System’s NPP, provide the subject with a copy of the NPP. The subject should sign a copy of the
University Health System’s NPP Acknowledgement form. The original, signed copy of the NPP
Acknowledgement form must be retained in the research file for a period of six years from the
date the NPP Acknowledgement was signed (or longer, according to sponsor requirements). The
University Health System’s NPP and NPP Acknowledgement form are available in electronic
format on the Office of Responsible Research Practices (ORRP) website at http://www.orrp.ohio-
state.edu/ as well as the Medical Center’s website at http://www.osumedcenter.edu.

5c. If the research involves the use of health records at other non-University Health
System clinics or facilities (including the sites listed above in item 3b.) and the subject has not received a copy of the facility or clinic’s individual NPP, provide the subject with a copy of the NPP. Contact the director of the applicable health center, school, clinic or practice group to obtain a copy of the NPP and the NPP Acknowledgement form. The original, signed copy of the NPP Acknowledgement form must be retained in the research file for a period of six years from the date the NPP Acknowledgement was signed (or longer, according to sponsor requirements).
Title of the Study: A prospective randomized, double-blind study of the anesthetic efficacy of buffered articaine as a primary buccal infiltration of the mandibular first molar.

OSU Protocol Number: 2013H0040

Principal Investigator: Dr. John M. Nusstein

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. John Nusstein at the College of Dentistry, 305 w 12th avenue, the Ohio State University, Columbus, Ohio 43210 or Dr. Fonda Robinson at the College of Dentistry, 305 w 12th avenue, the Ohio State University, Columbus, Ohio 43210.

- 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 Mr. Matthew Stalsworth at the College of Dentistry, 1130 F Postle Hall 305 w 12th avenue, the Ohio State University, Columbus, Ohio 43210, 614-292-3016.

- If you have any questions relating to the research, please contact Dr. John Nusstein at the College of Dentistry, 305 w 12th avenue, the Ohio State University, Columbus, Ohio 43210.

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. John Nusstein 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 G

Primary Buccal Infiltration Pain Rating Form
Primary Buccal Infiltration Pain Rating

Date: __________

Patient #: __________

Needle Insertion

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

   None      Faint      Weak      Mild      Moderate      Strong      Intense      Maximum
   Possible

Needle Placement

2. Please place an “X” on the line below to rank the level of pain felt during needle placement.

   None      Faint      Weak      Mild      Moderate      Strong      Intense      Maximum
   Possible

Formulation Deposition

3. Please place an “X” on the line below to rank the level of pain felt during formulation deposition.

   None      Faint      Weak      Mild      Moderate      Strong      Intense      Maximum
   Possible
Appendix H

EPT Values Recording Sheet
# EPT Values

Pulp Tester ______________________
Date __________
Patient # ___________________ Code # ______________________
Appointment # ______________ Side _______________________

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<th>1st molar</th>
<th>Contra- lateral canine</th>
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</thead>
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<td>Min. Pre-test</td>
<td></td>
<td></td>
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<tr>
<td>Min. Pre-test</td>
<td></td>
<td></td>
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<tr>
<td>Base-line</td>
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<td></td>
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</tbody>
</table>

* indicates tooth will be tested with a mock electrode

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<th>1st molar</th>
<th>2nd premolar</th>
<th>1st premolar</th>
<th>Contra- lateral canine</th>
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Appendix I

Postoperative Survey
Patient #:__________________

POST INJECTION SURVEY

Please answer the following questions regarding the injection (shot) that was administered.

**Immediately following the injection when the numbness wears off:**
Please rate the discomfort, soreness, or pain where the shot was administered by marking an “x” on the point on the line that best describes your pain.

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

Please note any additional comments and/or side effects not relating to pain or discomfort (e.g. numbness, swelling, bruising, nausea, light headed feeling, etc)

______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________

**First day following the injection when you get up in the morning:**
Please rate the discomfort, soreness, or pain where the shot was administered by marking an “x” on the point on the line that best describes your pain.

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

Please note any additional comments and/or side effects not relating to pain or discomfort (e.g. numbness, swelling, bruising, etc.)

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
Second day following the injection when you get up in the morning:

Please rate the discomfort, soreness, or pain where the shot was administered by marking an “x” on the point on the line that best describes your pain.

[Line with points labeled: None, Faint, Weak, Mild, Moderate, Strong, Intense, Maximum Possible]

Please note any additional comments and/or side effects not relating to pain or discomfort (e.g. numbness, swelling, bruising, etc.).

______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________

Third day following the injection when you get up in the morning:

Please rate the discomfort, soreness, or pain where the shot was administered by marking an “x” on the point on the line that best describes your pain.

[Line with points labeled: None, Faint, Weak, Mild, Moderate, Strong, Intense, Maximum Possible]

Please note any additional comments and/or side effects not relating to pain or discomfort (e.g. numbness, swelling, bruising, etc.).

______________________________________________________________________________
______________________________________________________________________________