Comparison of Articaine Mandibular Infiltration to

Lidocaine Inferior Alveolar Nerve Block in Pediatric Patients

BY

IVAN LIANG ZHANG
BA, Bowdoin College, 2011
DMD, University of Pennsylvania School of Dental Medicine, 2018

THESIS

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Defense Committee:

Dr. Evelina Kratunova, MDS, MFD, DChDent, FFD, Department of Pediatric Dentistry, Chair and Advisor
Dr. Ian Marion, DDS, MS, Department of Pediatric Dentistry
Dr. Marcio da Fonseca, DDS, MS, Department of Pediatric Dentistry
Dr. Michael Han, DDS, Department of Oral and Maxillofacial Surgery

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AAPD	American Academy of Pediatric Dentistry
ADA	American Dental Association
ASA	American Society of Anesthesiologists
COD	College of Dentistry
DMM	Deciduous Mandibular Molar(s)
FDA	Food and Drug Administration
IANB	Inferior Alveolar Nerve Block
EHR	Electronic Health Record
HCl	Hydrochloride
IDC	Initial Data Capture
IRB	Institutional Review Board
LA	Local Anesthesia/Anesthetic
MBPS	Modified Behavioral Pain Scale
PI	Principal Investigator
PIL	Patient Information Leaflet
PG	Post-graduate
PRS	Pain Response Scale
SSC	Stainless Steel Crown
UIC	University of Illinois at Chicago
VAS	Visual Analog Scale
WBS	Wong-Baker FACES® Pain Rating Scale

SUMMARY

This study was a prospective, single-blind, randomized control clinical trial with parallel design that aimed to investigate the effectiveness of mandibular infiltration with four percent articaine (1:100,000 epinephrine) versus that of inferior alveolar nerve block with two percent lidocaine (1:100,000 epinephrine) when administered for restorative treatment of deciduous (or primary) mandibular molars (DMM). Thirty subjects, between four and ten years of age, fulfilling strict inclusion and exclusion eligibility criteria, were enrolled and randomly assigned into two study groups: Lidocaine group (control) or Articaine group (variable). A single, designated operator using consistent anesthetic administration techniques provided all local anesthesia (LA). Clinical outcome data was collected to assess the perception of pain using two different validated rating systems. The Modified Behavioral Pain Scale (MBPS), exhibiting numerical categories of facial expression, crying, and movement, was scored by two kinds of trained and calibrated examiners who were blinded to the LA type. Examiners A (dental assistant) observed and rated the subjects' behavior during LA administration. Examiner B (pediatric dental resident) performed dental treatment and thereafter rated the observed subjects' behavior throughout the overall appointment. The Wong-Baker FACES® Pain Rating Scale (WBS) was used by the subjects at the end of the appointment to self-report their own level of experienced pain throughout the whole appointment. Blood pressure and pulse of the subjects were also recorded throughout the appointment as quantitative measures of pain. Data was statistically analyzed to determine if there were any clinical or behavioral differences in the effectiveness of either local anesthetic agent administered via their respective techniques when performing restorative treatment on DMM.

I. INTRODUCTION

A. Background

Successful pain control is a fundamental priority when performing operative dental treatment especially in children. Without it, pediatric patients may immediately retract their cooperation upon experiencing any pain or discomfort, which may compromise the quality of oral health care delivered. Local anesthesia (LA) is commonly utilized in dentistry to enable temporary inhibition of pain by blocking the nerve conductance that transmits pain sensation from the point of administration to the brain. The local anesthetic drugs reversibly bind to sodium channels in neuronal membranes, blocking the influx of sodium and subsequently also preventing action potential initiation and propagation. A variety of local anesthetic agents with diverse properties can be administered through different techniques, depending on the clinical scenario and anatomical innervation of the tissue to be anesthetized. Dental clinicians should select an ideal local anesthetic drug that achieves optimal effectiveness through a minimal number of injections, using techniques that provide the least distress while minimizing the risk of adverse events.[1] Profound LA not only helps to control pain, but also “alleviates fear and anxiety and aids in building trust between the pediatric dentist and patient to promote a positive dental experience”.[2]

LA is routinely administered via local infiltration or nerve block injection. Local infiltration involves injecting the LA agent directly into the vicinity of the tissue being operated on. This method of injection is technically simpler and theoretically less painful due to its direct visualization and lower depth of needle penetration, and is associated with fewer adverse outcomes.[3] Nonetheless, the extent of its operative field is limited and its effectiveness may not be sufficient across thick or dense cortical bone, such as the

mandible.[4] While local infiltration serves to numb a single tooth and its immediate surrounding soft tissue, nerve block injection aims to anesthetize a larger area, often several teeth and their adjacent soft tissues. The inferior alveolar nerve block (IANB), for example, anesthetizes all unilateral mandibular teeth on the ipsilateral side of injection. However, nerve block injections are more technically challenging and are associated with greater complications due to its requisite precise needle positioning through multiple tissue layers that are not as easily visualized and deeper level of needle penetration. Reported complications from IANB include needle breakage at the site of injection, trismus, hematomas, facial paralysis, and visual impairment.[5] Furthermore, lack of profound local anesthesia administered via nerve block may be a result of inappropriate identification of anatomical landmarks or presence of anatomical variations associated with the nerves in different individuals.[6] The difficulty of administering the more technique-sensitive IANB is compounded in an uncooperative patient, particularly in a child that is highly anxious and overwhelmingly mobile.

Lidocaine, the most widely marketed and used amide local anesthetic agent in dentistry, remains the “gold standard” LA drug of choice in many parts of the world due to its efficacy and safety with minimally reported toxicity and allergic reactions.[7] Whereas lidocaine can be administered via maxillary infiltration, it is often not as successful when administered via mandibular infiltration. The relatively denser cortical bone in the mandible hinders sufficient diffusion of the LA solution.[8] Therefore, lidocaine is often injected via IANB to fulfill local anesthesia of mandibular teeth.

Articaine, developed approximately 28 years after the introduction of lidocaine, is a local anesthetic agent that is becoming more increasingly popular. It possesses clinical

actions similar to lidocaine but has additional properties that make it more attractive. Compared to lidocaine, articaine is also an amide, but the latter exhibits a thiophene rather than a benzene group. This chemical substitution increases the lipophilicity and liposolubility of the drug, thus facilitating the diffusion potential of articaine through hard and soft tissues. It is also the only amide LA agent that contains an ester group, which allows for faster, dual metabolism of the drug not just in the liver, but also in the blood where plasma esterase is present.[9]

In the United States, the two LA agents are available in different formulations: two percent lidocaine hydrochloride (HCl) with (1:100,000 or 1:50,000) epinephrine and four percent articaine hydrochloride with (1:100,000 or 1:200,000) epinephrine. The HCl salt stabilizes the local anesthetic base in solution. As a vasoconstrictor, epinephrine slows the local anesthetic drug's absorption thus extending the duration of LA and decreasing systemic toxicity, while delivering hemostasis in the operative field.[9] Epinephrine activates both beta-one receptors in the sinoatrial node and myocardial cells and also beta-two receptors on the systemic arteries; the former "raise heart rate and systolic blood pressure while the latter decrease diastolic blood pressure".[9] Therefore, LA agents with epinephrine must be used with caution or simply administered without epinephrine in a patient with compromised cardiovascular status. Bisulfite preservatives are added to LA agents that contain vasoconstrictors to prevent their biodegradation by oxygen; as such, LA agents with vasoconstrictors are contraindicated in individuals with bisulfate allergies.[2,9]

II. REVIEW OF LITERATURE

A. Lidocaine

As the first amide local anesthetic on the market, lidocaine has transformed dentistry since its introduction and approval in 1948 by the United States Food and Drug Administration (FDA), replacing procaine (Novocain) as the local anesthetic agent of choice as it showed more favorable properties. It displays a faster onset (three to five minutes) than procaine (six to ten minutes), lasts longer, is more potent, and yields more profound anesthesia.[10] True, documented allergic reactions to amide local anesthetics are much rarer compared to ester local anesthetics. In fact, allergy to one amide LA agent does not prohibit the use of another amide LA agent; however, cross-allergenicity exists between different ester LA agents.[2] According to the American Academy of Pediatric Dentistry (AAPD) Reference Manual of Pediatric Dentistry, lidocaine's ubiquitous indication for all dental injections can afford anesthesia of pulpal tissue lasting 60 minutes (via maxillary infiltration) to 85 minutes (via mandibular block) and anesthesia of soft tissue for 170 (via maxillary infiltration) to 190 minutes (via mandibular block).[2] Though lidocaine can be easily and effectively infiltrated into the maxilla, the increased density of the mandible prevents lidocaine from diffusing and achieving ample anesthesia in posterior mandibular teeth.

Injectable lidocaine is most frequently distributed in a two percent concentration with either 1:50,000 or 1:100,000 epinephrine. Lidocaine without any vasoconstrictor has been eliminated in dental cartridges in North America since August 2011.[10] In children, the maximum recommended dosage is 4.4 mg/kg or 2.0 mg/lb, with a maximum total dosage not to exceed 300 mg.[10] Although mainly injected, lidocaine is also available as

a topical solution or ointment up to five percent and as a spray up to 10%.[2] It can be found in compounded topical anesthetics with other local anesthetic agents in various concentrations; however, the FDA does not regulate these amalgamated anesthetics and cautions against their application.[2]

B. Articaine

While lidocaine has dominated as the gold standard LA agent for the past 70 years, articaine is a newer amide LA agent that shows comparable, promising effectiveness. It was initially developed in Germany in 1976, gradually entered Canada in 1983 and the United Kingdom in 1998, and finally gained FDA approval in the U.S. in 2000.[11] Articaine is an increasingly popular LA agent, as it is the second most used local anesthetic in dentistry in the United States, making up approximately 40% of the market share.[10] Although classified as an amide, articaine possesses both amide and ester characteristics and its distinct chemical structure affords several advantages over other amide LA agents.[10] Like other amides, it is metabolized in the liver via hepatic microsomal enzymes.[11] However, its unique ester side chain confers additional biotransformation into its inactive form in the blood due to the presence of plasma esterase.[1] As a result, it is 0.6 times as toxic as lidocaine.[1] Additionally in articaine, a thiophene ring replaces the benzene that is characteristically found in other amides, thus increasing its liposolubility and potency (1.5 times that of lidocaine) and allowing it to be more readily diffusible through hard and soft tissues.[1] These properties collectively enable a smaller amount of articaine to be administered and effectively permeate through dense mandibular bone, permitting local anesthesia of mandibular molars through just local infiltration.[1,12]

Articaine is available only in injectable form as a four percent concentration solution with either 1:100,000 or 1:200,000 epinephrine. Duration of pulpal anesthesia ranges from 45 to 60 minutes in the maxilla via infiltration and 60 to 90 minutes in the mandible via block, while duration of soft tissue ranges from 180 to 190 minutes in the maxilla and 230-240 minutes in the mandible.[2] As a result of its more rapid metabolism relative to that of lidocaine, articaine has a maximum recommended dosage of 7.0 mg/kg or 3.2 mg/lb.[2] Articaine usage is not recommended for children less than four years of age due to insufficient data available to support its administration below that age threshold.[10] A concern in pediatrics is the relative ease of producing an overdose; the maximum total dose of articaine should not exceed 500 mg.[2] In advance of LA administration, the dentist should measure the child's weight and calculate the maximum dose. It has been advised that the maximum dose of 5.0 mg/kg for articaine should be used in children as a safer limit, especially if it is used in combination with sedative drugs.[1]

Studies have demonstrated that four percent articaine HCl is 1.5 times more potent but 0.6 times less toxic than two percent lidocaine HCl, as explained by the former's increased liposolubility and dual metabolism via hepatic clearance and plasma esterase hydrolysis, respectively.[1,9] Its increased potency allows less volume of solution of higher concentration to be administered, perhaps reducing the discomfort when a smaller amount is injected.[1] In fact, the maximum recommended dosage for four percent articaine HCl is 7.0 mg/kg while that of two percent lidocaine HCl is 4.4 mg/kg within a 1.7 milliliter cartridge.[2] Since 2000, the FDA has approved the use of articaine for dental treatment in adults and only children four years of age and older, as there have been no studies to date to that thoroughly evaluate the safety and efficacy of its use in patients younger than

four years of age. Although the FDA approved of articaine for both infiltration and nerve block anesthesia, there have been anecdotal reports, albeit scarce, of temporary or permanent paresthesia following its administration via nerve block.[13] Nonetheless, a mini systematic review of the literature revealed no conclusive evidence that four percent articaine HCl poses a greater risk of nerve damage than two percent lidocaine HCl.[14]

Strong evidence from many studies verify the safe and efficacious use of articaine local infiltration versus lidocaine inferior alveolar nerve block in adults, but there is still limited research among children.[15] Of these few studies on pediatric patients, mixed findings exist on the effectiveness of articaine in achieving adequate anesthesia through infiltration in mandibular posterior teeth.[15] Claims have been made that articaine can diffuse through hard and soft tissue from a buccal infiltration to provide lingual or palatal soft tissue anesthesia, but studies have not yet substantiated these claims.[10] There is a need to further evaluate the effectiveness of articaine administered via local infiltration versus the gold standard lidocaine administered via IANB for profound anesthesia of deciduous mandibular molars (DMM), as the former may prove to be a safer and simpler alternative when treating pediatric patients.

C. Local Anesthesia Techniques

The conventional technique for administering LA for restorative care of mandibular posterior teeth in pediatric patients has been the IANB with two percent lidocaine with 1:100,000 epinephrine.[15] IANB anesthetizes all the teeth on one side of the mandible on the ipsilateral side where the LA agent is injected. It is highly technique sensitive, as it necessitates accurate and deep positioning of the needle into an area beyond the most

posterior tooth that cannot be directly visualized. Anatomic variation of the inferior alveolar nerve between different individuals further complicates successful administration of the IANB.[6] These obstacles result in unpredictable, varying success rates of IANB ranging from 55% to 92%.[12]

Inappropriate needle placement is the most frequent technicality contributing to failure of anesthesia by the IANB.[16] To perform the IANB, the operator must first position his or her thumb on the coronoid notch of the anterior border of the ramus to guide the needle insertion between the internal oblique ridge and pterygomandibular raphe.[17] The needle is then advanced 19 to 25 mm into the soft tissue. Prior to depositing the LA agent, a negative aspiration is essential. Otherwise, a positive aspiration results in intravascular injection, vascular damage, and hematoma with possible overdose and toxicity.[18] The success of the IANB depends on the proximity between the mandibular foramen and the needle.[16] In pediatric patients, the success of IANB in achieving anesthesia is further complicated by the variable positioning of the mandibular foramen relative to the occlusal plane according to the child's age. While the mandibular foramen is usually located below the occlusal plane in a child four years and younger, it moves to a more superior position as the child grows.[17] In fact, by nine years old, the mandibular foramen is approximately at the level of the occlusal plane and is about four millimeters above it when adulthood is reached.[16]

Complications, although rare, related to IANB may arise either intraoperatively or postoperatively. As aforementioned, hematoma arising from intravascular injection is possible. Nerve paresthesia, pain, and trismus due to mucosal tearing during needle insertion or withdrawal as well as ocular complications may also occur.[5] Needle breakage

at the site of injection may be more frequently encountered in uncooperative patients due to their increased mobility. In a case series that investigated 16 reports of local anesthetic needle fractures, 15 of the breakages were associated with IANB; of those 15 occurrences, five of them involved children younger than ten years of age who moved abruptly and violently upon needle insertion.[19] In order for a surgeon to retrieve the needle in all these cases, all these affected patients had to be operated on under general anesthesia.[19] These dangers inherently exhibit a higher risk of occurrence in a pediatric patient that is already uncooperative.

Local infiltration (or infiltration anesthesia) is a less technique sensitive method of local anesthetic administration and is associated with less discomfort and fewer adverse outcomes compared to IANB. It makes use of direct visualization to deposit the LA agent the immediate vicinity of the tooth, anesthetizing the hard and soft tissues around it. The success of infiltration anesthesia depends on the density of the bone that surrounds the innervation of the tooth. A more highly dense bone, such as the posterior mandible, limits the LA agent from permeating easily through to the nerves. However, the mandibular bone shows reduced density among children, which may facilitate the success of local infiltration in pediatric patients.[15] Over time, the physiologic increase in biomechanical loading will ultimately increase the bone mineral density within the mandible as an individual matures, making it more difficult for the LA agent to diffuse through.[20] The unique chemical characteristics of articaine enhances its diffusion across the mandible to yield profound anesthesia, which is typically impossible to achieve with other local anesthetics.

D. Indications for Use

The goal of LA is to induce transient inhibition of pain in a specific area. In dentistry, LA is especially integral when treating children, as they can become increasingly uncooperative and jeopardize the rest of the appointment upon feeling any sensation of pain. Therefore, it is absolutely essential that the LA agents be administered as safely and effectively as possible.

So far, the gold standard for anesthetizing DMM is the IANB with lidocaine. Compared to IANB, local infiltration is easier to administer and associated with less discomfort. Even if lidocaine is deposited into the soft tissue via perfectly administered local infiltration, it cannot penetrate through the thick buccal cortical plate of the mandible to reach the innervations of the mandibular molars. Mandibular local infiltration with lidocaine is therefore ineffective.

Articaine, with its unique chemical structure, presents with increased liposolubility and potency which facilitates its diffusion across the mandible and into the nerve supply of the mandibular molars. As a result, mandibular local infiltration with articaine is achievable. The FDA has approved articaine for infiltration and nerve block anesthesia. Numerous studies and a systematic review have revealed that infiltration with four percent articaine HCl was as effective as IANB with two percent lidocaine HCl in effectively anesthetizing permanent mandibular molars with irreversible pulpitis in adults.[21–24] However, only a handful of similar studies exist that focus on children. A recent randomized clinical trial confirmed that articaine buccal infiltration can be used successfully for pulpotomies of mandibular primary second molars.[25] Ghadimi *et al*. (2018) determined that the pediatric patients' feeling during injection and post-treatment

complications did not differ between the two study groups (infiltration with four percent articaine with 1:100,000 epinephrine vs. IANB with two percent lidocaine with 1:100,000 epinephrine), but the behavior during pulpotomy was significantly better in those patients receiving articaine infiltration.[25] Nonetheless, there remains insufficient evidence to support that articaine infiltration should substitute the gold standard, lidocaine IANB, for anesthetizing mandibular primary molars.

Although articaine is FDA-approved for nerve block injections, there have been reports of heightened risk of paresthesia when it is administered via IANB due to its higher (four percent) concentration relative to other LA agents.[26] These claims, however, are based on weak scientific evidence and remain unproven. There is a greater amount of literature that suggests that articaine can be used safely for all types of injection including IANB and local infiltration.[1,12] Furthermore, a literature review concluded that four percent articaine is not more neurotoxic than other LA agents and therefore can be safely and effectively used in all aspects of clinical dentistry.[27]

E. Use in Children

As a dental local anesthetic, four percent articaine HCl with 1:100,000 epinephrine has been approved by the FDA for safe use in both children and adults. The FDA and the manufacturer of Septocaine® (Septodont, Lancaster, PA, USA) both advise that articaine be only used for individuals four years and older due to the lack of evidence demonstrating adequate safety and efficacy in patients younger than this age. In fact, there is only one published study – a retrospective report – that described the use of articaine infiltration and nerve block in children under four years of age.[28] In the report, no adverse systemic

reactions were noted when articaine was administered to patients younger than four years old, but the evidence was inadequate to recommend articaine usage for this younger age group.[28] To date, there are only a few randomized clinical trials that have evaluated the efficacy of articaine infiltration versus lidocaine IANB in anesthetizing DMM in pediatric patients.[7] Table 1 summarizes the mixed findings of the available literature comparing the use of four percent articaine infiltration to two percent lidocaine IANB in children. However, the quality of these randomized clinical trials is poor and inadequate with a high potential of bias; thus, there is weak scientific evidence to suggest that articaine infiltration and lidocaine IANB present with equal effectiveness when used for routine dental procedures.[7] Better designed randomized clinical trials are necessary to investigate the effectiveness of both LA agents and their respective techniques for anesthetizing DMM in the pediatric population.

TABLE I

SUMMARY OF LITERATURE: ARTICAINE INFILTRATION VS. LIDOCAINE ALVEOLAR NERVE BLOCK IN CHILDREN

Study	Number of Subjects (Gender[a])	Age (Years)	Study Design	Outcomes
Arrow (2012)[15]	57 (21 M, 36 F)	5.9-16.9 (mean 12.7)	Cross-over	• Higher proportion of LA success via mandibular buccal infiltration (BI) with 4% articaine (71%) than 2% lidocaine (64%) • Lower success with mandibular BI (67%) than IANB (100%), regardless of LA agent used*
Arali and Mytri (2015)[29]	40 (NR)	5-8	Double blind, cross-over	• 4% articaine mandibular BI is equally as effective as 2% lidocaine IANB when performing pulpectomies on DMM • Compared to 2% lidocaine IANB, 4% articaine mandibular BI showed shorter duration, quicker onset of anesthesia, lower need for supplemental injection, and lower subjective pain scores*
Chopra *et al*. (2016)[30]	30 (12 M, 8 F)	4-8 (mean 5.4)	Cross-over	• More movements during injection with 2% lidocaine IANB than 4% articaine BI* • Higher pain scores during pulp therapy of DMM with 2% lidocaine IANB than 4% articaine BI*

[a] Gender abbreviations: M = male, F = female, NR = not reported.

* Statistically significant difference was observed, $p<0.05$.

F. Behavior Rating Scales for Pain Perception in Children

1. Modified Behavioral Pain Scale

The Modified Behavioral Pain Scale (MBPS) is used as an indicator of pain perception in children. It was originally developed to measure pain intensity in infants receiving routine immunizations.[31] The MBPS is comprised of a combination of three behaviors typically indicative of pain (facial expression, cry, and bodily movements). These behaviors are assessed by observation, scored, and tallied to yield a total pain intensity from zero to ten, with ten depicting maximum pain. The MBPS has been validated as a reliable pain rating scale comparable to the validated visual analog scale (VAS) and can be used to evaluate procedural pain in children.[31]

2. Wong-Baker FACES® Pain Rating Scale

The Wong-Baker FACES® Pain Rating Scale (WBS) is a self-reported visual pain severity assessment tool used particularly in children due to its simplicity and highly comprehendible usage, as it does not necessitate any verbal communication. It is type of VAS that displays six facial expressions ranging from laughter to tears. A numerical value is associated with each facial expression and can be used to facilitate statistical analysis. The WBS has been compared to another validated VAS without any statistically significant differences detected; accordingly, the WBS is also validated as a reliable pain rating scale to evaluate the subjective perception of pain in children.[32,33]

G. Gaps in the Current Literature

There is a lack of studies that compares the effectiveness of articaine local infiltration to lidocaine IANB in anesthetizing mandibular molars in children. Most of the studies comparing the two LA agents have been focused on adults. Additional research is required to assess the effectiveness of the two LA agents using their respective techniques in achieving adequate anesthesia in mandibular molars in pediatric patients. Greater, stronger scientific evidence is needed to support safe and effective ways of administering LA particularly in the pediatric population. Our study addressed this literature gap. Its design is unique and has not been utilized in prior research.

IV. PURPOSE AND OBJECTIVES OF THE STUDY

The purpose of this study was to investigate the effectiveness of articaine infiltration versus lidocaine IANB in restorative treatment of DMM.

The objectives of this study were:

- To evaluate and compare articaine infiltration with lidocaine IANB for achieving successful LA for restorative treatment in DMM.
- To assess and compare the observed behavior (facial expression, cry, and bodily movements), subjective pain perception, and physiological signs (blood pressure and pulse) in pediatric patients during administration of each LA agent and during subsequent dental treatment.
- To establish whether articaine infiltration is a suitable alternative to lidocaine IANB for achieving adequate LA for restorative treatment of DMM.

V. HYPOTHESES OF THE STUDY

The null hypothesis is:

- There is no statistically significant difference in effectiveness between four percent articaine (1:100,000 epinephrine) infiltration and two percent lidocaine (1:100,000 epinephrine) IANB for restorative treatment in DMM.

The alternative hypotheses are:

- When used for restorative treatment in DMM, four percent articaine (1:100,000 epinephrine) infiltration shows greater effectiveness than two percent lidocaine (1:100,000 epinephrine) IANB.
- When used for restorative treatment in DMM, two percent lidocaine (1:100,000 epinephrine) IANB shows greater effectiveness than four percent articaine (1:100,000 epinephrine) infiltration.

VI. MATERIALS AND METHODS

A. Overview

The Institutional Review Board (IRB) of the University of Illinois at Chicago (UIC) granted approval of this study (Protocol #2019-0160) on June 5, 2019 (Appendix A).

This study was a prospective, single-blind randomized controlled clinical trial with parallel design. Participants (hereafter also referred to as “subjects” or “patients”) were recruited from the patient population attending the Post-graduate (PG) Pediatric Clinic at the Department of Pediatric Dentistry, College of Dentistry (COD) at UIC.

B. Study Site, Participants and Enrollment Process

1. Study Site

The study was conducted at the PG Pediatric Dental Clinic, Department of Pediatric Dentistry, COD at UIC. This site was selected because there was a projected abundance of potential participants that fulfilled the inclusion criteria. The PG Pediatric Clinic contained six quiet rooms and twelve operatories within an open bay, all available for restorative treatment.

2. Operator

One single appointed operator, an experienced pediatric dentist, completed the LA administration in all participants. A tutorial on how to administer each LA agent and its corresponding technique was reviewed and carefully followed step-by-step by the operator. The dose of each LA agent was recorded in the participant’s electronic medical record and never surpassed the maximum recommended dose for each anesthetic agent which was calculated based on the participant’s weight.

3. Examiners

There were two kinds of examiners (examiner A and examiner B) that observed and rated each participant's behavior by completing the MBPS forms (Appendices J and K). All examiners were trained and calibrated. The Principal Investigator (PI) provided blank MBPS forms and demonstrated how to fill them out to assess the participant's behavior. Each examiner watched a video of a child being treated in the dental chair by a dentist and rated the child's behavior using the MBPS form afterward. Inter-rater reliability was statistically analyzed using the MBPS scores obtained from each examiner. Intra-rater reliability was statistically evaluated after all of examiners watched the same video again a few weeks later and subsequently rated the MBPS scores once more.

Examiner A was a dental assistant who assisted both the operator and pediatric dental resident that treated the participant. A total of six different examiners A participated in the study. The dental assistant observed the participant's behavior during the administration of LA agent and subsequently recorded the MBPS form. Examiners A were not completely blinded to the LA agent used, as they had to be vigilant of both the operator and participant during the administration of the LA agent.

Examiner B was a pediatric dental resident who performed restorative treatment (and pulp therapy, if indicated) on the participant's deciduous mandibular molar(s) after the LA agent was administered by the operator. A total of nine different examiners B partook in the study. The pediatric dental resident observed the participant's behavior throughout treatment and subsequently completed the MBPS form. Examiner B was blinded to the type of LA agent used for anesthesia of the deciduous mandibular molar to be treated.

4. Study Subjects

Eligible participants, or study subjects, were selected from the patient population attending the PG Pediatric Dental Clinic of the Department of Pediatric Dentistry, COD at UIC. The PI reviewed the daily schedule in the AxiUm® electronic health record (EHR) system to browse for potential participants that fulfilled the inclusion and exclusion criteria. Preliminary screening included cooperative (Frankl three or four) patients between the ages of four and ten years old requiring restorative treatment on a DMM with a prior history of receiving local anesthetic. A total of thirty subjects were recruited and randomized into either the Lidocaine group (n=15; to receive two percent lidocaine with 1:100,000 epinephrine as local anesthetic administration) and Articaine group (n=15; to receive four percent articaine with 1:100,000 epinephrine as LA administration).

5. Inclusion Criteria

- Age – between age range of four and ten years.

  Patients between the ages of four and ten years old were eligible. Within this age group, the cortical mandible is relatively thin, porous, and permeable. The minimum age limit was set at four years old because the FDA has approved usage of four percent articaine with 1:100,000 epinephrine only for individuals four years of age and older. The maximum age limit was set at ten years old because at least one DMM is usually still present at that age.

- Health status – healthy or with well-controlled medical conditions.

  The American Society of Anesthesiologists (ASA) Physical Status Classification System was used to determine patient eligibility. Patients that were healthy without

any medical conditions (ASA I) or those with mild, systemic disease without any functional limitations (ASA II) were included in the study. The AxiUm® EHR contained medical history of each patient that was reported by his or her legal guardian, and the pediatric dental resident (examiner A) was responsible for asking the legal guardian for any medical changes since their previous appointment.

- Cooperation for dental treatment – cooperative patients with previous history of treatment with local anesthesia.

  Patients that did not require pharmacological behavioral management techniques were eligible for the study. In particular, only cooperative patients were considered. The behavior of each patient during each appointment was routinely rated using the Frankl Behavioral Rating Scale and was documented in the clinical notes within the AxiUm® EHR. Patients with previously documented Frankl scores of three (positive; acceptance of treatment with willingness to cooperate, but cautious at times and with reservation) or four (definitively positive; good rapport with dentist with possible interest in dental procedure, laughter, or enjoyment) during a prior dental appointment that required LA were included in the study. External factors affecting the results of the study would be limited as such, as cooperative patients will more likely offer a less biased rating of the WBS.

- Language – English literacy.

  Patients and their legal guardians had to speak and understand English in order to be eligible for the study. All study documents were written in English.

- Treatment requirement – deciduous mandibular molar requiring restoration (with or without pulp therapy).

The ultimate eligibility of the patient relied on the eligibility of the tooth to be treated as well. Qualified patients exhibited at least one deciduous mandibular molar that was treatment planned for restorative treatment requiring local anesthetic administration. A restoration must be indicated due to caries, pulp treatment, developmental defects, or tooth surface loss as a result of erosion or attrition. If a tooth required pulpal therapy, then indirect pulp cap, pulpotomy, or pulpectomy was performed prior to the final restoration. Both direct intracoronal (composite resins) and extracoronal (stainless steel crowns (SSCs), pre-veneered SSCs, and zirconia crowns) were included in the study.

6. Exclusion Criteria

- Age – younger than four or older than ten years of age.

  Children below the age of four years were excluded because four percent articaine with 1:100,000 epinephrine is not FDA-approved for this age range. Additionally, patients younger than four years old are likely not reliable or mindful reporters of pain due to limited comprehension. Patients older than ten years of age were also excluded because of the potential absence of deciduous primary molars, either due to exfoliation or premature extraction, consistent with their physiological dental development and dental age.

- Health status – compromised medical status (ASA III and above).

  Patients with compromised medical conditions – those labeled as ASA III (non-life threatening severe systemic disease), ASA IV (severe systemic disease that is a constant threat to life), or greater – were excluded from the study. Health status

was determined by asking the patient's medical history and documenting it upon initial encounter and each encounter thereafter in the AxiUm® EHR.

- Cooperation for dental treatment – uncooperative behavior for dentistry.

  Patients who had prior dental treatment and were deemed uncooperative, exhibiting a Frankl score of one (definitely negative; rejection of treatment, forceful crying, strong fear, or extreme negativism) or two (negative; hesitancy toward treatment, uncooperative, and negative withdrawn or sullen attitude), were excluded from the study.

- History of prior dental treatment with local anesthesia.

  Patients who did not experience prior dental treatment that required local anesthesia, regardless of their cooperation at previous encounters, were not qualified for the study.

- Language – lack of literacy of English Language.

  Legal guardians and patients who could not speak or understand English were excluded, as they were unable to sufficiently understand the study.

- Treatment requirement – tooth other than mandibular primary molar or a mandibular primary molar requiring extraction.

  Non-restorable DMM in which extractions were indicated and teeth other than DMM were excluded from the study. Furthermore, patients with a DMM that had been treatment planned for a restoration that did not require use of a local anesthetic (i.e., superficial incipient Class I occlusal carious lesion) were disqualified.

C. Subject Enrollment

All subjects were chosen from the patient population at the PG Pediatric Clinic, Department of Pediatric Dentistry, COD at UIC. The PI accessed the clinic schedule on the AxiUm® EHR system on a weekly basis and performed a preliminary search of potential participants that were within the target age group and had an existing treatment planned restoration of a DMM. Once these two criteria were fulfilled, further eligibility was confirmed by thoroughly reviewing the participant's clinical notes to determine participant's medical status, level of cooperation, and history of any prior dental treatment with local anesthesia.

Once the inclusion and exclusion criteria were all met, with the exception of obtaining informed consent which would occur when the legal guardian presented for the patient's treatment, a list of potential patients and their associated EHR patient chart numbers were recorded. The PI approached the patient and his or her legal guardian at the beginning of the dental appointment for treatment of the DMM. After providing a verbal explanation of the study to both the patient and his or her legal guardian, the PI handed out a Patient Information Leaflet (PIL; Appendix B) that described the study more thoroughly with clear details outlining the two types of LA agents used and their corresponding techniques, advantages and disadvantages, risks, and benefits, possible complications, and the study participation process. Written, informed consent (Appendices C and D) was obtained from the legal guardian after all questions and concerns were addressed. Verbal assent (Appendix E) was obtained from participants that were seven to ten years of age. In case informed consent was denied or the other inclusion criteria were not satisfied, the potential participant was disqualified from the

study but proceeded with the planned dental treatment as originally scheduled. Delivery of a LA agent was still used in the planned dental treatment, even if the patient did not enroll in the study, as a standard of routine dental care.

Once the participant was successfully enrolled, he or she was assigned a study identification number. This study identification number and the participant's associated EHR patient chart number was documented in a master list. The master list served as a reference of the enrollment progress and was used to identify any patients that were enrolled more than once for treatment of at least two DMM on opposite quadrants. Upon completion of data collection, the master list was shredded.

There were no financial benefits gained by the patient, his or her legal guardian, or the PG Pediatric Dental Clinic from the study. Dental fees and clinic reimbursements were identical regardless of patient enrollment. No incentive or compensation were associated with the study.

D. Armamentarium

The equipment used to administer LA agents included a cartridge containing the LA agent, syringe, and needle. Each cartridge contained 1.7 mL of either four percent articaine HCl with 1:100,000 epinephrine or two percent lidocaine HCl with 1:100,000 epinephrine. Details on each specific manufacturer of the LA agents are provided below (Table 2 and Table 3). These brands were used because they were the two available LA agents already and regularly supplied in the PG Pediatric Clinic, Department of Pediatric Dentistry, COD at UIC.

1. Articaine

Septocaine® (Figure 1), manufactured by Septodont, is the brand of articaine that used was in the study. It contains a sterile, aqueous solution of four percent articaine HCl (40 mg/mL) with 1:100,000 epinephrine bitartrate, sodium chloride (1.6 mg/mL), and sodium metabisulfite (0.5 mg/mL). According to both the FDA and Septodont, articaine cannot be used in individuals younger than 4 years old because there is a lack of evidence supporting safety and efficacy for use in children below this age threshold. While the maximum recommended dosage for articaine is 7.0 mg per kg of body weight (not to exceed 500 mg) in this study the more conservative dose limit of 5.0 mg/kg was adopted. This LA agent has a fast onset (1-9 minutes) with a duration ranging from 60-190 minutes.

TABLE II

SEPTOCAINE® FOUR PERCENT ARTICAINE WITH 1:100,000 EPINEPHRINE BY SEPTODONT

Brand	Manufacturer
Septocaine® (4% articaine HCl with 1:100,000 epinephrine)	**Septodont USA** 205 Granite Run Drive, Suite 150 Lancaster, PA 17601

Figure 1. Septocaine® Articaine Cartridge

2. Lidocaine

The cartridges of two percent lidocaine with 1:100,000 epinephrine used in this study were supplied by Henry Schein® (Novocol, Cambridge, Ontario, Canada). The lidocaine cartridge contains an aqueous solution of two percent lidocaine with 1:100,000 epinephrine bitartrate, sodium chloride (6.5 mg/mL), potassium metabisulfite (1.2 mg/mL), and edetate bisodium (1.2 mg/mL). According to both the FDA and Novocol, this LA agent can be safely administered to individuals of all ages. The maximum recommended dosage of lidocaine is 4.4 mg per kg of body weight, not to exceed 300 mg. With a rapid onset (3-5 minutes), its duration ranges from 60-190 minutes.

TABLE III

HENRY SCHEIN® TWO PERCENT LIDOCAINE WITH 1:100,000 EPINEPHRINE BY NOVOCOL

Brand	Manufacturer
Henry Schein® (2% lidocaine HCl with 1:100,000 epinephrine)	**Novocol Pharma** 25 Wolseley Court Cambridge, Ontario, Canada N1R 6X3

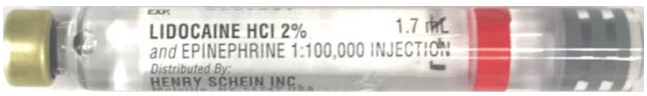


Figure 2. Henry Schein® Lidocaine Cartridge

3. Regulatory Compliance

The FDA has approved the safe and effective use of both four percent articaine with 1:100,000 epinephrine and two percent lidocaine with 1:100,000 epinephrine for children and adults. Both LA agents comply with U.S. and international standards and regulations for product safety. Regulatory information is documented on the material and safety data sheets (MSDS) for each product and is abbreviated below (Table 4).

TABLE IV

REGULATORY INFORMATION FROM MATERIAL SAFETY DATA SHEETS OF ARTICAINE AND LIDOCAINE

Regulatory Information	Septocaine® Articaine (4% articaine with 1:100,000 epinephrine)	Henry Schein® Lidocaine (2% lidocaine with 1:100,000 epinephrine)
OSHA[a] Regulatory Status	Epinephrine bitartrate is not listed as a hazardous product in the Resource Conservation and Recovery Act (RCRA) and Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) regulations	
Regulatory Status	This product is exempt from current Workplace Hazardous Material Information System (WHMIS) legislation as a drug product	
FDA Approval	Approved in 2005 for infiltration or nerve block anesthesia in dentistry	Approved in 1980 for infiltration or nerve block anesthesia in dentistry

[a] Occupational Safety and Health Association (OSHA)

4. Needles

According to the AAPD, proper needle selection is paramount to facilitate profound anesthesia and adequate aspiration.[2] The type of needle used in this study for administering articaine via infiltration was a 30-gauge short needle (Figure 3; 0.3112 mm in diameter, 20 mm in length), while that used for administering lidocaine via IANB was a 27-gauge long needle (Figure 4; 0.4126 mm in diameter, 32 mm in length). Both types of needles, manufactured by Henry Schein® (Melville, NY, USA), were sterile and disposable and contained a bevel to ease tissue penetration. A single-use, disposable ProTector® Needle Sheath Prop (Certol® International LLC, Commerce City, Colorado, USA), was used to secure the needle cap and aid in safe disassembly. A new needle was used for each patient and disposed of in a sharps container afterwards.

Figure 3. Henry Schein® 30-gauge short needle.

Figure 4. Henry Schein® 27-gauge long needle.

5. Syringe

A standard, stainless steel dental syringe, sterilized in an autoclave machine, was used to deliver and express the LA agent. The anesthetic cartridge was loaded onto the central chamber of the syringe and the dental needle was attached to the hub of the syringe. Pushing the plunger of the syringe allowed advancement of the LA agent out of the cartridge, through the needle, and deposition into the soft tissue where the needle is.

Figure 5. Dental syringe.

E. Injection Technique

A step-by-step tutorial was created to outline the injection techniques used for IANB and infiltration anesthesia (Appendices F and G). This tutorial was based on recommendations set forth in the textbook, *McDonald and Avery's Dentistry for the Child and Adolescent*.[34] The operator, an experienced pediatric dentist who administered the LA agent in all participants, studied the tutorial and ensured consistent injection technique.

F. Initial Data Capture

Information regarding details on the delivery of local anesthesia and the dental treatment conferred was initially recorded by the operator administering the LA and then completed by the PI after the conclusion of treatment. This information was documented on the Initial Data Capture (IDC) form (Appendix H). Specifically, the IDC form detailed the participant's study number, date of the procedure, participant's age, and participant' weight (to determine maximum dosage of the LA agent). The operator would record the type of LA was used, its corresponding injection technique, and actual volume of LA agent used. Finally, the PI would record the identity of the specific tooth treated (left or right, first DMM or second DMM) and treatment completed, including the type of pulp therapy (indirect pulp cap, pulpotomy, or pulpectomy) if it was indicated.

G. Randomization Process

Each participant was randomly assigned into the Articaine group (those that received four percent articaine with 1:100,000 epinephrine via local infiltration) or Lidocaine group (those that received two percent lidocaine with 1:100,000 epinephrine via IANB). A random digit table generated a list of 30 consecutive numbers (1-30) in a random order. In the order of enrollment, each participant was assigned a study number from the random digit table that corresponded to the order sequence. Those participants with an odd study number were allocated to the Articaine group, while those with an even study number were assigned to the Lidocaine group.

H. Clinical Outcome Data

Pain perception, and therefore the success and effectiveness of the LA agent, was evaluated by recording observable, subjective, and quantitative measures that were either direct or surrogate representations of pain. Two different rating systems were used to assess behavior and pain perception: MBPS and the WBS. Physiological vital signs (blood pressure and pulse) were recorded as well.

The MBPS aims to assess and quantify pain intensity in children.[35] Three different observable parameters that are deemed to be indicative of pain constitute the scale: facial expression, cry, and (bodily) movement. These parameters are delineated into different quantitative intensities, each ranging from zero to three or four, with a higher score depicting a greater level of pain. A completely neutral facial expression (one), absence of crying (one), and usual movement or resting/relaxed position (zero) would yield a baseline measurement of two, which would infer no pain according to the observed neutral characteristics. Yet, a positive facial expression like smiling (zero), laughing and giggling (zero), and usual movement or resting/relaxed position (zero) would yield a minimal total of zero, which would infer no pain, but rather an enjoyable, blissful experience. The scores from each of the three parameters were summed up to receive a total score out of 10, with 10 being the maximum amount of behavioral pain observed. The MBPS was originally created to evaluate pain perceived by infants during the immunization injections.[35] As the injection of a vaccine is comparable to that of a LA agent, the MBPS was used by the two types of examiners in this study to assess observable behavioral pain of the subject at different time points. Both examiners A (dental assistants) and

examiners B (pediatric dental residents) were trained and calibrated with respect to using the MBPS form.

Whereas the MBPS is evaluated by an individual observing the subject, the WBS utilizes self-assessment by the subject (Figure 6). Even though age can be a significant predictor of a child's ability to accurately communicate about his or her pain, the WBS has been frequently used in multiple pediatric pain assessment settings and has been proven to be internationally valid and reliable in individuals three years and older.[32] The WBS utilizes facial expression drawings that portray an ordinal spectrum of pain intensity. Because this WBS is easily comprehensible for the targeted age range in this study, it was used to measure self-reported experience of pain in the pediatric subjects. Approval to use the WBS for research and publication was approved by the Wong-Baker FACES Foundation (Appendix I).

The WBS illustrates a spectrum of emotions (from happy, to neutral, to sad) through facial expression drawings that correlate to a quantitative value of pain. For the facial expression exhibiting the most pronounced smile, a value of zero is assigned, which denotes "no hurt". In contrast, for the facial expression showing the most pronounced frown with tears streaming down the eyes, a value of 10 is assigned, which denotes "hurts worst". From zero to 10, consecutive even integers symbolize an increasing level of pain: two (mild smile) signifies "hurts little bit", four (neutral expression) signifies "hurts little more", six (mild frown) signifies "hurts even more", and eight (severe frown without tears) signifies "hurts whole lot".

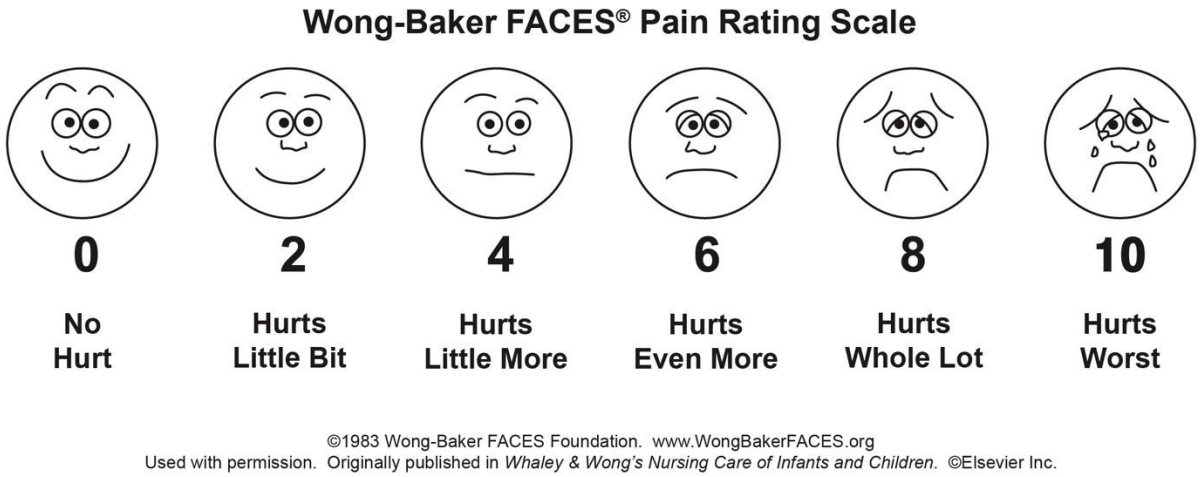


Figure 6. Wong-Baker FACES® pain rating scale.

1. Participants' Reaction to Injection (LA Administration)

Examiners A (dental assistants) observed the participant's reactions during LA administration and subsequently completed the corresponding MBPS form (MBPS #A; Appendix J) at the conclusion of the visit. Although they were technically not blinded to the type of LA agent used because they had to observe both the operator and participant simultaneously, examiners A were not actually told which LA agent was administered.

2. Participants' Reaction to Dental Treatment

Examiners B (pediatric dental residents) used the same MBPS as examiners A but on a different form (MBPS #B; Appendix K) to evaluate the participant's reactions during the whole dental treatment. To eliminate possible opinion bias, examiners B were completely blinded to the type of LA agent that was administered. Examiners B were instructed to step away from the operatory as the operator delivered the randomly

assigned LA agent through its respective technique. After confirming adequate anesthesia, the operator left as examiner B returned and performed the dental treatment as planned. At the conclusion of the appointment, Examiner B would complete MBPS #B, scoring the participant's behavior during treatment.

3. Basic Vital Signs Recording

Once the participant was officially enrolled in the study, the PI connected a pulse and blood pressure monitor (DRE Medical Equipment, Louisville, Kentucky, USA) onto the participant. The four monitor units (DRE Waveline EZ Portable Patient Monitor with Touchscreen) used in the study were calibrated by a medical device technician and were readily available due to their existing, routine use by the PG Pediatric Dental Clinic during oral conscious moderate sedations. The monitor was programmed to digitally record the vital signs every 10 minutes throughout the appointment. An initial measurement of the participant's pulse and blood pressure at rest was recorded as a baseline record. At the conclusion of the appointment, the digital records from the monitor were transferred onto the Basic Vital Signs Form (Appendix L) by the PI. Values of the pulse and blood pressure were statistically analyzed between both the Lidocaine and Articaine groups. Pulse and blood pressure also were compared to normal values according to age as referenced in the AAPD manual. An increase in blood pressure or pulse during treatment is often associated with higher stress and discomfort. Additionally, blood pressure and pulse may act as surrogates of pain, as a rise in both or either may be quantitatively indicative of pain.

4. Self-Reported Perception of Pain

The WBS (Appendix M) was scored by the participant at the conclusion of the appointment to record the self-reported perception of pain. As a validated and reliable VAS for children ages three years and older, the WBS (Figure 6) illustrates a continuum of facial expressions ranging from exuberant smiles, to neutral expression, and to frowny tears that corresponded with an ordinal, numerical scale of pain (zero representing “no hurt” with a smiley face; ten signifying “hurts worst” with a crying face).[32,33] It was a suitable form of communicating pain especially for the pediatric participant as verbal communication is not required and the scale is easily comprehensible at a universal level.

I. Flow Chart of the Study Process

A diagram to present the flow of participants through each stage of the study process is shown in Figure 7. This flow chart is an illustration of the enrollment of subjects, their allocation to treatment, disposition status, and how data was analyzed in the trial.

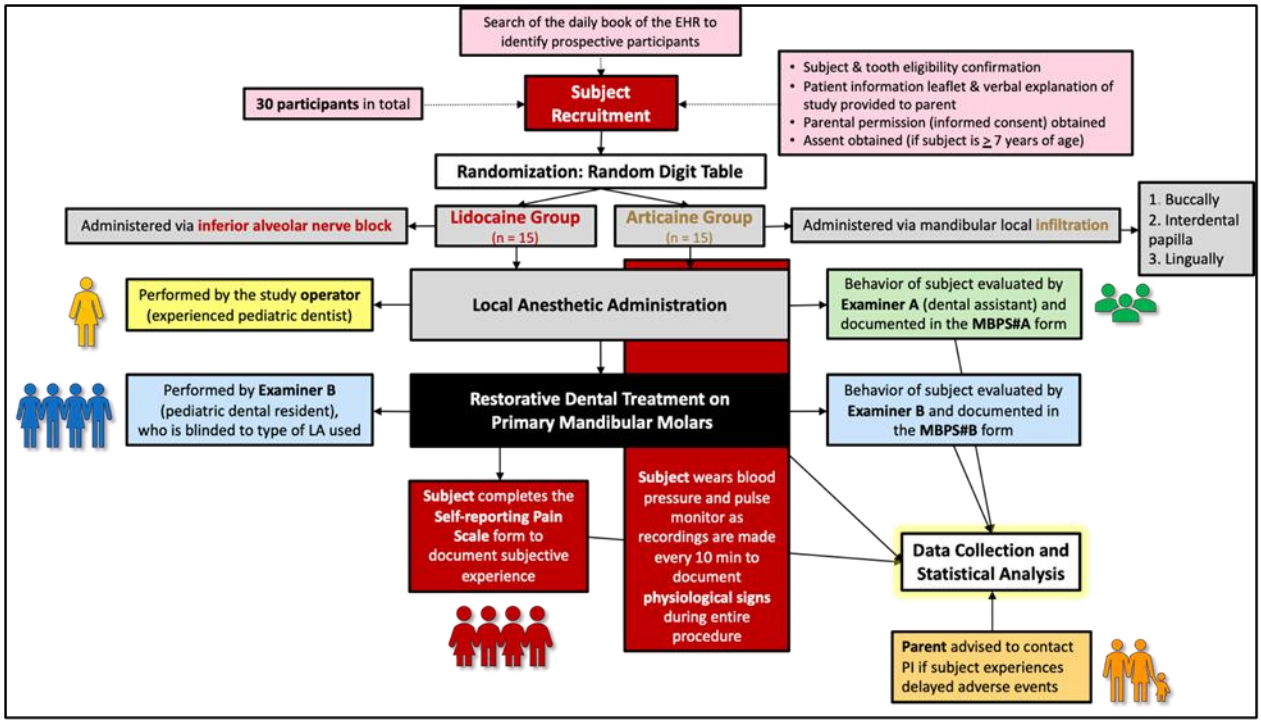


Figure 7. Flow chart of the study process.

J. Criteria for Clinical Success

The determinants for clinical success in this study were defined by:

- Successful completion of the planned dental treatment without any interruptions or need for supplemental LA administration
- Cooperative behavior (Frankl three or four) maintained throughout the whole appointment
- Absence of any adverse medical or dental complications, either intraoperatively or postoperatively

If one or more of these criteria for clinical success were not fulfilled, then the case was regarded as a “failure” of the LA for the purposes of this study and consequently excluded from statistical analysis.

K. Statistical Analysis

Data generated on all study forms (IDC, MBPS #A, MBPS #B, WBS, and Basic Vital Signs) were transferred, organized onto a Microsoft Excel Spreadsheet (Microsoft Inc., Redmond, Washington, USA), and stored on a password-protected computer. The data was then coded numerically and exported onto the IBM SPSS statistical software program (IBM, Armonk, New York, USA) for statistical analysis.

Using numerical subjective pain results from a similar study (Arali and Mytri, 2005) for two independent samples t-test, a prospective power analysis was performed to allow for unequal variance.[29] The power calculation revealed that group sample sizes of 15 participants each would achieve 71% power to reject the null hypothesis of equal means. The power would have been 98% if the sample size included 40 participants in each group. IRB granted permission to recruit 80 participants total. However, due to logistical restrictions (duration of pediatric dental residency program, clinic schedule, and availability of operator and PI), a sample size of 30 total participants (15 in each group) was selected.

L. Data Analysis

Data analysis included use of both univariate descriptive statistics and bivariate statistics. Univariate descriptive statistics, consisting of frequency, mean, and standard deviation, were used to assess demographic information. Bivariate statistics, which included independent t-tests and Mann Whitney-U, were used to examine observed behavioral pain rating scores (MBPS #A and MBPS #B) and subjective visual analog scores (WBS) between the Lidocaine and Articaine groups. A p-value of <0.05 defined a statistically significant difference. Physiologic vitals (blood pressure and pulse) were analyzed using Repeated Measures ANOVA, with Pillai's Trace used to determine significance for the multivariate test.

VII. RESULTS

A. Study Sample

Data was collected over a five-month period. Thirty participants were recruited and randomly assigned to either the Lidocaine group (n=15) or Articaine group (n=15). No intraoperative complications occurred, and no postoperative adverse events related to the study were reported for either group. Supplemental anesthesia was not needed for any subject in either group. Every subject from both groups maintained cooperative behavior (Frankl three or four) throughout the entire appointment. All of the determinants for clinical success were fulfilled; none of the cases were considered failures. Therefore, the clinical outcome data for all subjects in both groups were included for statistical analysis.

B. Demographic Characteristics of Study Sample

Demographic characteristics of all 30 participants are summarized in Table 5. Participants' ages ranged from four to ten years. Of the 30 participants, 53% (n=16) were males and 47% (n=14) were females. Within the Lidocaine group (n=15), eight participants were males and seven were females. The Articaine group (n=15) coincidentally had the same number of males and females.

Table V

DEMOGRAPHIC CHARACTERISTICS OF STUDY SAMPLE

Characteristics	Lidocaine (n=15)	Articaine (n=15)	Total (n=30)
Mean Age (years) (with standard deviation)	6.60 ± 1.18	6.67 ± 1.59	6.63 ± 1.38
Gender (frequency)	Males = 8 Females = 7	Males = 8 Females = 7	Males = 16 Females = 14

C. Types of Restorative Treatment

The variety of restorations completed for each LA group is illustrated in Figure 8 and summarized in Table 6. Treatment types for the DMM included both intracoronal (composite resins) and extracoronal (SSCs, pre-veneered SSCs, and zirconia crowns) restorations. A simple frequency analysis determined the amount of each treatment type for each LA group. In the Lidocaine group, the following number of treatments were completed: composite resins (five), SSCs (10), pre-veneered SSC (one), zirconia crowns (two), and pulpotomies (zero). In the Articaine group, the following number of treatments were performed: composite resins (four), SSCs (12), pre-veneered SSCs (two), zirconia crowns (zero), and pulpotomies (two). Five subjects in the Lidocaine group and three subjects in the Articaine group received treatment on multiple teeth simultaneously.

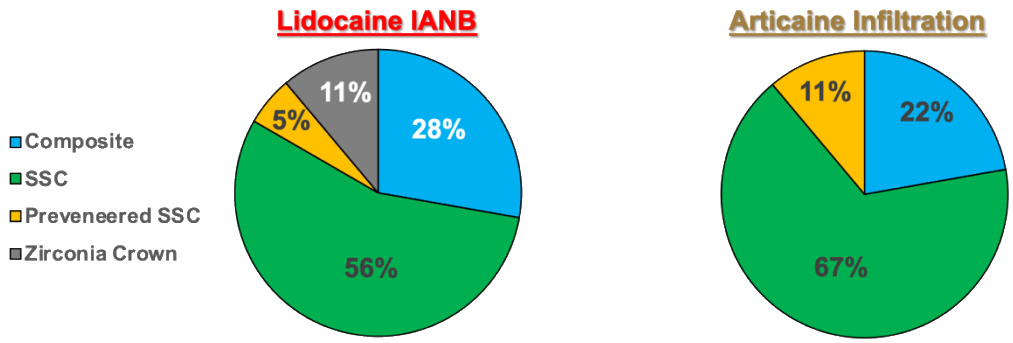


Figure 8. Percentage of restorative treatment types.

TABLE VI

FREQUENCY OF TREATMENT TYPES[a]

Treatment Type	Lidocaine IANB	Articaine Infiltration
Composite Resin	5	4
Stainless Steel Crown	10	12
Pre-veneered Stainless Steel Crown	1	2
Zirconia Crown	2	0
Pulpotomy (with MTA[b])	0	2
Cases with Multiple Teeth Treated Simultaneously[c]	5	3

[a] Frequency was defined as the number of deciduous mandibular molars treated per treatment type.

[b] Mineral trioxide aggregate (MTA) was the agent of choice for all pulpotomies performed in the clinic.

[c] Either with different types of restorations or same type of restoration.

Of the DMM treated in the Lidocaine group, 48% were primary first molars and 52% were primary second molars. In the Articaine group, of the DMM treated, 65% were primary first molars and 35% were primary second molars.

D. Pain Rating Scales

The perception of the participant's pain during LA administration and throughout the subsequent dental treatment is summarized in Table 7, Figure 9, and Figure 10. Collectively, scores from both pain rating scales (MBPS and WBS) illustrated the differences and similarities of the participant's observed and self-evaluated pain perception between the two LA groups.

TABLE VII

MEAN MODIFIED BEHAVIORAL PAIN SCALE SCORES DURING
LOCAL ANESTHETIC ADMINISTRATION AND THROUGHOUT TREATMENT

	Category	LA Group	Mean Score	Standard Deviation	*p*-value*
MBPS #A (During LA Administration)	Facial Expression	Lidocaine	1.33	0.617	0.085
		Articaine	1.00	0.378	
	Cry	Lidocaine	1.47	0.640	0.022*
		Articaine	1.00	0.378	
	Movement	Lidocaine	0.27	0.704	0.559
		Articaine	0.13	0.516	
	Total	Lidocaine	3.07	1.624	0.063
		Articaine	2.13	0.915	
MBPS #B (Throughout Treatment)	Facial Expression	Lidocaine	0.80	0.414	0.299
		Articaine	0.93	0.258	
	Cry	Lidocaine	1.10	0.458	0.577
		Articaine	1.00	0	
	Movement	Lidocaine	0	0	1.000
		Articaine	0	0	
	Total	Lidocaine	1.87	0.743	0.745
		Articaine	1.90	0.258	

* Statistical significance for this study was set at $p<0.05$. Independent samples t-tests were performed to yield *p*-values. The only MBPS parameter that exhibited a statistically significant difference between the two LA groups was MBPS #A cry, which was observed and rated by examiners #A during injection of the LA agent.

The average total MBPS score during the administration of LA (MBPS #A), as rated by examiners A, was 3.07 (± 1.62) when lidocaine was delivered via IANB and 2.13 (± 0.92) when articaine was delivered via local infiltration (p=0.063) (Table 7 and Figure 9). The mean MBPS #A score for cry, the only MBPS #A parameter with a statistically significant difference, was 1.47 in the Lidocaine group versus 1.00 in the Articaine group (p=0.022). In all three MBPS #A categories (facial expression, cry, and movement), the scores in the Lidocaine group were higher than the Articaine group.

The average total MBPS score throughout the dental treatment (MBPS #B), as rated by examiners #B, was 1.87 (± 0.74) and 1.90 (± 0.26) after lidocaine IANB and articaine local infiltration were administered, respectively (p=0.745), (Table 7 and Figure 9). None of the results from data acquired from the MBPS #B forms yielded a statistically significant difference between the two LA groups.

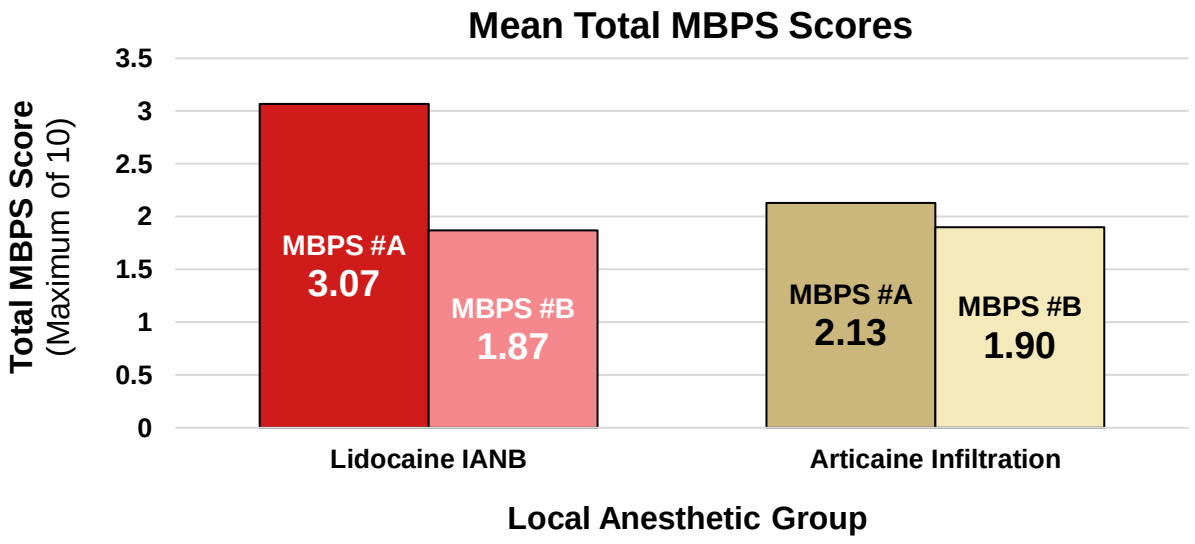


Figure 9. Mean total modified behavioral pain scale scores.

From subjects' perspective, the average WBS score of pain throughout the entire appointment (Figure 10) was low in both groups: 1.33 (± 1.45) for the Lidocaine group and 0.53 (± 0.92) for the Articaine group (p=0.081).

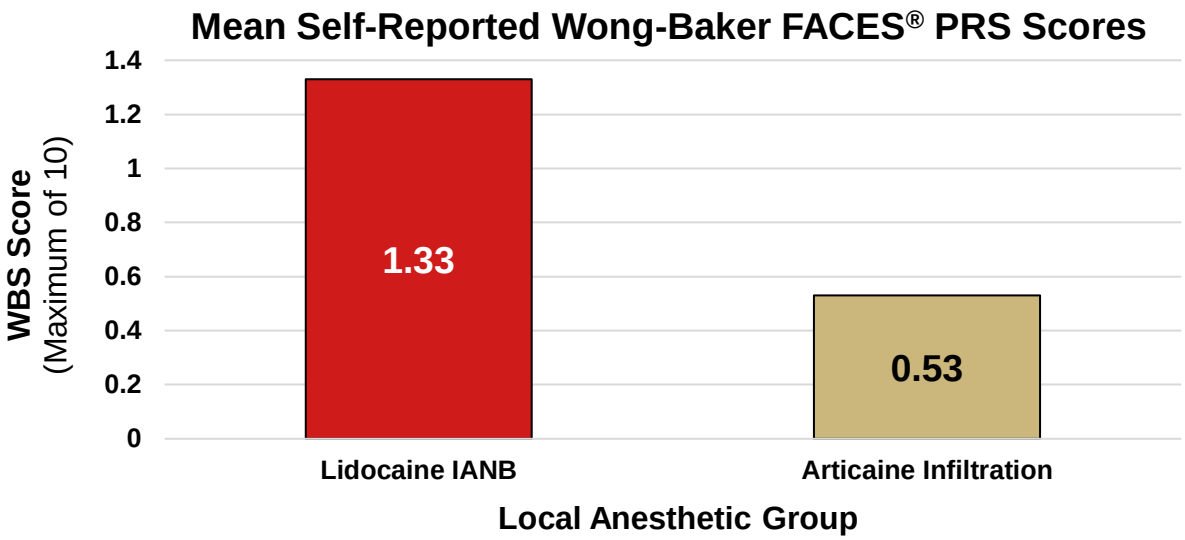


Figure 10. Mean self-reported Wong-Baker FACES® pain rating scale scores.

Data associated with both pain rating scales were analyzed by independent samples t-tests. The only statistically significant difference in the scores of the pain rating scales between the two LA groups was for the MBPS #A cry parameter (p=0.022). All other mean values of the subcategories of MBPS, as well as the mean total MBPS scores and mean WBS scores, did not yield any statistically significant differences.

E. Blood Pressure and Pulse

The blood pressure and pulse of each participant were recorded at baseline, during injection of the LA agent, and every 10 minutes thereafter during dental treatment. Although all dental treatment was completed within 40 minutes, the exact duration varied based on the clinical situation. As such, an average treatment blood pressure and an average treatment pulse were calculated and included in statistical analysis. Multivariate repeated measures ANOVA test was applied to determine if there were any statistically significant differences in blood pressure and pulse at the three time points (baseline, injection, and treatment) between the Lidocaine and Articaine groups (Table 8). Each participant's vital signs at the different time periods were also compared to the normal range of a child of the same age; none of the participants displayed any atypical measurements beyond the normal, healthy values. To compare the change in blood pressure and pulse over time between the two LA agents, Pillai's test was used.

TABLE VIII

BASIC VITALS AT BASELINE, DURING LOCAL ANESTHETIC INJECTION, AND THROUGHOUT TREATMENT

Vital Sign at Time Point		LA Group	Mean	Standard Deviation	*p*-value* (between groups)
Systolic BP[a] (mm Hg)	Baseline	Lidocaine	96.3	10.2	0.106
		Articaine	103.9	12.9	
	Injection	Lidocaine	102.5	13.2	
		Articaine	103.0	16.0	
	Treatment	Lidocaine	100.4	8.8	
		Articaine	101.2	9.4	
Diastolic BP (mm Hg)	Baseline	Lidocaine	55.9	12.6	0.213
		Articaine	56.9	10.1	
	Injection	Lidocaine	59.6	11.8	
		Articaine	53.2	6.8	
	Treatment	Lidocaine	57.9	9.9	
		Articaine	55.6	9.3	
Pulse (beats per min)	Baseline	Lidocaine	88.3	15.7	0.030*
		Articaine	81.3	13.8	
	Injection	Lidocaine	93.9	15.0	
		Articaine	85.8	9.6	
	Treatment	Lidocaine	90.0	12.6	
		Articaine	78.8	11.2	

* Statistical significance for this study was set at $p<0.05$. *P*-values were obtained by using Pillai's test.

[a] BP = blood pressure.

In terms of the systolic and diastolic blood pressures, no statistically significant difference was detected at baseline, injection, or during treatment between the Lidocaine and Articaine groups. However, Pillai's test revealed a statistically significant difference in the pulse values over the three different time points between the two LA groups. To further investigate this, a Mann-Whitney U test was run and revealed a statistically significant difference (p=0.010) in the average pulse during treatment; the mean treatment pulse for the Lidocaine group (90 beats per minute, or bpm) was higher than that for the Articaine group (78.8 bpm) by approximately 11.2 bpm. Mauchly's Test of Sphericity also confirmed that there was no difference in the change in blood pressure between both groups at the three time points (p=0.545). Although there was this single statistically significant difference, this result does not exhibit any clinical significance as all reported values were within normal limits for the healthy pediatric population.

F. Examiner Calibration

Intra-examiner and inter-examiner agreement analyses were performed. The results demonstrated that all values were similar if not identical, which indicated excellent agreement within the same examiner and between different examiners.

VIII. DISCUSSION

A. Infiltration vs. IANB

This study ultimately demonstrated that local infiltration with four percent articaine with 1:100,000 epinephrine is as effective as IANB with two percent lidocaine with 1:100,000 epinephrine for restorative dental treatment of DMM. All 30 participants (15 in each of the Lidocaine and Articaine groups) involved in the study exhibited no failures in anesthesia as no supplemental LA administration was required to complete all treatment. Additionally, no intraoperative complications were observed, and no postoperative adverse events related to LA were reported for either LA agent. Blood pressure and pulse were overall within normal limits for both groups at baseline, time of injection, and throughout treatment. The mean scores for observable behavioral pain, rated with the MBPS (minimum of zero, maximum of 10 indicating most pain), were generally lower for the Articaine group than the Lidocaine group during LA administration but nearly identical for both LA agents throughout treatment. Furthermore, mean scores for subjective pain perception, rated with the WBS (minimum of zero indicating “no hurt”, maximum of 10 indicating “hurts worst”), were lower for the Articaine group than the Lidocaine group. However, none of the differences in the total mean MBPS scores and WBS scores were statistically significant; thus, the null hypothesis was accepted.

During LA administration, lidocaine IANB generally resulted in a slightly higher observed pain score, as rated by examiners A during the injection of the LA agent into the participant’s oral cavity. The only MBPS #A parameter that revealed a statistically significant difference between the two LA groups was the level of cry during the administration of LA. The MBPS #A cry score was slightly higher for the Lidocaine group

(1.47) than for the Articaine group (1.00). This difference in the MBPS #A cry score indicated that it was marginally more common for the Lidocaine group to express moaning or a gentle, whimpering cry during LA administration (MBPS #A cry score of two) than no cry at all (MBPS #A cry score of one). One can imagine that the increase in cry score for the Lidocaine group may be due to the deeper needle penetration required for IANB compared to infiltration. Yet, as the difference in the average cumulative, total MBPS #A scores between the two LA groups was not statistically significant, it cannot be concluded that articaine infiltration (mean total MBPS #A score of 2.13) indeed was considerably less painful than lidocaine IANB (mean total MBPS #A score of 3.07). Rather, the lack of statistical significance implies that lidocaine IANB and articaine infiltration were almost equally as painful upon LA administration.

Throughout treatment, both LA groups appeared to confer equally sufficient anesthesia. Both lidocaine IANB (mean total MBPS #B score of 1.87) and articaine infiltration (mean total MBPS #B score of 1.90) exhibited very similar, almost negligible levels of pain in the participants when examiners B observed their reactions and behavior during treatment. Although this slight difference may indicate that the participants in the Lidocaine group showed less indication of pain throughout treatment, it was not statistically significant. Thus, it can be concluded that the observed perception of pain was the equally low throughout treatment, regardless of the type of LA agent used.

According to the pediatric patients, the self-perceived level of pain throughout the entire appointment was lower in the Articaine group than in the Lidocaine group. A subjective evaluation of pain perceived by the patient was obtained at the conclusion of the appointment by asking each subject to complete the WBS. While the mean WBS

score was 1.3 out of 10 for the Lidocaine group, it was only 0.5 out of 10 for the Articaine group. Nonetheless, this difference was not statistically significant. Therefore, it can be concluded that the subjective perception of pain throughout treatment was identically very low, regardless of the type of LA agent administered. As pain is subjective and can be alleviated with LA, this finding further confirms the similar effectiveness of both articaine infiltration and lidocaine IANB in achieving adequate anesthesia of DMM.

Throughout the appointment, blood pressure and pulse were recorded as potential quantitative surrogates of pain. As indirect, quantitative measures of pain response, blood pressure and pulse can serve to complement direct observation and subjective measures because they are not subject to observer bias.[36] The only statistically significant, and possibly incidental, difference between the two LA agents regarding the measured vital signs was that the average pulse during treatment was slightly greater when lidocaine IANB was administered. The higher pulse during treatment in the Lidocaine group may have been due to the higher mean number of cartridges (1.21 for Lidocaine vs. 0.98 for Articaine) and thus higher resultant increased volume of epinephrine (0.020 mg for Lidocaine vs. 0.016 mg) that was administered. Epinephrine has effects on the cardiovascular system, which may have contributed to these hemodynamic changes particularly in the pulse rate.[37] This slight increase in average pulse was still within healthy, normal physiologic limits. However, none of the other differences in the results of blood pressure and pulse at the three different time points (baseline, during injection, and throughout treatment) were significant. Overall, it can be concluded that lidocaine IANB and articaine infiltration exhibit similar physiologic responses in terms of blood pressure and pulse. Moreover, though pain can be expressed without an increase in

blood pressure and pulse, the lack of significant changes in blood pressure and pulse does not invalidate other indicators of pain in the study.

Within this study, there were three subjects that participated twice in separate appointments. One subject was randomly assigned to the Lidocaine group twice. Total MBPS #A and MBPS #B scores were equal and consistent with a value of two, but there was a slight difference in the self-reported WBS score (two at the first visit vs. zero at the subsequent visit). This slight variation in self-perceived pain may be due to increased tolerance and familiarity of the dental procedure at the second visit. The two other subjects that participated twice incidentally experienced a split-mouth design. Both subjects displayed the same total MBPS #A and MBPS #B scores (two) and WBS scores (zero per one participant vs. two per the other participant) in their respective first and second visits. The consistent scoring of the perception of pain in these two patients further confirms that articaine infiltration is as effective as lidocaine IANB for LA.

B. Clinical Relevance

The results of this study collectively demonstrate that articaine infiltration, compared to lidocaine IANB, may be associated with slightly more overall comfort for the subject while yielding an equivalent level of sufficient anesthesia when restoring DMM. Infiltration anesthesia is a simpler technique of LA administration that works by depositing the LA agent directly into the soft tissue in the immediate vicinity of the tooth to be treated. IANB, on the other hand, is more technique sensitive, necessitating deeper needle penetration in a more posterior location than infiltration that is less easily visualized. In a pediatric patient, it may be increasingly challenging to administer LA, particularly lidocaine

IANB, when mouth opening is quite limited, and cooperation is not ideal. Uncontrollable mobility of the patient further compounds the risk of adverse events associated with IANB due to its highly technique sensitive procedure, which may result in needle breakage and hematoma if improperly administered.

IANB anesthetizes not only all posterior mandibular teeth ipsilateral to the side of injection, but also the anterior two-thirds of the tongue on the same side due to its downstream anesthesia of the lingual nerve. As a result, this excessive soft tissue numbness may overwhelm and irritate the pediatric patient, possibly leading to self-injurious tongue biting if left unsupervised. In contrast, infiltration anesthesia anesthetizes only the tooth to be treated and its neighboring soft tissue; as such, this smaller field of anesthesia decreases the risk of soft tissue irritation. Nonetheless, when treating several ipsilateral mandibular primary teeth, it may be more reasonable to administer lidocaine IANB than articaine infiltration due to the need to inject at additional sites when the latter technique is used.

There are certain clinical scenarios that favor the use of articaine infiltration over lidocaine IANB. A patient with hemophilia or other congenital bleeding disorder requiring treatment on mandibular molars may benefit from articaine infiltration because administering any LA agent via IANB may likely result in a hematoma.[38] For these patients, prophylactic factor replacement therapy is indicated prior to administering the IANB; otherwise, the hematoma may spread to the retromolar or pterygoid space, leading to potential airway compromise.[39] Similarly, lingual infiltration should also be avoided without replacement therapy due to the rich vascular supply in the lingual area, predisposing to a hematoma.[39] Local infiltration with articaine however can still be

achieved with buccal and intrapapillary injections without any necessary hemostatic coverage.[38] Furthermore, individuals with hepatic impairment may preclude the use of lidocaine, as lidocaine is mainly metabolized by the liver and systemic toxicity may otherwise ensue.[9] As an amide LA, articaine is also metabolized in the liver, but to a much lesser extent; rather, a majority of articaine is metabolized in the blood by plasma cholinesterase due to the presence of its unique ester side chain.[40] Therefore, articaine can be used more safely in patients with hepatic compromise, as its elimination half-life is only 20-40 minutes compared to >90 for lidocaine and other amide LAs that necessitate hepatic clearance.[9]

Pain control is a significant priority particularly in pediatric patients who can immediately withdraw cooperation at the first sensation of pain or discomfort. Consequently, the importance of adequate anesthesia and achieving it in a safe, effective manner is even more relevant in children. Due to its unique chemical structure, articaine inherently exhibits greater liposolubility and potency and is less toxic than lidocaine. These properties allow articaine to more easily permeate through the less dense mandibular bone in children and attain sufficient anesthesia in DMM through local infiltration. This study delivers reassurance to clinicians that articaine can be safely used among children, and the results illustrate that the less technique sensitive articaine infiltration may serve as a suitable, safer alternative for achieving as sufficient anesthesia as lidocaine IANB in restoring DMM in pediatric patients.

C. Articaine Limitations

Although articaine infiltration may seem ideal in certain situations, it should not be considered a substitution for the gold standard of anesthetizing mandibular teeth with lidocaine IANB. More practitioners should understand articaine as an additional tool in their clinical armamentarium. It should be universally acknowledged that infiltration anesthesia may be more suitable on certain occasions than a nerve block. Nonetheless, there are several clinical circumstances in which lidocaine IANB may be more preferable than articaine infiltration.

When multiple primary mandibular teeth require restorations with the use of local anesthesia, the decision whether to administer lidocaine IANB or articaine infiltration depends on a variety of factors. If there are two DMM on contralateral quadrants that require anesthesia, articaine infiltration may be the choice of LA. Administering lidocaine IANB in both the lower left and right quadrants would effectively numb the whole anterior two-thirds tongue, which may overwhelm and aggravate the patient. In contrast, if more than one tooth needs to be treated within the same quadrant in the mandible, or if rubber dam isolation is indicated with the clamp that needs to be placed on a more posterior tooth that is not to be treated, then lidocaine IANB may be the more appropriate, more comfortable, and faster option, as numbing multiple individual teeth would otherwise necessitate several infiltration injections. An IANB with lidocaine can deliver anesthesia to all teeth within the mandibular quadrant with a single injection. In the case of multiple teeth within a mandibular quadrant requiring local anesthesia, lidocaine IANB would be more desirable.

The higher concentration of articaine may limit its usage especially if the treatment to be rendered is extensive and requires additional anesthesia. Articaine is formulated in a four percent solution unlike lidocaine which is formulated in a two percent solution. Because of its increased potency, a lower total volume of articaine can be used until maximum dose is reached. As a result, this restriction may be a limiting factor in the extent of treatment that can be completed in a single encounter. This is an important consideration when involving more invasive procedures, such as extractions. Because tooth extractions require manipulation of all periodontal hard and soft tissues along with the teeth themselves, infiltration anesthesia may not provide sufficient anesthesia in all the tissues. For more extensive and invasive procedures, lidocaine IANB may be more appropriate.

Moreover, the use of articaine depends on the patient's age. According to the manufacturer recommendations, FDA approval, and AAPD guidelines, articaine should not be administered to individuals younger than four years of age. Although the safety and efficacy of articaine in children under four years old has been studied in a few clinical trials, there is insufficient data to support the use of articaine below this age limitation. Thus, lidocaine remains the LA agent of choice for all patients younger than four years of age that require local anesthesia.

D. Pain Rating Scales

The MBPS and WBS, two validated pain rating indices, were used in this study to measure the participant's perceived pain. While the MBPS was evaluated by observers (examiners #A and #B) who visually examined the patient's reactions during the

administration of LA and throughout treatment, the WBS was assessed by the subjects themselves who reported their personal perception of pain experienced throughout the appointment. All examiners were trained and calibrated in completing the MBPS forms to diminish the risk of possible study biases. Results from the intra- and inter-examiner agreement analyses revealed consistent, nearly uniform agreement within and between each examiner. Due to the limited variation of the ordinal scores for each of the three MBPS parameters, the results cannot be formally reported. Similarly, a reliability analysis cannot be formally reported either due to the inherent challenge of extrapolating meaningful statistical analysis indicating reliability in data with such a limited range.

The WBS was aptly chosen to measure the participant's perception of pain due to its easily comprehensible, pictorial depictions of discomfort and pain. A systematic review revealed that out of the four most widely researched visual pain scales with strong psychometric properties, the scale most children preferred to use was the WBS.[41] Children, even the younger ones approaching preschool age, were able to comprehend how to use the scale with minimal explanation.

Although they may appear to understand the directions on how to rate their pain, children are not always reliable reporters. Additionally, their self-reported level of pain did not always correlate with the level of pain that was observed and evaluated by the examiners. Occasionally, children may underrate their experience of pain according to what they believe will please the authority figures and legal guardians. A few subjects in the Lidocaine group may have marked their experience throughout the appointment as "zero; no hurt" even if they displayed signs of discomfort and anxiety, such as whimpering during the LA administration and subsequently throughout the remainder of treatment.

Conversely, children may overestimate their perception of pain due to a variety of reasons. They may seek attention from authority figures by reporting a level of pain on the WBS that is higher than their actual level of pain experienced. Pain may also be overrated because children cannot accurately distinguish pain versus pressure. Because local anesthesia only inhibits the sensation of pain but not pressure, the child may perceive any feeling of pressure as pain due to hyperawareness. One subject in the Articaine group did not move, wince, or cry during LA administration or treatment. However, the subjective self-reported pain perception was marked as “four; hurts little more”. This subject subsequently explained the reasoning behind the score, which was associated with uncomfortable pressure from seating the SSC. There was also a case in the Articaine group in which a subject rated the appointment as “hurts little more” because of the discomfort associated with the IsoDry isolation system. As a result of their eagerness to please, unreliable reporting, and misinterpretation of pain versus pressure, the pediatric patients’ rating of the WBS were more variable and less consistent with the MBPS scores that were assessed by trained and calibrated adults.

Yet, regardless of these potential complicating factors, the WBS served as the best available pain index to gauge the subjects’ pain perception in this study. Because pain is mainly a subjective experience, self-reported measures are fundamental and should be obtained when feasible to assess pain.[42] Our study followed published recommendations for clinical practice when using children’s self-report of pain intensities by complementing the subjective reports with observation.[42] The inconsistencies related to the child’s ability to properly assess the experience of pain were counterbalanced with the observed pain

measured through the MBPS evaluations and recordings of blood pressure and pain to aid in painting a more precise depiction of pain experienced by the child.

E. Relevance to Current Literature

The results from this study yield conclusions similar to those found in previous studies comparing the effectiveness of articaine infiltration versus lidocaine IANB in the treatment of DMM. In general, the objective and subjective results agree with findings from similar studies in which higher pain scores were observed with lidocaine than articaine despite any statistically significant differences present.[15,43–45] Arali and Mytri (2015) and Ghadimi *et al*. (2018) demonstrated that four percent articaine buccal infiltration can achieve as sufficient local anesthesia as two percent lidocaine IANB for pulpectomies and pulpotomies of DMM.[25,29] Both studies, like ours, utilized the MBPS and a VAS with evaluations of the participants' pain perception assessed at different time points by different individuals.[25,29] In contrast, Arrow (2012) found that four percent articaine displayed lower success when administered via buccal infiltration (71%) than two percent lidocaine when administered via IANB (100%).[15] Nonetheless, it should be noted that mainly permanent, not primary, molars were treated and treatment consisted of only Class I (buccal or occlusal) or Class II intracoronal restorations. The mean age of the subjects (12.4 years) in Arrow's study was also older, which may explain why a majority of the teeth treated (86%) were on permanent molars.[15] In contrast, our study focused exclusively on primary molars, most of which required more invasive, extracoronal restorations. Furthermore, in that study, the clinicians performing the treatment and evaluating the patient's perception of pain via a lesser known pain scale

(Children's Hospital of Eastern Ontario Pain Scale) were not completely blinded to the LA type as they had to administer the LA agent, which further increased study bias.[15] Our higher quality study was designed as such to minimize biases and optimize the measurement of perceived pain using two universally validated pain scales, MBPS and WBS, rated by three individuals (examiner A, examiner B, and subject) who were all blinded to the type of LA agent used. Additionally, our study utilized the additional quantitative assessment of blood pressure and pulse as possible surrogates of pain at three different time points, which no previous similar study has done.

F. Study Strengths

A majority of research investigating the effectiveness of articaine has been focused on adult patients. This study was conducted to further support the scarce literature that elucidates the effectiveness of articaine on the pediatric population. Although it has been demonstrated that articaine can be used successfully for the extraction and pulp therapy of permanent mandibular posterior teeth in adults, this finding cannot be generalized and extrapolated to include the younger population.[12,46,47] Of the few studies involving pediatric subjects, there have been mixed results on its ability to achieve adequate anesthesia through infiltration in mandibular posterior teeth. Although most studies involve mandibular buccal infiltration, there are limited studies like ours that include interdental papilla infiltration and lingual infiltration of articaine as well. This study was a prospective, randomized controlled clinical trial with parallel design, which is one of the most ideal methods to qualitatively evaluate effectiveness. To our knowledge, there are no publications that compare the effectiveness of articaine infiltration versus lidocaine

IANB local anesthesia for pulp therapy and a variety of restorations (i.e., composite resins, SSCs, pre-veneered SSCs, and zirconia crowns) in DMM. This was also the first study of its kind to include ubiquitous local infiltration (buccally, interdental papillary, and lingually). Infiltration from multiple directions ensures sufficient LA despite anatomical variations of the locations of the roots (i.e., some roots of mandibular teeth may be more lingually positioned closer to the lingual, not buccal, cortical plate of the mandible).

One of the strengths of this study was the use of a single operator who administered local anesthesia to every participant. The operator, an experienced pediatric dentist, consistently followed a step-by-step tutorial to reduce variability and maintain uniformity in delivering the LA agents. Introducing more than one operator to administer local anesthesia would further increase variability and as well as confounding factors. Therefore, to minimize this risk of bias, only one operator was utilized to administer all local anesthesia.

Opinion bias may have been another confounding factor that may influence the examiners on their rating of the MBPS forms. While examiners A were not explicitly told of the LA agent used for each participant, the dental assistants had to observe the operator and participants simultaneously during LA administration as the standard of care. It was also unlikely that the dental assistants exhibited a preference for either LA agent because they cannot administer LA. However, it was more likely that examiners B, the pediatric dental residents, expressed a preference to use a particular LA agent. Because of this potential, examiners B were completely blinded to the type of LA agent used until after they rated the MBPS #B forms, as they had to complete the clinical note after the appointment documenting the type of LA agent used, method of administration,

and amount administered. This precaution of blinding was included to minimize any opinion bias within the study stakeholders.

To further minimize biases and optimize the results of the study, pain experienced by the subject was evaluated in multiple ways. Trained and calibrated adult examiners A and B who observed the subject during LA administration and throughout the subsequent dental treatment, respectively, assessed the pain using the respective validated MBPS forms. The participants themselves also subjectively self-reported their own perception of pain throughout the appointment with the validated WBS. Blood pressure and pulse were measured as possible quantitative surrogates of pain. Although these measurements individually have some inherent limitations, they collectively supplement each other to generate a more accurate assessment of each participant's experience of pain.

G. Study Limitations

At first glance, one of the limitations of the study is the sample size. Although recruitment of up to 80 participants was approved by the IRB, only 30 were successfully enrolled. A limited number of subjects fulfilled the strict inclusion and exclusion criteria, which contributed to the small sample size. Additionally, the operator and PI had different clinic schedules, which restricted the time that they were both mutually available to proceed with the study. Within the study sample, a majority of treatment completed consisted of SSCs and composite resin restorations. As such, there is limited data to support more invasive procedures, such as pre-veneered SSCs and zirconia crowns that require additional reduction of tooth structure. Due to the limited supply of pre-veneered SSCs and zirconia crowns available in the clinic, we could not offer those options to all

participants. Although the study intended to investigate the effectiveness of articaine for pulp therapy as well, there were only two cases in which pulpotomies were indicated. It should be noted that in both of these two pulpotomy cases, the total MBPS #A and MBPS #B scores were identical (two), and the subject either rated the WBS as either zero ("no hurt") or two ("hurts little bit"), exemplifying the clinical success of articaine for pulpotomies. However, a majority of the restorative cases that were selected did not have pulp therapy (i.e., indirect pulp cap, pulpotomy, or pulpectomy) treatment planned. Additionally, despite the randomization process, only two participants in the Articaine group and none in the Lidocaine group needed pulp therapy. Therefore, due to the limited number of teeth that required pulp therapy, there is insufficient data to conclude that articaine should be routinely used as local anesthesia for pulp therapy of DMM.

Additionally, the use of a single, academic clinic setting served as a limitation. The study sample was recruited from the patient pool attending the PG Pediatric Clinic, Department of Pediatric Dentistry, COD at UIC. A majority of these patients were originally referred to this clinic as a result of their high anxiety and poor cooperation. Treatment on these patients were sometimes attempted but often aborted by their referring, outside providers due to their increasingly difficult behavior. As a result, most patients within our study sample already exhibited a baseline anxiety level due to a prior negative dental experience. This inherent bias may have influenced some of the overestimated ratings of the WBS. Furthermore, participants may have had increased anxiety due to the open bay environment and academically influenced prolonged appointments. The participants may have heard neighboring patients' cries or walked by operatories where protective immobile stabilization was utilized. In addition, in an

academic-based clinic, appointments are typically prolonged due to the time allotted for logistical checks and possible faculty interventions. Furthermore, each pediatric dental resident works at a different speed. Regardless, a prolonged appointment may have a negative impact on the participant as impatience develops. These external factors may amplify the participant's inherent anxiety and affect his or her behavior and/or evaluation of the pain rating scales, further contributing to the overestimation of pain perception.

The number of examiners/observers used in this study was an additional limitation. Despite having all 6 examiners A and 9 examiners B trained and calibrated with respect to evaluating observed pain and completing the MBPS forms, there is a possibility that they still rated pain marginally different from one another. Nonetheless, multiple examiners were inevitable due to the logistics of the clinic. Dental assistants (examiners A) rotated regularly with different pediatric dental residents (examiners B). Due to the time constraint of recruiting study participants within the IRB approval dates, multiple pediatric dental residents were used to enroll as many subjects as possible. Dental residents and assistants have their own style of non-pharmacologic behavior management, which may influence the behavioral outcome of the procedure. Therefore, the diversity of behavior management techniques used by these two roles further complicates the variables that may affect the results of the study.

H. Future Studies

Future studies with a larger number of patients should be considered to yield more profound statistical power and greater confidence in either accepting or rejecting the null hypothesis. A prospective sample size calculation, based on this study's results of subjective pain perception (mean WBS scores), using two independent samples t-test revealed that a sample size of 48 participants in each group would be necessary to reject the null hypothesis of equal means with a power of 90%. With the strong study design, this pilot study encourages a continuous study to recruit additional patients. The effectiveness of articaine infiltration should be evaluated on additional cases of invasive dental procedures, such as pulp therapy (e.g., pulpotomies and pulpectomies), restorations (e.g., pre-veneered SSCs and zirconia crowns) and extractions of DMM. Knowledge about the effectiveness of articaine infiltration would be expanded beyond what is already known about more conservative treatments. Introducing a split-mouth, cross-over design would reduce inter-subject variability from the measured behavioral outcome as well. To more accurately assess for pain without the increased baseline anxiety seen in the typical patient in our clinic, it would be interesting to consider conducting this study in a private practice setting. Performing the treatment in a quiet treatment room versus an open bay may eliminate external factors (i.e., neighboring patient's cry) that affect the patient's perception of pain. Additionally, utilizing only one assigned provider and assistant would ensure more consistent non-pharmacological behavior management, which would decrease confounding variables. For what it's worth, it may also be valuable to ask the subject to rate his/her level of pain perception using the WBS immediately after injection to determine the pain level of each injection technique.

IX. CONCLUSIONS

Based on the results of this study, the following conclusions are realized:

- Articaine infiltration was as effective as lidocaine IANB for restorative treatment of DMM in pediatric patients.
- While not statistically significantly different, less observable and self-reported pain was reported for articaine infiltration than lidocaine.
- Articaine infiltration can be considered a suitable alternative to routine lidocaine IANB administration for restorative treatment of DMM.

APPENDICES

Appendix A: IRB Approval Notice

Approval Notice
Initial Review – Expedited Review

June 5, 2019
Ivan Zhang
Pediatric Dentistry

RE: **Protocol # 2019-0160**
"Comparison of Articaine Mandibular Infiltration to Lidocaine Inferior Alveolar Nerve Block in Pediatric Patients"

Dear Dr. Zhang:

Members of Institutional Review Board (IRB) #1 reviewed and approved your research protocol under expedited review procedures [45 CFR 46.110(b)(1) and/or 21 CFR 56.110(b)(1)] on June 5, 2019. You may now begin your research.

Your research meets the criteria for approval under the following category(ies):

Please note the following information about your approved research protocol:

Protocol Approval Date:	June 5, 2019 - June 4, 2020
Approved Subject Enrollment #:	80
Performance Sites:	UIC
Sponsor:	None

Research Protocol(s):

a) Comparison of Articaine Mandibular Infiltration to Lidocaine Inferior Alveolar Nerve Block in Pediatric Patients, Version 2, 4/1/2019

Documents that require an approval stamp or separate signature can be accessed via OPRS Live. The documents will be located in the specific protocol workspace. You must access and use only the approved documents to recruit and enroll subjects into this research project.

Recruitment Material(s):

a) Patient Information Leaflet, Version 1, 4/1/19

Informed Consent(s):

a) Exception of informed consent granted [45 CFR 46.116(g)] for the identification of potential subjects in the recruitment phase of the research.

Assent(s):

a) Verbal Assent for children 7 to 10, Version 2, 4/1/19

UNIVERSITY OF ILLINOIS AT CHICAGO
Office for the Protection of Research Subjects
201 AOB (MC 672)
1737 West Polk Street
Chicago, Illinois 60612
Phone (312) 996-1711

Parental Permission(s):

a) Comparison of Articaine Infiltration to Lidocaine Inferior Alveolar Nerve Block in Pediatric Patients Version 2, 6/5/2019

HIPAA Authorization(s):

a) Review Preparatory to Research acknowledged [45 CFR 164.512(i)(1)(ii)]

Additional Determinations for Research Involving Minors: The Board determined that this research satisfies 45CFR46.404 and 21 CFR 50.51, research not involving greater than minimal risk. Therefore, in accordance with 45CFR46.408, the IRB determined that only one parent's/legal guardian's permission/signature is needed.

Please remember to:

→ **Use only the IRB-approved and stamped consent document(s) when enrolling new subjects.**

→ Use your **research protocol number** (2019-0160) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with the policies of the UIC Human Subjects Protection Program (HSPP) and the guidance ***Investigator Responsibilities***.

Please note that the UIC IRB has the right to ask further questions, seek additional information, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact the OPRS office at (312) 996-1711 or me at (312) 413-9680. Please send any correspondence about this protocol to OPRS via OPRS Live.

Sincerely,

Jovana Ljuboje, MPA
Assistant Director, IRB # 1
Office for the Protection of Research Subjects

cc: Evelina Kratunova, Faculty Sponsor
Marcio da Fonseca, Pediatric Dentistry, M/C 850

UNIVERSITY OF ILLINOIS AT CHICAGO
Office for the Protection of Research Subjects
201 AOB (MC 672)
1737 West Polk Street
Chicago, Illinois 60612
Phone (312) 996-1711

Appendix B: Patient Informational Leaflet

Patient Information Leaflet

APPROVED

DATE: 06/05/2019

UIC UNIVERSITY OF ILLINOIS AT CHICAGO INSTITUTIONAL REVIEW BOARD

Research Project

Comparison of Articaine Mandibular Infiltration to Lidocaine Inferior Alveolar Nerve Block in Pediatric Patients

Introduction:

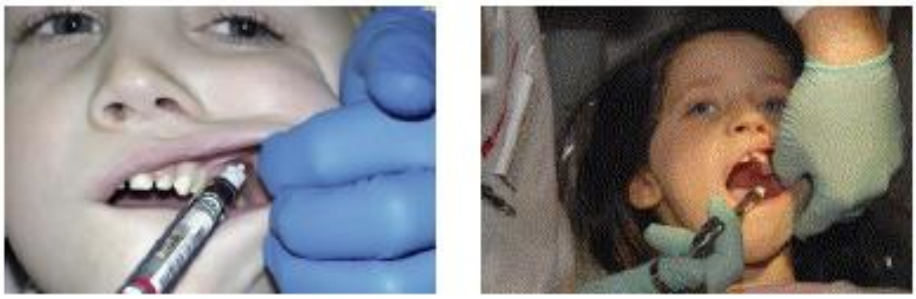
Your child requires dental treatment on his/her baby back teeth (molars). In order to fix the baby teeth, a medicine called local anesthetic is given to numb the teeth. Local anesthetic is an important part of dentistry because without it dental treatment would be very uncomfortable and painful. In order for local anesthetic to work, it needs to be given near the nerves of the teeth. Since the nerves are located under the gums and bone the only way this can be done is by giving an injection.

In this research project, we are evaluating two different methods of numbing baby teeth in the lower jaw. One of these methods is Articaine infiltration and the other is Lidocaine nerve block. Lidocaine and Articaine are two of the most common local anesthetic drugs used in dentistry to numb the teeth. The two main types of injections for numbing teeth are infiltration injection and nerve block. Infiltration injection is given near the area that will be treated while a nerve block is given in a different location than the area that will be treated. A nerve block is often necessary in areas where the bone is thick and infiltration injection will not be sufficient. Due to the thick bone in the lower jaw the most common method of numbing teeth in this area is giving a nerve block using lidocaine. An alternative method of numbing teeth in the lower jaw is using Articaine which is a newer local anesthetic that is FDA approved for use in children and adults. Articaine is a unique anesthetic because it is able to penetrate even thick bone allowing it to be given as an infiltration injection even in the lower jaw. There are many studies proving Articaine and Lidocaine to be safe and effective and we want to see how well each method works on baby teeth.

Patient Information Leaflet

Figure 1: Articaine (Left), Lidocaine (Right)

Figure 2: Infiltration injection (Left), Nerve Block (Right)



What does this involve?

Monitors measuring blood pressure and heart rate will be placed on your child's arm or leg. An experienced pediatric dentist will give your child the local anesthetic injection. The type of local anesthetic used will be randomly selected and only that dentist will know which one is used. The dental assistant will record your child's response to receiving the local anesthetic injection. A second dentist (pediatric dental resident) will then complete the planned treatment. The treatment that has been planned by your child's dentist will not change as a result of participating in this study. In other words, even if you do not participate the same treatment will be completed on your child. At the end of the visit, your child will be asked to rate their experience by pointing to a visual chart (see below).

Figure 3: Visual scale (Wong-Baker FACES Pain Rating Scale)

Patient Information Leaflet

Where will this treatment take place?

This research trial will be performed at the Pediatric Dentistry Department, College of Dentistry, UIC (801 S Paulina St, Chicago, IL 60612).

How long will this take?

On average, treatment visits last about an hour.

Your child will only participate in this study for one of their dental visits. The number of dental visits your child needs depends on their treatment plan. The rest of the visits will be completed as normal in the UIC Pediatric Dentistry Department.

Do I have to take part?

No, you do not have to be a part of this study. If you decide that you do not want your child included in the study, we will still carry out treatment of your child's back tooth. It will not affect your right to treatment.

Can I withdraw my child from the study?

Yes, you can decide to withdraw from the study at any point even if you have been involved at the start.

Confidentiality:
Your child's identity will remain confidential. His/her name will not be published and will not be disclosed to anyone outside the study group.

Confidentiality of Information:
Your child will be identified on all records/data by a participant's number. Access to your child's records and data from this study will be limited to the dentists in the research group. Any computerised information will be stored on password-protected computers with restricted access. The study data will be kept for 5 years after the study is completed in a locked cabinet but will not be used for any future unrelated studies without your permission.

Access to Data:
The data collected regarding your child will be available for you to see at any point during the study by asking a team member.

Permission:
Study permission is granted by the UIC Institutional Review Board.

Use of the data:

The results from this study will be published in a suitable dental journal or can be presented in a lecture format so others can benefit from the information.

Appendix C: HIPAA Authorization

University of Illinois at Chicago
Authorization To Use And Disclose (Release) Health Information For a Research Study

Comparison of Articaine Mandibular Infiltration to Lidocaine Inferior Alveolar Nerve Block in Pediatric Patients

State and Federal laws, including the Health Insurance Portability and Accountability Act (HIPAA), require researchers to protect your child's health information. This form describes how researchers, with your authorization (permission), may use and release (disclose or share) your child's protected health information in this research study. **Please read this form carefully.**

Your child has been asked to take part in a research study. The study has already been described to you in a separate consent form. By signing this form, you are permitting Dr. Ivan Zhang, Pediatric Dentistry Department, COD, UIC and his research team to create, get, use, store, and share protected health information that identifies your child for the purposes of this research study.

Description of protected health information that may be used and released (disclosed or shared)
The health information includes all information created and/or collected during the research as described in the 'Parental Permission for Participation in Research' entitled Research Information and Parental Permission for Participation in Biomedical Research.
Protected health information may include results of tests, procedures or surveys that are part of the research. Health information in your child dental record may be used and released if it is needed for the research; for example, past medical conditions or medications or information related to illness or hospitalizations that occur during your participation in the research

The dental health information includes name, phone numbers, email addresses, date of birth and dental record number.

Research use of your protected health information:
During the conduct of the research, the researchers may use or share your health information:
- With each other and with other researchers involved with the study;
- With law enforcement or other agencies, when required by law;
- With representatives of government agencies: Food and Drug Administration, review boards including the University of Illinois at Chicago Institutional Review Board and other persons who watch over the conduct of research;

Protection of your health information
The researchers agree to protect your health information and will only share this information as described in this Authorization and the Parental Permission for Participation in Biomedical Research Form.

When your health information is given to people outside of the research study, those agencies that receive your health information may not be required by federal privacy laws (such as the Privacy Rule) to protect it. They may also share your information with others without your permission, if permitted by laws that they have to follow.

Expiration of Authorization
This Authorization expires at the end of the study but can be canceled sooner if you decide to withdraw your permission.

Withdrawal or removal from the study
You may change your mind and cancel this Authorization at any time. To cancel this Authorization, you must write to:

Ivan Zhang, DMD
Pediatric Dentistry Department, COD, UIC
801 S. Paulina Street,
Room 267 (MC 850)
Chicago, IL 60612-7211
Phone 312-996-7532
Fax: 312-413-8006
Email: izhang5@uic.edu

If you cancel this Authorization, your child may no longer be allowed to take part in the research study. Even if you cancel this Authorization, the researchers may still use and disclose health information they have already obtained to maintain the integrity and reliability of the research and to report any adverse (bad) effects that may have happened to your child.

Contact information for questions about my rights under HIPAA
If you have questions or concerns regarding your privacy rights under HIPAA, you should contact the University of Illinois at Chicago Privacy Officer at phone number: (312) 996-2271.

If you have not already received a copy of the Notice of Privacy Practices, you should ask for one. You will be given a copy of this Authorization after it has been signed to keep for your records.

Right to Refuse to Sign this Authorization
You do not have to sign this Authorization. However, because your child's dental health information is required for research participation, if you decide not to sign this Authorization form, it will only mean your child cannot take part in this research. Not signing this form will not affect your child's non-research related treatment, payment or enrollment in any health plans or your child's eligibility for other medical benefits.

Signature of Subject

I have read (or someone has read to me) the above information. I have been given an opportunity to ask questions, and my questions have been answered to my satisfaction. I authorize the use and disclosure of my child's protected health information for this research.

_____

Printed name of Subject

_____ _____

Signature of Parent / Guardian of Subject Date

_____

Printed name of Parent / Guardian

Describe relationship to subject (Check one below):

☐ Parent
☐ Legal guardian
☐ Other; specify _____

_____

_____

Appendix D: Informed Consent Form

APPROVAL
STARTS 06/05/2019 — EXPIRES 06/04/2020
UIC UNIVERSITY OF ILLINOIS AT CHICAGO INSTITUTIONAL REVIEW BOARD

University of Illinois at Chicago

Research Information and Consent [Parental Permission]
for Participation in Biomedical Research

Comparison of Articaine Mandibular Infiltration to
Lidocaine Inferior Alveolar Nerve Block in Pediatric Patients

Principal Investigator/Researcher Name and Title: Dr. Ivan Zhang, DMD
Pediatric Dental Resident
Department and Institution: Pediatric Dentistry Department, University of Illinois at Chicago
Address and Contact Information: 801 S. Paulina Street
Room 267 (MC 850)
Chicago, IL 60612-7211
Phone: 312-996-1984
Fax: 312-413-8006
E-mail: izhang5@uic.edu

About this research study
You are being asked to participate in a research study. Research studies answer important questions that might help change or improve the way we do things in the future. This research study is a clinical trial in which participants are assigned to groups that receive one or more intervention/treatment so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes.

Taking part in this study is voluntary
Your participation in this research study is voluntary. You may choose to not take part in this study or may choose to leave the study at any time. Deciding not to participate, or deciding to leave the study later, will not result in any penalty or loss of benefits to which you are entitled and will not affect your relationship with the University of Illinois Hospital and Health Sciences System (UI Health) and/or University of Illinois at Chicago (UIC).

This consent form will give you information about the research study to help you decide whether you want to participate. Please read this form and ask any questions you have before agreeing to be in the study.

Note: This research includes subjects who are minors who are not able to consent for themselves. If you are a parent, guardian, or legal representative, the terms "you" or "your" refer to the research subject.

Important Information

This information gives you an overview of the research. More information about these topics may be found in the pages that follow.

WHY IS THIS STUDY BEING DONE?	The study is being done to test how well two types of medications (lidocaine and articaine) work in a child's mouth to numb the teeth. Our goal is to examine how good these medications are for back baby teeth. A number of items including blood pressure, heart rate, any discomfort during injection, any discomfort during the procedure, and the child's perception of the procedure will be examined. These numbing medications have been available on the dental market for a number of years and many pediatric dentists are using them in their clinics. Both types of medications are FDA-approved as safe and effective for use in children and adults. We hope to find out if there is any difference between the two medication types and if articaine can be routinely used instead of lidocaine. Your dentist has considered treatment options for your dental caries (cavities). Participation in this study and receipt of this experimental drug (articaine) and associated intervention (mandibular infiltration) is one of your treatment options.
WHAT WILL HAPPEN TO ME DURING THE STUDY?	In order to numb the tooth, numbing medication will be injected in the area around the tooth before beginning dental treatment. Either lidocaine or articaine, determined via randomization, will be used as the numbing medication. For more information, please see the "What Procedures Are Involved?" section below.
HOW MUCH TIME WILL I SPEND ON THE STUDY?	There is a one study visit that will last about 1 hour, which includes the time to numb the tooth and the time to perform the dental treatment.
ARE THERE ANY BENEFITS TO TAKING PART IN THE STUDY?	There may be no direct benefits to your child by participating in the study. It is hoped that knowledge gained from this research may benefit others that will require treatment with these two type local anesthetics in the future.
WHAT ARE THE MAIN RISKS OF THE STUDY?	Although the risk is minimal, the main risk of the study is loss of confidentiality.

DO I HAVE OTHER OPTIONS BESIDES TAKING PART IN THE STUDY?	If you decide that you do not want your child included in the study, he/she will receive the dental care as originally planned.
QUESTIONS ABOUT THE STUDY?	For questions, concerns, or complaints about the study, please contact Dr. Ivan Zhang, DMD (Pediatric Dental Resident) at 312-996-7532 or email at izhang5@uic.edu. You may also contact Dr. Evelina Kratunova, BDS, MDS, DChDent (Pediatric Dental Faculty) at 312-996-1984 or e-mail at evekrat@uic.edu. If you have a research related injury, you should immediately contact the pediatric dental resident on-call at 312-996-2242, extension 6901. If you have questions about your rights as a study subject; including questions, concerns, complaints, or if you feel you have not been treated according to the description in this form; or to offer input you may call the UIC Office for the Protection of Research Subjects (OPRS) at 312-996-1711 or 1-866-789-6215 (toll-free) or e-mail OPRS at uicirb@uic.edu.

Please review the rest of this document for details about these topics and additional things you should know before making a decision about whether to participate in this research. Please also feel free to ask the study team questions at any time.

Who may participate in the study?

You are being asked to participate in the research study because your child fits the eligibility criteria. He/she is medically healthy, is between 4 to 10 years old, has a past history of dental treatment using local anesthetic (to numb the teeth), was previously cooperative for dental treatment, and can understand English or Spanish.

Approximately 80 subjects may be involved in this study at UIC.

What procedures are involved?

This research will be performed at the Post-graduate Pediatric Dental Clinic, College of Dentistry, University of Illinois at Chicago (801 S. Paulina St, Chicago, IL 60612).

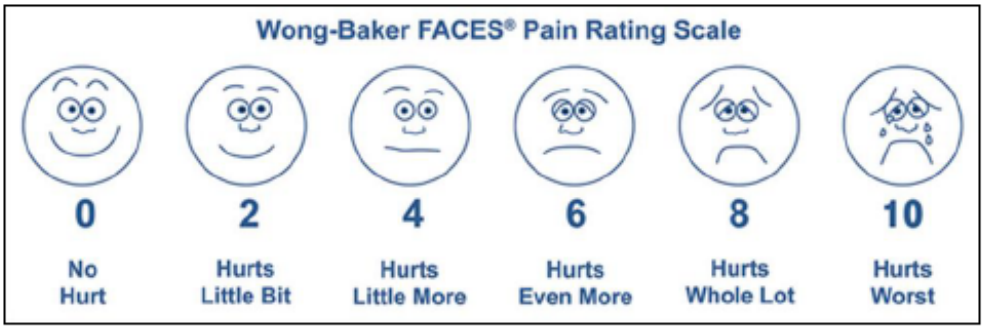
If you agree to be in the study, your child will be asked to rate his/her pain experience during the dental visit using a visual rating scale (Figure 1). Your child requires dental treatment on his/her lower baby (primary) back teeth (molars). It is important to hold on to the baby back teeth in order

to have space for the adult teeth to grow/erupt. Dental treatment on these back molars will typically involve the placement of white fillings or silver crowns.

In order to comfortably complete the dental treatment, local anesthesia will be used to numb the teeth. Local anesthesia is a type of drug that is used to decrease the feeling of pain by injecting it to numb a particular area without putting you to sleep. The two main ways to numb teeth are giving the injection near the tooth (infiltration injection) or giving the injection further back in the mouth which numbs the whole section (nerve block). Infiltration injection is less complicated because the injection site is easier to see, and the injection is given near the area that will be treated. A nerve block is more complicated because the injection is given further back in the mouth in a different location than the area that will be treated. A nerve block is often needed in areas where the bone is thick and infiltration injection will not go deep enough through the bone. Due to the thick bone in the lower jaw, the most common method of numbing teeth in this area is giving a nerve block using a medicine called lidocaine. An alternative method of numbing teeth in the lower jaw is using a medicine called articaine, which is a newer numbing medication that is approved by the U.S. Government for use in children and adults. Articaine is a unique numbing medication because it is able to go through even thick bone allowing it to be given as an infiltration injection even in the lower jaw.

We are asking your permission for your child to be a participant in a research study that investigates the effectiveness of two types of numbing medications for baby molar teeth: 2% lidocaine with epinephrine and 4% articaine with epinephrine.

Figure 1. Visual Rating Scale of Child's Pain Experience During Dental Visit



During this study, Dr. Zhang and his research team will collect information about your child for the purposes of this research. In addition to your child's rating of his/her experience with the dental treatment, we will also collect information regarding your child's reactions during the injection and during the overall dental treatment. All of this information is being collected to help evaluate the effectiveness of the numbing medication.

What are the potential risks and discomforts of the study?

Side effects, risks, and/or discomforts from participation in this study include:

- The total duration of the dental visit may be longer than planned.
- There are risks associated with the use of local anesthesia itself, including tachycardia (fast heart beat), hematoma (a black or blue bruise), temporary facial nerve paralysis, nerve damage, and secondary soft tissue trauma. These risks are uncommon and local anesthesia will be necessary for dental treatment, regardless of participation in the study.
- The teeth that are restored during the study may develop later complications, such as pain, infection, or discomfort. This is a risk apparent with any restorative dental intervention (i.e., white fillings and silver crowns), regardless of the anesthetic option used. Should this occur, an appropriate follow-up treatment will be provided.

There may be risks from the study that are not known at this time.

A risk of this research is a loss of privacy (revealing to others that you are taking part in this study) or confidentiality (revealing information about you to others to whom you have not given permission to see this information).

What about privacy and confidentiality?

Efforts will be made to keep your personal information confidential; however, we cannot guarantee absolute confidentiality. In general, information about you, or provided by you, during the research study, will not be disclosed to others without your written permission. However, laws and university rules might require us to tell certain people about you. For example, study information which identifies you and the consent form signed by you may be looked at and/or copied for quality assurance and data analysis include:

- Representatives of the university committee and office that reviews and approves research studies, the Institutional Review Board (IRB) and Office for the Protection of Research Subjects.
- Other representatives of the State and University responsible for ethical, regulatory, or financial oversight of research.
- Government Regulatory Agencies, such as the Office for Human Research Protections (OHRP).

A possible risk of the study is that your participation in the study or information about you and your health might become known to individuals outside the study. Your research data will be encrypted and stored on a password protected computer to prevent access by unauthorized personnel.

Your individual data will be destroyed 5 years after completion of the study.

When the results of the study are published or discussed in conferences, no one will know that you were in the study.

Will health information about you be created, used or shared with others during this study?

State and federal laws, including the Health Insurance Portability and Accountability Act (HIPAA), require researchers to protect your health information. This section of this form describes how researchers, with your authorization (permission), may use and release (disclose or share) your protected health information in this research study. By signing this form, you are authorizing Dr. Zhang and his research team to create, get, use, store, and share protected health information that identifies you for the purposes of this research.

The health information includes all information created and/or collected during the research as described within this consent form and/or any health information in your medical record that is needed for the research and that specifically includes your age, weight, particular tooth treated, type of dental treatment planned, type of local anesthetic numbing medication used, type of injection administered to deliver the numbing medication, total volume of numbing medication used, blood pressure and pulse throughout the dental visit, and self-reported pain rating of the overall dental visit.

During the conduct of the research, the researchers may use or share your health information:

- With each other and with other researchers involved with the study; and
- With representatives of government agencies (i.e., Food and Drug Administration), review boards including the University of Illinois at Chicago Institutional Review Board, the University of Illinois Medical Center and its representatives, and other persons who watch over the safety, effectiveness, and conduct of research.

If all information that identifies you is removed from your health information, the remaining information is no longer subject to the limits of this Authorization or to the HIPAA privacy laws. Therefore, the de-identified information may be used and released by the researchers (as permitted by law) for other purposes, such as other research projects.

How will your health information be protected?

The researchers agree to protect your health information and will only share this information as described within this research consent/authorization form.

When your health information is given to people outside of the research study, those agencies that receive your health information may not be required by federal privacy laws (such as the Privacy Rule) to protect it. They may also share your information with others without your permission, if permitted by laws that they have to follow.

What if I am injured as a result of my participation?

If you get ill or injured from being in the study, UIC will help you get medical treatment. You should let the study doctor know right away that you are ill or injured. If you believe you have become ill or injured from this study, you should contact Dr. Zhang at 312-994-2242, ext. 6901.

You should let any health care provider who treats you know that you are in a research study. If you do seek medical treatment, please take a copy of this document with you because it may help the doctors where you seek treatment to treat you. It will also provide the doctors where you seek treatment with information they may need if they want to contact the research doctors.

You or your health insurance plan will be billed. No money has been set aside to pay the costs of this treatment. Health insurance plans may or may not cover costs of research-related injury or illness. You should check with your insurance company before deciding to participate in this research study. Costs not covered by insurance could be substantial.

UIC has not set aside any money to pay you or to pay for your treatment if you get ill or injured from being in the study. There are no plans for the University to provide other forms of compensation (such as lost wages or pain and suffering) to you for research related illnesses or injuries. The only exception to this policy is if it is proven that your injury or illness is directly caused by the negligence of UIC.

By signing this form, you are not giving up any legal rights to seek compensation of injury.

What are the costs for participating in this research study?
There are no costs to you for participating in this research study.

Will I be reimbursed for any of my expenses or paid for my participation in this research study?
You will not be offered payment for being in this study.

Will I be told about new information that may affect my decision to participate?
During the course of the study, you will be informed of any significant new research findings (either good or bad), such as changes in the risks or benefits resulting from participation in the research or new alternatives to participation, that might cause you to change your mind about continuing in the study. If new information is provided to you, your consent to continue participating in this study may be re-obtained.

Can I withdraw or be removed from the study?
If you decide to participate, you have the right to withdraw your consent and leave the study at any time without penalty.

For your safety, you should consider the researcher's advice about how to leave the study. If you opt to leave the study before the completion of the planned study visit, then the researcher will honor your request and the dental treatment will still be completed as originally planned.

The researcher also has the right to stop your participation in this study without your consent if:
- They believe it is in your best interests;
- You were to object to any future changes that may be made in the study plan.

If you choose to no longer be in the study and you do not want any of your future health information to be used, you must inform Dr. Zhang in writing at the address on the first page.
Dr. Zhang may still use your information that was collected prior to your written notice.

Your Authorization for release of health information for this research study expires at the end of the study, but can be canceled sooner if you decide to withdraw your permission.

You may change your mind and cancel this Authorization at any time. To cancel this Authorization, you must write to: Dr. Ivan Zhang, 801 S. Paulina Street, Room 267 (MC 850), Chicago, IL 60605-7211

If you cancel this Authorization, you may no longer be allowed to take part in the research study. Even if you cancel this Authorization, the researchers may still use and disclose health information they have already obtained as necessary to maintain the integrity and reliability of the research and to report any adverse (bad) effects that may have happened to you.

What are my rights as a research subject?
If you have questions or concerns regarding your privacy rights under HIPAA, you should contact the University of Illinois at Chicago Privacy Officer at Ph: (312) 996-2271.

Right to Refuse to Sign this Authorization
You do not have to sign this Consent/Authorization. However, because your health information is required for research participation, you cannot be in this research study if you do not sign this form. If you decide not to sign this Consent/Authorization form, it will only mean you cannot take part in this research. Not signing this form will not affect your non-research related treatment, payment or enrollment in any health plans or your eligibility for other medical benefits.

Remember:
Your participation in this research study is voluntary. Your decision whether or not to participate will not affect your current or future relations with the University. If you decide to participate, you are free to withdraw at any time without affecting that relationship.

Signature of Subject or Legally Authorized Representative

I have read (or someone has read to me) the above information. I have been given an opportunity to ask questions and my questions have been answered to my satisfaction. I agree to participate in this research study. I will be given a copy of the signed and dated form.

If you have not already received a copy of the Notice of Privacy Practices, you should ask for one.

Your signature below indicates that you are providing both consent to participate in the research study and authorization for the researcher to use and share your health information for the research.

_____ _____

Signature of Parent / Guardian or Legally Authorized Representative of Subject

Date (must be same as Subject's)

_____

Printed name of Parent / Guardian or Legally Authorized Representative of Subject

Describe relationship to subject including the legal authority this individual has to act on behalf of the subject. (Check one below)

- ☐ Parent
- ☐ Medical Power of attorney/representative
- ☐ Legal guardian
- ☐ Health care surrogate
- ☐ Other; specify

_____

_____

_____

Appendix E: Verbal Assent

University of Illinois at Chicago

APPROVAL
STARTS 06/05/2019 — EXPIRES 06/04/2020
UIC UNIVERSITY OF ILLINOIS AT CHICAGO INSTITUTIONAL REVIEW BOARD

VERBAL ASSENT TO PARTICIPATE IN RESEARCH
For children 7 to 10 years of age

Title: Comparison of Articaine Mandibular Infiltration to Lidocaine Inferior Alveolar Nerve Block in Pediatric Patients

1. My name is Dr. Ivan Zhang

2. We are asking you to take part in a research study because we are trying to learn more about medicines called local anesthetics used to numb teeth.
   - ✓ A local anesthetic is a medicine that is given by the dentist to numb the teeth for dental procedures.
   - ✓ The teeth are numbed so that it is not painful when we fix the teeth.
   - ✓ We are testing two different types of medicine to see if one will work better than the other. One is called articaine and the other is called lidocaine.
   - ✓ Even if you decide not to be in this study, you will still need this medicine to fix your teeth.

3. If you agree to be in this study:
   - ✓ You will get one of these medicines, either lidocaine or articaine, for one side of your bottom baby teeth.
   - ✓ Your baby teeth that are ill, will be cleaned and and fixed with either a white filling or a silver crown. A crown is like a cap that is glued over your whole tooth.
   - ✓ We will be checking your blood pressure and heart rate with a special machine the whole time you are here.
   - ✓ At the end of the visit you will be asked if you have any pain from the procedure by showing how it felt when the medicine was given by pointing on a chart that has different faces.

4. The numbing usually lasts 2-3 hours so you need to be careful not to accidentally bite your cheek, lip, or tongue:
   - ✓ Do not bite or chew on hard or sticky foods until the numbing goes away.
   - ✓ The numbing can feel strange but do not play with or bite your cheek, lip, or tongue. If you accidentally bite yourself it will hurt after the numbing goes away and can last for 7 to 10 days.

5. By taking part of our study you will get to have your teeth fixed with one type of numbing medicine but you or the doctor fixing your teeth will not know which one.

6. Please talk this over with your parents before you decide whether or not to participate. We will also ask your parents to give their permission for you to take part in this study. But even if your parent(s) say "yes", you can still decide not to do this.

7. If you don't want to be in this study, you don't have to participate. Remember, being in this study is up to you and no one will be upset if you don't want to participate or even if you change your mind later and want to stop.

8. You can ask any questions that you have about the study. If you have a question later that you didn't think of now, you can call me on phone number: **312-996-1984** or ask me next time.

9. Your dentist will continue to treat you whether or not you participate in this study. You and your parents will be given a copy of this form.

Appendix F: Tutorial Guide for IANB in a Pediatric Patient

- Dry injection site with gauze. Apply small amount of topical anesthetic with cotton-tipped applicator.
- The location of the mandibular foramen is situated below the occlusal plane in the pediatric patient; therefore, the injection must be made slightly lower and more posteriorly than for an adult patient.
- Thumb is laid on the occlusal surface of the molars, with the tip of the thumb resting on the internal oblique ridge and the ball of the thumb resting in the retromolar fossa. Firm support during the injection procedure can be given when the ball of the middle finger is resting on the posterior border of the mandible.
- The barrel of the syringe should be directed on a plane between the two primary molars on the opposite side of the arch. It is advisable to inject a small amount of the solution as soon as the tissue is penetrated and to continue to inject minute quantities as the needle is directed toward the mandibular foramen.
- The depth of insertion averages about 15 mm but varies with the size of the mandible.

  Insert to the depth that is adjacent to bone.
- Aspirate.
- Slowly inject bolus of anesthetic at a rate of 1 mL/min.
- Remove needle.

Appendix G: Tutorial Guide for Infiltration Anesthesia in a Pediatric Patient

- Dry injection site with gauze. Apply small amount of topical anesthetic with cotton-tipped applicator.
- Reflect tissue to expose injection site.
- Orient bevel of the needle to be parallel to the bone and insert needle into mucobuccal fold
- Proceed to the depth that approximates the apices of the buccal roots of the primary molars.
- Aspirate.
- Deposit bolus of anesthetic slowly at a rate of 1 mL/min.
- Remove needle.
- Repeat deposition of anesthetic into the interdental papilla and then into the lingual gingiva.

Appendix H: Initial Data Capture Form

Comparison of Articaine Mandibular Infiltration to Lidocaine Inferior Alveolar Nerve Block in Pediatric Patients

Initial Data Capture Form

Participant Study Number	
Date of Procedure	
Participant's Age (years)	
Participant's Weight (lbs)	
Tooth Treated	Left / Right First Molar / Second Molar
Type of Planned Treatment	Composite / SSC *If pulp therapy: IPC / Pulpotomy / Pulpectomy*
Type of Local Anesthetic Used	2% Lidocaine with 1:100,000 epinephrine / 4% Articaine with 1:100,000 epinephrine
Type of Injection Administered	Inferior alveolar nerve block / Mandibular local infiltration
Total Volume of Local Anesthetic Used (mg)	

Appendix I: Approval Letter from Wong-Baker FACES Foundation

Having trouble viewing this email? Click here

WONG-BAKER FACES FOUNDATION

Our Foundation Exists to Provide Global Access to our Scale and to Promote Optimal Pain Assessment, Pain Management, and Atraumatic Care.

Dear Dr. Zhang,

I apologize for the delay.

Thank you for contacting our foundation and completing the web form.

You have permission to use our scale in your research, without a licensing requirement or fee.

Please follow these four conditions:

- The information below is for your use only. We ask that you not share it with other unlicensed organizations.
- Use the authorized image of the scale provided below.
- Use the scale as the instructions indicate, without modifications.
- Do not use the scale for profit.

To assure proper use in your research please review the following:

- The FACES Scale is recommended for people ages three and older, not just for children.
- The FACES Scale is designed to measure physical pain, only.
- This self-assessment tool must be understood by the patient, so they are able to choose the face that best illustrates the pain they are experiencing. The tool is not for use with infants or patients who are unresponsive.
- It is not a tool to be used by a third person, parents, healthcare professionals, or caregivers, to assess the patient's pain. There are other tools for those purposes

Here are the JPEGs of the Wong-Baker FACES$^{Â®}$ Pain Rating Scale in English for your use: English_Blue , English_Black

When you have completed your study and are submitting your manuscript for publication, please use these images which include the necessary copyright and trademark information for publishing the research:
Publication_English_Blue, Publication_English_Black

The following example bibliography citation may be helpful to you:
Wong-Baker FACES Foundation (2020). Wong-Baker FACES$^{Â®}$ Pain Rating Scale. Retrieved from http://www.WongBakerFACES.org.

Please let me know if you need anything else. We would love to hear about the results of your research.

Kind regards,
Nick

Nick Baker
Licensing Specialist
Wong-Baker FACES Foundation
Nick@WongBakerFACES.org
WongBakerFACES.org

Appendix J: Modified Behavioral Pain Scale #A Form

Comparison of Articaine Mandibular Infiltration to Lidocaine Inferior Alveolar Nerve Block in Pediatric Patients

Modified Behavioral Pain Scale #A

Local Anesthetic Administration

Participant's Number: _____ **Date:** _____

Behavior Observed	Score
Facial Expression	
Definitive positive expression (i.e., smiling)	0
Neutral expression	1
Slightly negative expression (i.e., grimace)	2
Definite negative expression (i.e., furrow brows, eyes closed tightly)	3
Cry	
Laughing or giggling	0
Not crying	1
Moaning, quiet vocalizing, or gentle or whimpering cry	2
Full-lunged cry or sobbing	3
Full-lunged cry, clearly more than baseline	4
Movements	
Usual movements and activity, resting, and relaxed	0
Partial movement or attempt to avoid pain by withdrawing limb when procedure is done	2
Agitation with complex movements involving head, torso, or other limbs, or rigidity	3
Total Score	

Appendix K: Modified Behavioral Pain Scale #B Form

Comparison of Articaine Mandibular Infiltration to Lidocaine Inferior Alveolar Nerve Block in Pediatric Patients

Modified Behavioral Pain Scale #B

Dental Treatment

Participant's Number: _____ **Date:** _____

Behavior Observed	Score
Facial Expression	
Definitive positive expression (i.e., smiling)	0
Neutral expression	1
Slightly negative expression (i.e., grimace)	2
Definite negative expression (i.e., furrow brows, eyes closed tightly)	3
Cry	
Laughing or giggling	0
Not crying	1
Moaning, quiet vocalizing, or gentle or whimpering cry	2
Full-lunged cry or sobbing	3
Full-lunged cry, clearly more than baseline	4
Movements	
Usual movements and activity, resting, and relaxed	0
Partial movement or attempt to avoid pain by withdrawing limb when procedure is done	2
Agitation with complex movements involving head, torso, or other limbs, or rigidity	3
Total Score	

Appendix L: Basic Vital Signs Form

Comparison of Articaine Mandibular Infiltration to Lidocaine Inferior Alveolar Nerve Block in Pediatric Patients

Basic Vital Signs Form

Participant's Number: _____ **Date:** _____

Pulse and Blood Pressure Recordings:

Time	Pulse	Blood Pressure

Appendix M: Self-reported Pain Rating Scale Form

Comparison of Articaine Mandibular Infiltration to Lidocaine Inferior Alveolar Nerve Block in Pediatric Patients

Self-reported Pain Rating Scale Form

Participant's Number: _____ **Date:** _____

Wong-Baker FACES® Pain Rating Scale

0	2	4	6	8	10
No Hurt	Hurts Little Bit	Hurts Little More	Hurts Even More	Hurts Whole Lot	Hurts Worst

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VITA

IVAN L. ZHANG, DMD

EDUCATION

University of Illinois at Chicago, College of Dentistry – Chicago, IL June 2018 - Present
Certificate in Pediatric Dentistry (expected June 2020)
Master of Science in Oral Sciences (expected May 2020). GPA: 4.00
Master's Research Thesis: Comparison of Articaine Mandibular Infiltration to Lidocaine Inferior Alveolar Nerve Block in Pediatric Patients

University of Pennsylvania, School of Dental Medicine – Philadelphia, PA August 2014 – May 2018
Doctor of Dental Medicine with Community Oral Health Clinical Honors. GPA: 3.66

Bowdoin College – Brunswick, ME August 2007 – May 2011
Bachelor of Arts with Honors in Biochemistry, Minor in Economics. GPA: 3.44
Honors Research Thesis: Synthesis and Characterization of Closthioamide Derivatives

PROFESSIONAL EXPERIENCE

Apple Dental Care Pediatric Dentistry and Orthodontics – Chicago, IL July 2019 - Present
General Dentist (Moonlighting)
- Provided preventative, restorative, and urgent dental care to pediatric patients on Saturdays

Education Works – Philadelphia, PA June 2015 – August 2015
Bridging the Gaps Community Health Intern
- Mentored adolescents through Philadelphia Youth Networks' WorkReady summer program at Penn Treaty High School
- Promoted health, nutrition, and entrepreneurship with a focus on urban sustainability by facilitating interactive seminars

The Field School – Washington, D.C. August 2011 – June 2014
Upper School Science and Mathematics Teacher, Head Coach, and Club Adviser
- Instructed daily sections of Introductory-level Biology, General Chemistry, and Advanced Algebra with Trigonometry
- Designed and taught an honors seminar course, Modern Science: Epigenetics and Biomedicine
- Coached lower school boys' basketball and co-ed track and field teams
- Founded the Robotics Club, coordinated weekly meetings and competitions, and trained members in basic engineering projects

Private Tutor – Washington, D.C. January 2013 – June 2014
Advanced Placement Biology and Organic Chemistry Tutor
- Guided individual high school and college students in advanced science courses
- Formulated personalized study skills specific to each student's learning style

New Haven Public Schools – New Haven, CT June 2009 – August 2009
Paraprofessional Teacher
- Moderated remedial summer school classes for inner city third grade students
- Amended curriculum for classes in reading, writing, and mathematics to better suit interests of students

RESEARCH EXPERIENCE & PUBLICATIONS

Synthesis and Characterization of Closthioamide Derivatives
Mentor: Benjamin C. Gorske, PhD — Bowdoin College, Brunswick, ME

Dissection of Pol II Trigger Loop Function and Pol II Activity-Dependent Control of Start Site Selection
Mentor: Craig D. Kaplan, PhD — Texas A & M University, College Station, TX

Kaplan CD, Jin H, Zhang IL, Belyanin A (2012) Dissection of Pol II Trigger Loop Function and Pol II Activity–Dependent Control of Start Site Selection *In Vivo*. *PLOS Genetics* 8(4): e1002627.

AWARDS & HONORS

Dr. Indru Punwani Graduate Student Research Award — 2020
Illinois Society of Pediatric Dentists

Community Oral Health Clinical Honors — 2018
University of Pennsylvania, School of Dental Medicine

Raymond J. Harris Educational Scholarship — 2017
University of Pennsylvania, School of Dental Medicine

Howard Hughes Medical Institute Post-Baccalaureate Research Fellowship — 2011
Bowdoin College

National Science Foundation Grant for Summer Research Experience for Undergraduates — 2010
Texas A & M University

LICENSURE & CERTIFICATIONS

American Heart Association Basic Life Support for Healthcare Providers
American Heart Association Pediatric Advanced Life Support
District of Columbia Dental License
Illinois State Dental License
Maryland State Dental License

PROFESSIONAL AFFILIATIONS

American Academy of Pediatric Dentistry
American Dental Association
Chicago Dental Society
Illinois Society of Pediatric Dentists
Illinois State Dental Society