Pain Perception and Onset Associated with Administration of Buffered Lidocaine Versus Conventional Lidocaine in the Pediatric Dental Patient

Research Protocol – IRB 2019-0408

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1 ABBREVIATIONS USED IN THE PROTOCOL

Abbreviation	Term
IANB	Inferior Alveolar Nerve Block
GMC	Geisinger Medical Center
IRB	Institutional Review Board
ASA	American Society of Anesthesiologists
AAPD	American Academy of Pediatric Dentistry
MRN	Medical Record Number
PA	Pennsylvania
FLACC	Faces, Legs, Arms, Crying Consolability

2 ABSTRACT

Local anesthetic buffered with sodium bicarbonate has been suggested to reduce pain, discomfort and onset time of local anesthesia on injection into tissue, compared to non-buffered solutions. Buffered local anesthesia has been used in medicine, however intraoral injections with buffered solutions are less common in dentistry. Most research has focused on adult perception of pain on administration of buffered local anesthetic. There have been few studies and inconclusive evidence to show that buffered lidocaine reduces the perception of pain on administration in children. The purpose of this interventional study is to assess pain reduction and onset time on injection of buffered 2% lidocaine with 1:100,000 epinephrine in children.

3 BACKGROUND AND SIGNIFICANCE

Local anesthesia is a necessary component of dental treatment that aids in establishing patient comfort and reduction of anxiety. However, a local anesthesia injection is often uncomfortable and unpleasant. Injection of local anesthesia can elicit a painful or burning sensation. In children, profound anesthesia and ease of administration can help establish and maintain positive dental experiences and also reduce anxiety in the dental setting. The injection is not only uncomfortable during the penetration of the needle through the epidermis, but also during injection of acidic solution into the tissue.

Commercially available local anesthetics are often prepared with hydrochloric acid to increase their solubility and stability[1]. These local anesthetics range in pH from 3.5 to 5.5 and are significantly lower than the physiological pH of 7.35.[1] The acidity of a traditionally prepared local anesthetic solution has been shown to contribute to pain during injection of local anesthetic and also to an increased onset time of local anesthesia[2]. Buffering the traditional local anesthetic solution to a pH value closer to physiological pH has been done to aid in pain reduction associated with injection of solution[2]. Based on the Hederson-Hasselbach equation, it has been

shown that neutralizing the solution of local anesthesia can reduce the pain perception associated with administration of local anesthesia and decrease the onset time[3]. With an increase in pH of solution, more free base is available to cross the nerve sheath, reducing the onset of action[3].

Medicine has used buffered local anesthetic solutions with success and the literature reflects this adaptation into clinical practice.[3,4,5,6] Previous studies have investigated the difference in onset and the reduction of pain in administration of buffered lidocaine vs traditional lidocaine in both children and adults. There have been fewer studies investigating the perception of discomfort during injection and the difference in anesthesia onset time in children compared to adult subjects. The literature has shown varied results and conclusions in both children and adult study populations. Some of these studies have found a significant difference in onset time and perceived pain reduction with buffered solution compared to standard solution, while others have failed to find significant differences.[1,7,8,9,10,11]

This project's primary aim is to evaluate pain perception in buffered vs non-buffered local anesthetic administration in children undergoing routine dental treatment. The secondary aim is to evaluate if the buffered solution results in a faster onset of local anesthesia compared to conventional solution. Through a well-designed study, we hope to contribute to the profession's understanding of advanced local anesthesia techniques in children.

4. HYPOTHESIS AND SPECIFIC AIMS

4.1 HYPOTHESIS:

4.1.1 Null Hypothesis: There will be no significant difference between buffered local anesthesia vs conventional anesthesia in pain reduction.

4.1.2 Null Hypothesis: There will be no significant reduction in time between buffered local anesthesia vs conventional anesthesia achieving soft tissue anesthesia.

4.1.3 Hypothesis: There will be a statistically significant reduction in pain on intraoral administration of buffered 2% lidocaine with 1:100,000 epinephrine compared to non-buffered 2% lidocaine w/1:100,000 epinephrine in children.

4.1.4 Hypothesis: Buffered 2% lidocaine with 1:100,000 epinephrine will have a statically significant faster onset of soft tissue anesthesia compared to non-buffered 2% lidocaine w/1:100,000 epinephrine in children

4.2 SPECIFIC AIM 1:

To determine if buffering 2% lidocaine with 1:100,000 epinephrine reduces discomfort experienced on injection compared to non-buffered solution in children with a split mouth design

4.3 SPECIFIC AIM 2:

To compare infiltration vs inferior alveolar nerve block (IANB) in experience of pain reduction with buffered 2% lidocaine with 1:100,000 epinephrine on injection in children among different groups; patients will either receive two or more infiltrations or two or more IANBs.

4.4 SPECIFIC AIM 3:

To determine if buffering 2% lidocaine with 1:100,000 epinephrine reduces onset time of local anesthesia compared to non-buffered solution in children

4.5 SPECIFIC AIM 4:

To compare onset time of local anesthetic via infiltration versus IANB using buffered 2% lidocaine with 1:100,000 epinephrine in children

5. STUDY DESIGN

5.1 DESCRIPTION

This study has been designed as a longitudinal, double blind, crossover study. Specifically, a split mouth design will be implemented to investigate if there is a significant difference in pain perception between administering buffered local anesthesia versus conventional local anesthesia in a pediatric patient. We will also investigate time of onset of local anesthesia and compare buffered to non-buffered solutions. Patients will be treated by a single pediatric dental resident while being overseen by a board-certified attending pediatric dentist at Geisinger Medical Center (GMC). This study will be implemented upon receiving Institutional Review Board (IRB) approval.

The population of interest includes healthy children aged 4-17yo. Children selected for this study will be assessed using the American Society of Anesthesiologists (ASA) physical status classification system. In an effort to control for confounding variables, only healthy children classified as ASA I or ASA II will be included in this study. Children selected for this study will have been determined to require treatment on two or more occasions on opposite sides of the mouth. If a patient has multiple issues on each side of the mouth, the patient may be asked to participate in the study procedures for a second time. This could result in seeing the patient for 4 separate visits. Patients will not be excluded if they develop localized infection requiring treatment without systemic antibiotics, however, they will only remain in the study if both sides requiring treatment are either free of infection or if both sides have a localized pain or infection requiring treatment without systemic antibiotics. Patients must have no allergy to lidocaine or

history of adverse reactions to epinephrine, no history of hyperthyroidism, and no significant cardiovascular disease per recommendations for administration of local anesthetic according to the American Academy of Pediatric Dentistry (AAPD).[12] Buffered lidocaine has been approved for use in patients for medical and dental procedures. There is no additional cost to the patient for receiving buffered versus non-buffered solution.

Patients will be examined by the pediatric dental resident under supervision of the attending pediatric dentist. At the time of examination, patients that meet the inclusion criteria (see section 5.2.2 below) will be offered to enroll in this research study. Each patient will consent for treatment via a parent or legal guardian. The parent or legal guardian and the provider will review the inclusion and exclusion criteria, risks and benefits to participation in this study, and general information about the timeline and clinical expectations of the patient. The consent process will be completed by the pediatric dental resident under supervision of the attending pediatric dentist. The patient's parent or legal guardian will be given a chance to ask questions during the consent process. Parents and legal guardians will be given the option to have their child included in the study or to have their child proceed with traditional treatment with non-buffered local anesthesia. Study participants are those that will be consented to receive a blinded solution of either buffered or non-buffered solution over two or more appointments. There will be no financial compensation or incentive to participate in this study. There is no advantage or disadvantage for patients undergoing treatment in this study as compared to patients not included in the study. Compared to patient's not included in the study, there is no additional risk with patients electing to be removed from the study or for patients who fail to complete treatment. In addition to obtaining parental or guardian consent, patients aged 15-17 years of age will sign assent. Study participants will receive a copy of this consent/assent form.

Following patient selection (based on the inclusion and exclusion criteria listed below in section 5.2.2), and consent, each patient will be assigned number as they are added into the study. This number will be sequential; e.g. the first patient will be assigned a number of '1,' and the second patient will be assigned a number of '2.' Patients will be added to the study at time of consent after the initial examination by the dental resident.

On the day of the procedure, the side of the mouth that is treated first will be based on the patient's chief complaint. If the patient does not have a chief complaint, the side of the mouth that is treated first will be the side of the mouth with more significant dental caries. The attending pediatric dentist will flip a coin to determine if the patient will receive the buffered or conventional local anesthetic solution during the first visit, with the "heads" side being assigned to the buffered solution, and the "tails" side assigned to the non-buffered solution. At the patient's second visit, the alternative local anesthetic solution will be used, and the other side of the mouth will be treated.

The attending pediatric dentist will have access to a protected Excel spreadsheet containing information related to each patient including: patient name, medical record number (MRN), the patient's number assignment (as discussed above), date of the first and second visit, which local anesthetic solution was administered at each visit, the local anesthesia technique used (infiltration vs IANB), which arch (maxilla vs mandible) was treated, and which side of the mouth was treated. This document will be locked and the operator will not have access to this spreadsheet in order to preserve the double-blind nature of this study.

Vasoconstrictors, like epinephrine, become unstable with an increase in pH[9]. Local anesthetic solutions with a vasoconstrictor are traditionally prepared as an acidic solution to extend shelf life[9]. Buffering our local anesthesia containing epinephrine will reduce the stability of solution from approximately 8-12 months to a shelf life of only seven days[13]. Although the solution has been said to be stable for a week, to ensure stability of the solution, and control for confounding variables, the buffered solutions will be mixed immediately before administering the solution. Other study designs have used this approach to mix the solution immediately before administration[1,9].

During the appointment requiring the buffered local anesthesia solution, the attending will prepare 1:10 dilution of sodium bicarbonate to local anesthesia. A 1.7mL vial of commercially available 2% lidocaine hydrochloric acid with 1:100,000 epinephrine (Lignospan standard, Septodont Lancaster, Pennsylvania (PA) will be used. The cartridge of lidocaine and the bottle of sodium bicarbonate will be wiped with an alcohol pad. 0.17mL of 8.4 percent sodium bicarbonate will be added into the local anesthesia cartridge to make the final preparation. The pH of traditional 2% lidocaine with 1:100,000 epinephrine is typically acidic to prolong shelf life; the pH is approximately 4.5.[8] The buffered solution will be tested using a pH tester (Water Quality Test Meter Pancellent TDS PH EC Temperature 4 in 1 Kit, Pancellent) to evaluate the pH range of this preparation, and to verify a value above 5.5.

The attending will bring the cartridge of anesthetic to the operatory and load the syringe. The operator and patient will remain blinded to the type of local anesthesia that is used. For this study, if the patient requires treatment of the lower posterior teeth, a IANB will be the injection technique of choice. If the patient requires treatment in the posterior maxilla, an infiltration will be the injection technique of choice. After a period of no less than one week, the patient will return for a second visit. At the second visit, the solution of local anesthesia will be alternated, and the opposite side of the mouth will be treated.

Prior to initiation of treatment, patients will rate their pain using the Wong-Baker FACES Pain Scale in order to establish a baseline and to help eliminate confounding variables. Also before treatment, a tooth that will be anesthetized will be probed with a periodontal probe to establish a baseline perception of this sensation without local anesthesia. Upon probing without local anesthesia, the patient will ask if they feel a "pinch," in order to

establish this baseline. When asked if they feel a pinch, patients will respond with a "yes" or "no" answer, which will be recorded.

Topical 20% benzocaine (Ultracare Oral Anesthetic Gel, Ultradent, South Jordan, Utah will be used on the intraoral tissue at site of injection for 5 minutes, and then the tissue will be injected. Patients will be informed when the tissue is pierced and again when the local anesthesia is being administered. Participants receiving an IANB will be injected with 0.85mL (50% volume of a 1.7mL carpule) of 2% lidocaine with 1:100,000 epinephrine approximately. Patients receiving a buccal infiltration in the maxilla will receive 0.425mL (25% volume of a 1.7mL carpule) of solution over 15 seconds. The operator will aspirate prior to administration of local anesthetic solution in all cases; a positive aspiration will require redirection of the needle or repositioning before injection. Patients will be asked to rate their pain related to administration of solution (the second prompt) once the injection is finished. Patients will be observed during injection and assessed by the operator using the Faces, Legs, Arms, Crying Consolability (FLACC) scale. Immediately after local anesthesia, patients will be asked to rate the pain of injection of solution using the Wong-Baker FACES Pain Scale. These scales were selected because they are approved for use by the AAPD for children over the age of 3 and have been used successfully in previous studies investigating pain perception in child subjects.[7,14]

After administration of local anesthetic solution, the onset time of soft tissue anesthesia will be measured by using a periodontal probe in the sulcus of the anesthetized tooth or a single tooth in the anesthetized quadrant. This probing will be initiated 15 seconds after initial injection of anesthetic solution and will be repeated at 15 second intervals until local anesthesia is achieved. After each probing attempt, patients will be asked if they felt a "pinch". Once the patient answers "no," the time of onset, in number of seconds to achieve anesthesia from injection to a "no" answer, will be recorded.

In the event of a missed block, the patient will be excluded from the study. The second attempt for local anesthesia will be made with the effort to achieve profound local anesthesia, and the technique and type of local anesthesia will not be limited to the techniques or anesthetic solutions described in this study. Local anesthesia techniques and solutions used in the event of a missed block will be within the scope of practice for a pediatric dental patient, however, this event will be considered a potential confounding variable in our research study.

A second protected Excel spreadsheet will be used to record patient's scores for the Wong-Baker FACES Pain Scale, the FLACC scale and the time of onset of local anesthesia. This spreadsheet will also include the patient's name, MRN number, the side of the mouth that was treated, the location of the injection, the injection technique, and the date of each visit. This spreadsheet will be available to the operator in order to record the clinical outcomes related to each encounter; it will not affect the double-blind nature

of this study, as the operator will not know which local anesthetic preparation was used during each encounter.

After the first day of treatment, a "wash out" period of at least 1 week will be required before the patient can return for treatment on the other side of the mouth, and the administration of the alternate type of local anesthetic solution. Wash out periods have been used in many similar studies to minimize bias.[1,7,11]

5.2 STUDY POPULATION

5.2.1 Approximate Number of Subjects: 55

5.2.2 INCLUSION CRITERIA

1. Patients requiring restorative or surgical dental treatment on two or more occasions on opposite sides of the mouth; either both maxillary or both mandibular quadrant/sextant involving comparable teeth/areas
2. Patients able to undergo dental treatment in the dental clinic without general anesthesia, sedation, or anxiolysis
3. Patients 4-17 years of age
4. Patients classified as ASA I or ASA II
5. Patients of parents who can read, write and give consent in English

5.2.3 EXCLUSION CRITERIA

1. Patients with allergy to local anesthetic
2. Patients who are pregnant or nursing
3. Patients with cardiac concerns or contraindications to epinephrine
4. Patients unable to undergo dental treatment in the clinic for behavior or medical reasons
5. Patients requiring anxiolysis, sedation, or general anesthesia
6. Patients unable to keep dental appointments or return for dental appointments
7. Patients who do not meet inclusion criteria
8. Patients who experience a missed block (IANB) during injection

5.3 RECRUITMENT

Study participants will be screened by a treating dentist from a GMC dental clinic at time of comprehensive oral exam or periodic oral exam. Patients may be added to the study by the treating dentist based on the inclusion criteria. Study participants will be recruited from the outpatient Foss clinic of Geisinger Medical Center in Danville, PA and from the outpatient Milton clinic of Geisinger Medical Center in Milton, PA.

Recruitment of study participants will be done by the treating pediatric dental resident or attending pediatric dentist at the time of exam. Patients will be recruited from the outpatient Foss clinic in Danville, PA and the outpatient Milton clinic in Milton, PA at Geisinger Medical Center.

5.4 STUDY DURATION

5.4.1 Approximate Duration of Subject Participation: 2 or more dental visits, with each visit lasting between 30-90 minutes

5.4.2 Approximate Duration of Study: 12 months

5.5 STATISTICS

5.5.1 Statistical Analysis Plan

Data will be analyzed using t-tests to examine treatment differences. Given patients will be treated with both methods, they will act as their own controls and paired t-tests will be utilized. If covariates are identified (e.g., patients' baseline pain perception), Repeated measure ANOVAs will be utilized with patients as within-subject variable and the patient experience as the outcome.

5.5.2 Statistical Power and Sample Size Considerations

Approximately 55 patients will be included in the study. Based on a medium effect size (Cohen's d = .50) observed in similar research (Kurien, Goswami, & Singh, 2018), a sample of 55 patients with data from two timepoints will provide 90% power and allow for a 20% (n = 11) rate of attrition. For analyses examining paired differences between lidocaine treatments, a sample of 44 will provide adequate power.

6. **DATA MANAGEMENT**

Only approved study staff will have access to data collected for this research. Electronic data will be stored on Geisinger's secure network. Any hard copy data will be secured in a locked office or cabinet. Only research team members can access the data files. Records of data generated in the course of the study shall be retained for at least 6 years after the study ends and could be used for future research studies submitted and approved by the IRB. To protect the double-blind design, the randomization excel sheet will only be available to the study physicians until the end of the study.

7. REFERENCES

1. Chopra R, Jindal G, Sachdev V, Sandhu M. Double-blind crossover study to compare pain experience during inferior alveolar nerve block administration using buffered two percent lidocaine in children. *Pediatr Dent*. 2016;38(1):25-29.

2. Malamed SF, Falkel, M. Buffered local anaesthetics: the importance of pH and CO_2. *SAAD Digest.* 2013;29:9-17.

6 (3). Balasco M, Drum M, Reader A, Nusstein J, Beck M. Buffered lidocaine for incision and drainage: A prospective, randomized double-blind study. *Journal of Endodontics*. 2013;39(11):1329-1334. https://www.ncbi.nlm.nih.gov/pubmed/24139250/.

3 (4). Afolabi O, Murphy A, Chung B, Lalonde D. The effect of buffering on pain and duration of local anesthetic in the face: A double-blind, randomized controlled trial. *Can J Plast Surg*. 2013;21(4):209-212. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3910524/.

4 (5). Cepeda MS, Tzortzopoulou A, Thackrey M, Hudcova J, Arora Gandhi P, Schumann R. Adjusting the pH of lidocaine for reducing pain on injection. *Cochrane Database Syst Rev*. 2010;(12):CD006581. doi(12):CD006581. doi: 10.1002/14651858.CD006581.pub2 [doi].

5 (6). McKay W, Morris R, Mushlin P. Sodium bicarbonate attenuates pain on skin infiltration with lidocaine, with or without epinephrine. *Anesthesia & Analgesia*. 1987;66(6):572-574. https://insights.ovid.com/pubmed?pmid=3034106.

7. Kurien RS, Goswami M, Singh S. Comparative evaluation of anesthetic efficacy of warm, buffered and conventional 2% lignocaine for the success of inferior alveolar nerve block (IANB) in mandibular primary molars: A randomized controlled clinical trial. *J Dent Res Dent Clin Dent Prospects*. 2018;12(2):102-109. doi: 10.15171/joddd.2018.016 [doi].

8. Aulestia-Viera PV, Braga MM, Borsatti MA. The effect of adjusting the pH of local anaesthetics in dentistry: A systematic review and meta-analysis. *Int Endod J*. 2018;51(8):862-876. doi: 10.1111/iej.12899 [doi].

9. Comerci A, Maller S, Townsend R, Teepe J, Vandewalle K. Effect of a new local anesthetic buffering device on pain reduction during nerve block injections. *General Dentistry*. 2015;63(6):74-78. https://www.ncbi.nlm.nih.gov/pubmed/26545279.

10. Guo J, Yin K, Roges R, Enciso R. Efficacy of sodium bicarbonate buffered versus non-buffered lidocaine with epinephrine in inferior alveolar nerve block: A meta-analysis. *J Dent Anesth Pain Med*. 2018;18(3):129-142. doi: 10.17245/jdapm.2018.18.3.129 [doi].

11. Hobeich P, Simon S, Schneiderman E, He J. A prospective, randomized, double-blind comparison of the injection pain and anesthetic onset of 2% lidocaine with 1:100,000 epinephrine buffered with 5% and 10% sodium bicarbonate in maxillary infiltrations. *Journal of Endodontics*. 2013;39(5):597-599. https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S0099239913001362?returnurl=null&referrer=null.

12. Council on Clinical Affairs. Use of local anesthesia for pediatric dental patients. *American Academy of Pediatric Dentistry*. 2015:199-205. https://www.aapd.org/globalassets/media/policies_guidelines/bp_localanesthesia.pdf.

13. Bartfield J, Homer P, Ford D, Sternklar P. Buffered lidocaine as a local anesthetic: An investigation of shelf life. *Annals of Emergency Medicine*. 1992;21(1):16-19. https://www.sciencedirect.com/science/article/pii/S0196064405822309.

14. Wells M, Townsend J. Managing pain and behavior guidance. In: Nowak A, Casamassimo P, eds. *The handbook of pediatric dentistry.* 5th ed. Chicago, IL: The American Academy of Pediatric Dentistry; 2018:243-244.

https://wongbakerfaces.org

Instructions

Explain to the child that each face is for a person who feels happy because he has no pain (hurt) or sad because he has some or a lot of pain.

Face 0 is very happy because he doesn't hurt at all.
Face 1 hurts just a little bit.
Face 2 hurts a little more.
Face 3 hurts even more.
Face 4 hurts a whole lot more.
Face 5 hurts as much as you can imagine, although you do not have to be crying to feel this bad.

Ask the child to choose the face that best describes how he/she is feeling.

Reference: Hockenberry MJ, Wilson D, Winkelstein ML: *Wong's Essentials of Pediatric Nursing*, ed, 7, St Louis, 2005 p.1259.
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https://www1.health.gov.au/internet/publications/publishing.nsf/Content/triageqrg~triageqrg-pain~triageqrg-wong

The following table provides the criteria for the FLACC Behavioural pain scale.

Behaviour	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jow
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting, back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams, sobs, frequent complaints
Consolability	Content, relaxed	Reassured by touching, hugging or being talked to, distractible	Difficult to console or comfort

https://www1.health.gov.au/internet/publications/publishing.nsf/Content/triageqrg~triageqrg-pain~triageqrg-FLACC

Instructions

Patients who are awake:

- Observe for at least 2-5 minutes.
- Observe legs and body uncovered.
- Reposition patient or observe activity; assess body for tenseness and tone.
- Initiate consoling interventions if needed.

Patients who are asleep:

- Observe for at least 5 minutes or longer.
- Observe body and legs uncovered.
- If possible reposition the patient.
- Touch the body and assess for tenseness and tone.

Each category is scored on the 0-2 scale which results in a total score of 0-10.

Assessment of Behavioural Score:

0 = Relaxed and comfortable
1-3 = Mild discomfort
4-6 = Moderate pain
7-10 = Severe discomfort/pain

Reference: Merkel S, Voepel-Lewis T, Shayevitz JR, et al:*The GLACC: A behavioural scale for scoring postoperative pain in young children.* Pediatric nursing 1997; 23:293-797.