Buffered vs. Unbuffered Local Anesthesia using Lidocaine, Carbocaine, and Articaine in Mandibular Molars Diagnosed with Symptomatic Irreversible Pulpitis: A Controlled, Randomized, Double-blind Study

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1.0 Background & Rationale

The success rate for pulpal anesthesia in mandibular molars diagnosed with symptomatic irreversible pulpitis has been shown to be between 45-70% (1). While the specific mechanism for inadequacy is unknown, it has been proposed that expression of variable sodium channels during inflammation, changes in tissue pH and, peripheral blood flow may contribute (2). OnPharma™ offers a solution to increase the efficacy of local anesthetics by allowing the clinician to add a buffering agent to the solution prior to injection.

The OnPharma™ system adds sodium bicarbonate to the anesthetic solution to raise its pH to a level closer to the anesthetics pKa. In doing so, more of the free base form is present to

diffuse through cell membranes. The free base is the active ingredient in local anesthetic solutions that are responsible for analgesia. In addition, CO_2 and water are produced through the addition of sodium bicarbonate to the anesthetic solution. CO_2 converts the local anesthetic back into its active acid form once inside the cell membrane, trapping the local anesthetic inside (2,3).

Recent studies have suggested that buffered anesthetics do not improve Inferior alveolar nerve block (IANB) success rate in symptomatic teeth (4,5,6). This contrasts with another study showing increased success with sodium bicarbonate use with IANB blocks (7). While the field is not currently in agreement, Indiana University School of Dentistry (IUSD) has had a positive experience when using the OnPharma™ system to anesthetize symptomatic teeth.

Dr. Peter Alena, a previous resident of Indiana University Endodontics, investigated the efficacy of buffered and plain 2% lidocaine with 1:100k epinephrine. His data suggest that there is not a significant difference between the two when treating mandibular molars diagnosed with symptomatic irreversible pulpitis. This current iteration aims to investigate the synergistic ability of a combination of buffered anesthetics to improve patient analgesia. Previous studies have reported that a local infiltration of articaine with a IANB of lidocaine improve local anesthetic success rates in patients diagnosed with symptomatic irreversible pulpits (8,9). Carbocaine performs as well as lidocaine when used solely for an IANB but current data suggests it does not improve anesthesia when combined with other anesthetics (10,11).

This study will include the administration of 1.8mL of 2% Lidocaine with 1:100k epinephrine and 1.8mL of 3% Carbocaine through an IANB. 1.8 mL of 4% Articaine with 1:100k epinephrine will also be used to locally infiltrate. The anesthetic combination will either be unbuffered or buffered using the Onpharma™ protocol and will administered in a double blinded fashion.

Investigational Products:

2% Lidocaine with 1:100k epinephrine (Septodont Inc, New Castle, DE). A standard carpule of Lidocaine contains 1.8mL of solution. 1 carpule will be administered via a IANB of 2% Lidocaine w/ 1:100k epi as the standard anesthetic dosage.

3% Carbocaine without epinephrine (Septodont INC, New Castle, DE). Each carpule contains 1.8mL of solution. This will be administered via an IANB.

4% Articaine with 1:100k epinephrine (Septo Inc, New Castle, DE). A standard carpule contains 1.8 mL of solution. This will be used as a local infiltration.

The Onset 8.4% Sodium Bicarbonate buffering system is marketed by OnPharma (Carson City, NV). Aside from the sodium bicarbonate buffer itself, OnPharma offers the Onset Mixing Pen along with an Onset Cartridge Connector which formulates the buffered local anesthetic solution. The OnPharma mixing protocol will be used to mix each anesthetic prior to administration.

Vitality Scanner 2006 (Vitality Scanner 2006; SybronEndo, Orange, CA) is marketed and sold by Kerr Dental, and will be used to confirm pulpal anesthesia via Electric Pulp Testing (EPT).

Endo-Ice (1,1,1,2 tetrafluoroethane; Hygenic Corp, Akron, OH) will be used to diagnose each tooth prior to treatment and once again to confirm pulpal anesthesia.

2.0 Objective(s)

2.1 Primary Objective

2.1.1 The primary objective of this study is to determine whether pulpal anesthesia will be obtained faster and more profoundly compared to using unbuffered local anesthetic in teeth diagnosed with symptomatic irreversible pulpitis.

2.2 Secondary Objective

2.2.1 To measure a potential difference in the buffered anesthetic's effect on time and profoundness in achieving pulpal anesthesia between mandibular first, second, or third molars diagnosed with symptomatic irreversible pulpitis

3.0 Outcome Measures/Endpoints

3.1 Primary Outcome Measures

3.1.1 The primary outcome is to gauge the time it takes for the buffered anesthetic to provide profound anesthesia, displayed by an EPT reading of 80. The time will be censored at 15 minutes if profound anesthesia is not achieved within 15 minutes.

3.2 Secondary Outcome Measures

3.2.1 Failure to achieve profound anesthesia.

3.2.2 Pain scores measured using a Visual Analog Scale (VAS).

4.0 Eligibility Criteria

4.1 Inclusion Criteria

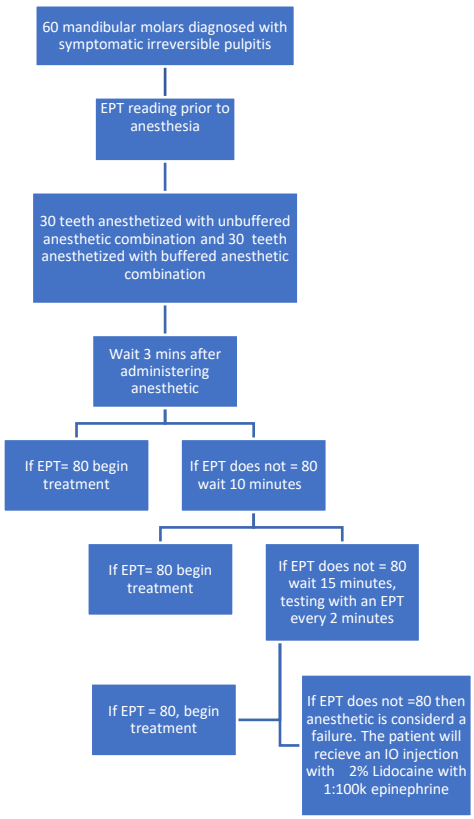
- Between the ages of 18 and 80 years old
- Ability and willingness to independently consent to treatment and study participation
- Uncomplicated medical history (ASA I and II)
- No allergies to local anesthetics/sulfites (confirmed or self-reported)
- Not taking any medications that may affect the proper assessment of the anesthetic (OTC analgesics within 6 hours of treatment)
- Not requiring nitrous oxide during treatment
- No active pathology in the injection area or any other pre-existing conditions that may compromise an accurate collection of data per PI's review of current and previous 30 days of medical history
- Must be experiencing signs of irreversible pulpitis (mild, moderate, or severe) in a vital mandibular posterior tooth at the time of conducting the study

4.2 Exclusion Criteria

- Patients lacking a response to cold in the affected tooth
- A radiographic periradicular pathosis more advanced than a widened periodontal ligament (radiograph taken as standard of care)
- No vital coronal pulp tissue noted upon access
- Patient reported pain (other than pressure) upon endodontic access/pulpotomy

5.0 Study Design

1. This study will be a single-center, controlled, randomized, double-blind (provider and subject), 2 treatment, 1 period, parallel study to determine the efficacy of buffered 2% Lidocaine w/ 1:100k epi, 3% Carbocaine and 4% Articaine with 1:100k epi, on the time of efficacy and ultimate profoundness of pulpal anesthesia in mandibular molars diagnosed with symptomatic irreversible pulpitis compared to traditional unbuffered 2% Lidocaine w/ 1:100k epi, 3 % Carbocaine and 4% Articaine with 1:100k epi. An electronic pulp tester (EPT) assesses the tooth's ability to feel sensation, with a reading of 80 showing the tooth is adequately anesthetized.



6.0 Enrollment/Randomization

Potential research subjects will be pooled from patients scheduled to receive an endodontic evaluation and/or clinical treatment in the Graduate Endodontic clinic at Indiana University School of Dentistry. There are currently 7 endodontic residents enrolled in the graduate program who will be eligible to screen patients presenting to the graduate clinic for elective, urgent, or emergency endodontic treatment. If an endodontic resident other than the student researcher (Dr. Steven Magura) diagnoses their respective patient's mandibular molar with symptomatic irreversible pulpitis, and all other inclusion/exclusion criteria are respected, then the student researcher will be eligible to further evaluate the patient and potentially include them in the study.

The study biostatistician will provide a two-product randomization scheme which will randomize each subject on the order of their entry into the study. Subjects will be randomized equally to the two treatments using a block randomization, participants receiving multiple root canal procedures will be treated as a single subject. 30 subjects per treatment will be enrolled. The randomization scheme will be provided to clinic assistants Bridgette Smith and James Driver. They will prepare each anesthetic solution behind closed doors and provide each carpule to the

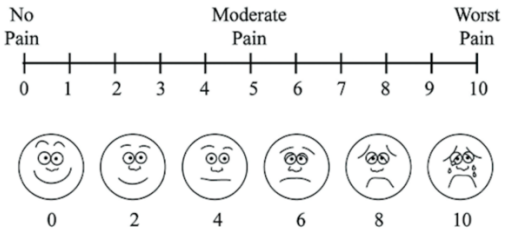
researcher at every appointment. The stopper of every carpule, regardless of experimental group, will be punctured to remove bias. The study subject will be blinded to treatment assignment.

7.0 Study Procedures

Single Visit: Screening and Study procedure

1. Review medical history (about 3-5 minutes)
    a. If previously on file, the patient will need to verbally confirm all forms are accurate
    b. If the patient is new to IUSD, then the proper medical history intake form will be completed and confirmed by the patient, as per standard of care
    c. Participants will be explained what an analgesic is, and will confirm they have not taken any within 6 hours prior to study participation
2. Customary sensibility testing, specifically cold and Electric Pulp Testing (EPT), will be completed to ensure a diagnosis of symptomatic irreversible pulpitis in a mandibular molar specifically on the same day that the warranted endodontic treatment is to be rendered (about 5-10 minutes) as per standard of care.
    a. Prospective study participants will be given brief instructions on cold and EPT usage/expectations
    b. A vital, asymptomatic, contralateral posterior tooth (ideally molar) will undergo cold and EPT testing prior to administering anesthesia to serve as an internal control
    c. The pulpal diagnosis will be primarily confirmed using Endo-Ice
3. Review inclusion/exclusion criteria to ensure that the subject qualifies to continue with the study (about 3 minutes)
4. Perform consenting procedures for both the Non-surgical Root Canal Therapy (NSRCT) and the research study (about 5-10 minutes)
    a. Study participants will receive a concise explanation regarding the nature of the 2 possible anesthetic formations and the EPT testing intervals that are expected to follow. Participants will be explicitly notified that the anesthetic formulation will not affect the overall prognosis of the endodontic treatment needing to be rendered. Once profound anesthesia is confirmed, the NSRCT will proceed as usual and customary.
5. Randomize the subject to the type of anesthetic formulation (about 5 minutes)
6. Apply topical benzocaine jelly after thoroughly drying the tissues surrounding the Inferior Alveolar Nerve Block (IANB) injection site and the buccal vestibule of the tooth to be treated (about 1 minute), as per standard of care
7. Administer **1 carpule** (1.8mL) of the previously determined formulation of 2% Lidocaine w/ 1:100k epi and 1 carpule of 3% Carbocaine plane via IANB, followed by 0.5 carpules (0.9mL) of 4% Septocaine with 1:100k epi via buccal infiltration and 0.5 carpules of 4% Septocaine with 1:100k epi via lingual infiltration (about 3 minutes)
8. Using a stopwatch, the student researcher will wait 3 minutes after administering anesthesia and then obtain the 2nd EPT reading on the tooth being treated, as well as assessing soft tissue anesthesia of the respective side of the mandible

   a. EPT=80 (maximum stimulation) without pulpal or soft tissue sensations indicates profound pulpal anesthesia and the endodontic access may be initiated
   b. EPT≠80 with pulpal and/or soft tissue sensations indicates a need to wait additional time
9. Retest the tooth being treated using EPT at 2-minute intervals until EPT=80 or when 15 minutes have passed
   a. Participants who did not demonstrate total soft tissue and/or pulpal anesthesia within 15 minutes will be categorized as a failure (lack of anesthetic profoundness), with time to anesthesia censored at 15 minutes. No additional study outcomes will be collected from the patients, who will be withdrawn from the study, and further managed according to the best clinical practice (additional block/supplementary injections) so that the endodontic treatment may continue appropriately
10. Patients who indicate any pain (excluding pressure) elicited from the tooth undergoing treatment upon endodontic access or a complete pulpotomy (after initially confirming pulpal anesthesia with the EPT) will also be categorized as a failure (lack of anesthetic profoundness), withdrawn from the study, and appropriately managed as previously described.
   a. Visual Analog Scales (VAS) shown below will be used to report the patient's perceived discomfort at the end of treatment.



11. The student researcher will chart the data for each uniquely identified study participant regarding the initial EPT readings (treated tooth and control), the amount of time taken to reach both soft tissue and pulpal anesthesia, and the conditions that lead to a "failed" profoundness of anesthesia
   a. A trained research assistant will separately record each patient's unique identifying code with the anesthetic formulation (buffered vs. unbuffered) that was prepared and administered

8.0 **Reportable Events**

There are no additionally anticipated risks or adverse reactions by using 2% Lidocaine w/ 1:100k epi, 3% carbocaine without epi and 4% septocaine with 1:100k epi plane or with a sodium bicarbonate buffer as compared to a traditional, non-buffered formulation of the same local anesthetic. However, potential adverse events involving the traditional method of administering local anesthetic for mandibular teeth may involve hematomas, a temporary increase in heart rate, needle tract infections, temporary nerve damage (including Bell's Palsy), and an inadequate

anesthetic delivery/lack of efficacy. Serious adverse events relating to local anesthetics may include overdose (drowsiness/loss of consciousness), permanent nerve damage, allergic reactions/anaphylaxis, or exacerbation of an underlying cardiovascular condition due to the presence of exogenous epinephrine.

9.0 Data Safety Monitoring

The PI and student PI will be responsible for the data and safety monitoring. They will monitor data quality, subject recruitment, accrual, retention, outcome and adverse event data, assessment of scientific reports or therapeutic development, results of related studies that may impact subject safety, and procedures designed to protect the privacy of subjects. Safety data will be monitored on a regular basis and immediately upon discover of any SAE or major study event or protocol deviation.

10.0 Study Withdrawal/Discontinuation

A subject may withdraw from the study for any reason and at any time during the study without penalty. There dental treatment will not be affected by their decision to stop study related procedures. The Principal Investigator may also withdraw the subject if he feels study participation is not safe for the study to continue, or if the subject is not cooperating with study procedures.

11.0 Statistical Considerations

The two groups will be compared for differences in the percentage of subjects who fail to achieve profound pulpal anesthesia using chi-square tests. The time needed to achieve profound pulpal anesthesia for the two groups will be compared using Kaplan-Meier survival curves and log-rank tests, with patients who fail to achieve profound pulpal anesthesia censored at 15 minutes. A logistic regression model for presence of profound pulpal anesthesia will be used to determine whether molar type (first, second, third molar) affects the group comparisons; the model will include both factors and their interaction. A similar Cox proportional hazards survival model will be used for the analysis of time needed to achieve profound pulpal anesthesia. VAS scores will be compared between treatments using a Wilcoxon Rank Sum test. A two-sided 5% significance level will be used for all tests.

With a sample size of 28 subjects per group, the study will have 80% power to detect a hazard ratio of 2.25 between the two groups for time to profound pulpal anesthesia, using calculations with a two-sided 5% significance level and based on a log-rank test with median time to anesthesia 10 minutes in the control group. Sample size calculations were performed using PASS 2019 (NCSS, LLC. Kaysville, UT). To account for up to 2 subjects per group with unusable data, the study will enroll 30 subjects per group.

12.0 Statistical Data Management

- Primary data will be collected via *direct data capture from measurement instrument (Electronic Pulp Tester/EPT), time to profound anesthesia, molar type and VAS score* and stored electronically in *SPSS files on Department Server*. The storage location will be backed up ***automatically*** every ***day***.

- All other data will be stored in either a locked cabinet in the department of Endodontics that only the study team will have access to or on an encrypted, password protected computer that only the study team can access.
- Data summary sheets will be stored for use by the statistician using an IRB approved sharable method such as Microsoft One Drive.

13.0 Privacy/Confidentiality Issues

- Privacy will be maintained by consenting the subjects and performing the study procedures in a private area like an endodontic operatory away from public places like the waiting room.
- All other data will be stored in either a locked cabinet in the department of Endodontics that only the study team will have access to or on an encrypted, password protected computer that only the study team can access.
- Data summary sheets will be stored for using an IRB approved method such as Microsoft One Drive.

14.0 Follow-up and Record Retention

The study will be either a one or two visit study, depending on whether the subject and research staff prefer to separate the screening visit from the study/procedure visit.

Study records will be stored for at least seven years, as per Indiana law.

15.0 References

1- Mikesell, P., Nusstein, J., Reader, A., Beck, M., & Weaver, J. (2005). A comparison of articaine and lidocaine for inferior alveolar nerve blocks. *Journal of endodontics*, *31*(4), 265–270.
2- Hargreaves, K.M. and Keiser, K. (2002), Local anesthetic failure in endodontics:. Endodontic Topics, 1: 26-39.
3- CONDOURIS, G. A., & SHAKALIS, A. (1964). POTENTIATION OF THE NERVE-DEPRESSANT EFFECT OF LOCAL ANAESTHETICS BY CARBON DIOXIDE. Nature, 204, 57–58.
4- Saatchi, M., Khademi, A., Baghaei, B., & Noormohammadi, H. (2015). Effect of sodium bicarbonate-buffered lidocaine on the success of inferior alveolar nerve block for teeth with symptomatic irreversible pulpitis: a prospective, randomized double-blind study. *Journal of endodontics*, *41*(1), 33–35.
5- Schellenberg, J., Drum, M., Reader, A., Nusstein, J., Fowler, S., & Beck, M. (2015). Effect of Buffered 4% Lidocaine on the Success of the Inferior Alveolar Nerve Block in Patients with Symptomatic Irreversible Pulpitis: A Prospective, Randomized, Double-blind Study. *Journal of endodontics*, *41*(6), 791–796.

6- Parirokh M. (2016). Buffered Lidocaine With Sodium Bicarbonate did not Increase Inferior Alveolar Nerve Block Success Rate in Patients Having Symptomatic Irreversible Pulpitis. *The journal of evidence-based dental practice*, *16*(1), 59–61.
7- Saatchi M, Farhad AR, Shenasa N, Haghighi SK. Effect of Sodium Bicarbonate Buccal Infiltration on the Success of Inferior Alveolar Nerve Block in Mandibular First Molars with Symptomatic Irreversible Pulpitis: A Prospective, Randomized Double-blind Study. J. Endod. 2016;42(10):1458-1461.
8- Su, N., Li, C., Wang, H., Shen, J., Liu, W., & Kou, L. (2016). Efficacy and safety of articaine versus lidocaine for irreversible pulpitis treatment: A systematic review and meta-analysis of randomised controlled trials. *Australian endodontic journal : the journal of the Australian Society of Endodontology Inc*, *42*(1), 4–15
9- Kung, J., McDonagh, M., & Sedgley, C. M. (2015). Does Articaine Provide an Advantage over Lidocaine in Patients with Symptomatic Irreversible Pulpitis? A Systematic Review and Meta-analysis. *Journal of endodontics*, *41*(11), 1784–1794
10- Lammers, E., Nusstein, J., Reader, A., Drum, M., Beck, M., & Fowler, S. (2014). Does the combination of 3% mepivacaine plain plus 2% lidocaine with epinephrine improve anesthesia and reduce the pain of anesthetic injection for the inferior alveolar nerve block? A prospective, randomized, double-blind study. *Journal of endodontics*, *40*(9), 1287–1292.
11- Vieira, W. A., Paranhos, L. R., Cericato, G. O., Franco, A., & Ribeiro, M. (2018). Is mepivacaine as effective as lidocaine during inferior alveolar nerve blocks in patients with symptomatic irreversible pulpitis? A systematic review and meta-analysis. *International endodontic journal*, *51*(10), 1104–1117