BUFFERED VS. UNBUFFERED LOCAL ANESTHESIA IN MANDIBULAR MOLARS DIAGNOSED WITH SYMPTOMATIC IRREVERSIBLE PULPITIS: A CONTROLLED, RANDOMIZED, DOUBLE-BLIND STUDY

NCT05227300

06/30/2022

PRIMARY MATERIALS

2% lidocaine with 1:100,000 epinephrine (Septodont Inc, New Castle, DE) was the only local anesthetic used in our study. A standard dental cartridge of 2% lidocaine w/ 1:100,000 epinephrine contains 1.8mL of solution, and the adult maximum recommended dose equates to 500mg (3.3mg/lb or 13.8 cartridges). For reasons of this study, we used a maximum of 3 total cartridges (5.4mL or 108mg) of 2% lidocaine w/ 1:100,000 epinephrine as the standard anesthetic dosage. The Onset 8.4% Sodium Bicarbonate buffering system is marketed by FDA-approved Onpharma (Carson City, NV) that recommends its concurrent use with 2% lidocaine w/ 1:100k epi. Aside from the sodium bicarbonate buffer itself, Onpharma offers the Onset Mixing Pen along with an Onset Cartridge Connector to properly formulate the buffered local anesthetic solution. The Onpharma Onset mixing protocol was incorporated to properly prepare the buffered 2% lidocaine w/ 1:100,000 epinephrine cartridges. Vitality Scanner 2006 (Vitality Scanner 2006; SybronEndo, Orange, CA) is marketed and sold by Kerr Dental, and was used to confirm pulpal anesthesia via Electric Pulp Testing (EPT). Endo-Ice (1,1,1,2 tetrafluoroethane; Hygenic Corp, Akron, OH) was used to initially confirm vitality and a diagnosis of symptomatic irreversible pulpitis.

VERIFICATION OF BUFFERING CAPACITY

To verify the advertised buffering capacity of an Onset Sodium Bicarbonate Cartridge, a pilot study using 2% lidocaine w/ 1:100k epi with and without an added buffer was completed. Both pH strips (Lab Rat Supplies, https://www.labrat-supplies.com) and a calibrated digital pH meter (Dr. meter, https://drmeter.com) were used to measure the pH of 2% lidocaine with 1:100k

epinephrine initially. Following Onpharma's Onset directions for use, 0.18mL of sodium bicarbonate buffer was added to a 1.8mL cartridge of 2% lidocaine with 1:100k epinephrine. This quantity of added buffer is commonly suggested by the manufacturer, and a historically recommended 10% ratio of sodium bicarbonate buffer to local anesthetic. The respective pH of each anesthetic group was recorded using each company's directions for use. Using the pH strips, we were able to observe that the 8.4% sodium bicarbonate buffer produced a pH between 8 and 9, while the calibrated digital pH meter indicated a reading of 8.08. Using the pH strips, standard 2% lidocaine w/ 1:100k epi had a pH between 4 and 5, and 2% lidocaine w/ 1:100k epi plus 0.18mL of added buffer had a pH between 7 and 8. The digital pH meter produced a reading of 4.35 for standard 2% lidocaine w/ 1:100k epi [94], and a pH of 7.34 for 2% lidocaine w/ 1:100k epi plus 0.18mL of added buffer (no precipitate ever formed). Ultimately, we were able to independently verify that the buffering capacity of Onpharma's Onset sodium bicarbonate buffer system is as advertised using 2 different method.

INCLUSION CRITERIA

To participate, subjects must be between the ages of 18 and 80 years old, have the ability and willingness to independently consent to treatment and study participation. They must have an uncomplicated medical history (ASA I and II), not be pregnant, and have no allergies to local anesthetics/sulfites (confirmed or self-reported). Due to concerns about plasma half-life concentrations, they must not be taking any medications that may affect the proper assessment of the anesthetic (no acetaminophen or short-acting NSAIDs such as ibuprofen within the previous 6 hours [96] [97]; no long-acting NSAIDs such as naproxen within the previous 16 hours). They must not require nitrous oxide during treatment, and the injection area should appear healthy

with no other pre-existing conditions or infections that may compromise an accurate collection of data. Since a localized periodontal examination is a routine portion of the endodontic examination, the potential presence of periodontal disease will not interfere in making a proper endodontic diagnosis. Subjects also must be experiencing signs of irreversible pulpitis (an exaggerated response to cold that lingers longer than 10 seconds) in a mandibular molar at the time of conducting the study.

EXCLUSION CRITERIA

No subjects will have a negative response to cold in the proposed treatment tooth. Also, no subject may have a radiographic periradicular pathosis more advanced than a widened periodontal ligament or have an intraoral swelling.

RECRUITMENT AND ENROLLMENT OF EXPERIMENTAL SUBJECTS

Potential research subjects were pooled from patients scheduled to receive an endodontic evaluation and/or a non-surgical root canal therapy (NSRCT) in the Graduate Endodontic clinic at Indiana University School of Dentistry. All 7 endodontic residents were eligible to screen, diagnose, explain the study goals, and consent patients presenting to the graduate clinic with symptomatic irreversible pulpitis of a mandibular molar. It is important to note that a general script was provided to each endodontic resident outlining key points to discuss with prospective study participants to establish some uniformity in the consenting process and calibration of residents. Each prospective study participant was explicitly made aware that using 2% lidocaine

w/ 1:100k epi is a standard anesthetic option in endodontic treatment regardless of their participation in the research study and the addition of a sodium bicarbonate buffer would not lead to a decrease in its efficacy. Participants were further informed that the addition of the buffer would either have no effect or actually improve the efficacy of a standard, customary local anesthetic.

If an endodontic resident other than the student researcher made a relevant diagnosis, all inclusion/exclusion criteria were respected, and the patient consented to both an NSRCT and participating in the study, then the student researcher was notified. Once the student researcher confirmed all pre-requisites and answered any questions, a trained research assistant prepared a maximum of 3 cartridges of the respective local anesthetic formulation as determined by the randomization scheme immediately prior to the planned administration. A professional statistician helped provide a two-product randomization scheme that randomized each of the potential 60 subjects on the order of their entry into the study. Only the blinded student researcher was eligible to administer the local anesthetic. However, all endodontic residents were calibrated and eligible to acquire and record the data (soft tissue anesthesia as later described, EPT readings, and any pertinent patient discomfort experienced upon access/pulpotomy as reflected on the Wong-Baker FACES Visual Analog Scale) obtained after the student researcher finished giving all 3 cartridges of anesthetic.

DIAGNOSIS

The patient's current chief complaint was recorded; "It hurts when I drink cold...", etc. The tooth/teeth that the patient complained about and the control teeth were subject to standard pulp sensibility testing to ensure a proper diagnosis of symptomatic irreversible pulpitis. If

applicable, this diagnosis was specifically confirmed on the same day that the warranted endodontic treatment was rendered. Prospective study participants were given brief instructions on cold and EPT usage/expectations. Regarding the cold testing, a cotton pellet was held with cotton forceps and thoroughly sprayed with Endo-Ice (Coltene) at -26.2 Celsius until the cotton pellet was soaked. The cotton pellet was then applied to the mid-buccal, natural surface of the tooth, and the patient's response was monitored. The soaked cotton pellet was removed once the patient felt a painful sensation on the tested tooth or if no sensation was felt after 10 seconds of an application. If pain was felt, the amount of time until the sensation subsided was measured. A continued pain for 10 seconds or longer was considered "lingering" pain. Exaggerated or lingering pain, as compared to adjacent or control teeth, was considered acute pain and further quantified on the Wong-Baker FACES Visual Analog Scale (VAS), ranging from 0-10. Patients were immediately presented with this VAS, and their baseline response was recorded. After any previously induced pain had subsided, an electrical pulp testing exam was done using an Electric Pulp Tester (EPT) Sybron Analytic to establish a baseline reading. A 2-3 mm dab of toothpaste was placed on the dried buccal tooth structure. The tip of the EPT was placed on the toothpaste and the EPT was activated once the patient held the end of the wand, thereby completing the circuit. The test was stopped when the patient felt pain or a "tingling" sensation after letting go of the wand or if the measurements reached a maximum value of 80. The EPT number was recorded by the resident on a designated data sheet. Ultimately, a diagnosis of symptomatic irreversible pulpitis was made if the patient had acute, lingering pain cold as compared to the control tooth.

BUFFERED ANESTHETIC PREPARATION

Although other local anesthetics may still be employed, Onpharma markets its Onset sodium bicarbonate buffer to ideally be used in combination with a standard cartridge of 2% lidocaine w/ 1:100k epi. Each of the Onset Sodium Bicarbonate Inj., 8.4%, USP Neutralizing Additive Solution cartridges contain 1.7 mL volume and are packaged in a four-cartridge package. A single cartridge can buffer 10 injections, 40 injections per 4-pack. Onset Sodium Bicarbonate Cartridges have a 3-year shelf life, but once a cartridge is placed in the Mixing Pen, the cartridge should ideally be used within 7 days. Before using, the Onset Mixing Pen was disassembled into its 2 parts, and a 3mL size cartridge was inserted into the Cartridge Chamber. The Mixing Pen should be re-assembled, and a 2nd fluid container (the 1.8mL anesthetic cartridge) was attached to the end of the Pen. To assist the attachment of the anesthetic cartridge to the end of the Pen, an Onset Cartridge Connector was used. Each number on the Mixing Pen corresponds with approximately .01 mL's of fluid, so the Pen's volume dispensing dial was adjusted to setting "18." Ultimately 0.18mL of 8.4% sodium bicarbonate was transferred from the 3mL size cartridge into the lidocaine cartridge after the equivalent amount of anesthetic was displaced into the holding reservoir, resulting in a 10% buffered local anesthetic. This process was repeated by a trained research assistant to produce 3 equivalently buffered cartridges of 2% lidocaine with 1:100,000 epinephrine immediately before it was given to the blinded student researcher.

QUALITY ASSURANCE

The same calibrated electronic pH meter (Dr.meter PH838) that was employed to test the pH in the pilot study was used to test a Sodium Bicarbonate Cartridge from the experimental pack and a cartridge of the standard 2% lidocaine w/ 1:100k epi from an experimental anesthetic package prior to the first administration of the study. Using the pH strips, standard 2% lidocaine

w/ 1:100k epi had a pH between 4 and 5, and 2% lidocaine w/ 1:100k epi plus 0.18mL of added buffer had a pH between 7 and 8. The digital pH meter produced a reading of 4.99 for standard 2% lidocaine w/ 1:100k epi, and a pH of 7.14 for 2% lidocaine w/ 1:100k epi plus 0.18mL of added buffer (no precipitate ever formed). These quality assurance measures are reflected in Figures 11-14. Ultimately, we were again able to independently verify that the buffering capacity of Onpharma's Onset sodium bicarbonate buffer system is as advertised using 2 different methods [94, 95] prior to using those packages of local anesthetic and Onset buffer on our first research participant.

ANESTHETIC ADMINISTRATION

After applying topical benzocaine to the respective administration sites for 1 minute, the student researcher administered 2 cartridges (3.6mL) of the previously determined formulation of 2% lidocaine w/ 1:100,000 epinephrine via IANB at the rate of 1.8mL per minute. Any patients who did not have signs of soft tissue anesthesia (successful IANB) within the following 10 minutes would receive a supplementary 1/2 cartridge (0.9mL) of the same anesthetic formulation via buccal infiltration and a 1/2 cartridge (0.9mL) via lingual infiltration at the affected tooth's apex with a rate of 1.8mL per minute. Along with being a commonplace clinical practice, previous studies have demonstrated an added effectiveness of supplementary buccal and lingual infiltrations in obtaining pulpal anesthesia.

ANESTHETIC TESTING AND DOCUMENTATION

Using an online stopwatch, the student researcher started the timer after administering both IANBs and then continually assessed soft tissue anesthesia of the respective side of the

mandible. Soft tissue anesthesia was considered profound when the patient subjectively attested that their lip, chin, and tongue on the respective treatment side felt “full” or “numb,” and a light stimulation with the tip of an explorer did not elicit any sensation other than pressure as compared to a “sharp” feeling the contralateral side. In the event that the patient denied any signs of soft tissue anesthesia (absolutely no change in feeling) 10 minutes after the 2 cartridges of anesthetic were given via inferior alveolar nerve block (IANB), then the blocks were to be considered “missed,” and the patient would need to be re-blocked as clinically appropriate. This situation would be grounds for withdrawing the patient from the study (with documentation) since a lack of anesthesia following the protocol cannot be attributed to the anesthetic formulation itself but rather operator technique/variable patient anatomy.

Once the patient attested to having soft tissue anesthesia, the amount of time surpassed since being blocked was documented on the designated datasheet, and the supplemental buccal and lingual infiltrations were then administered as previously described. The student researcher or other residents waited 2 minutes after all 3 cartridges of local anesthesia had been administered and then obtained an updated EPT reading on the tooth being treated. An EPT=80 (maximum stimulation) indicated profound pulpal anesthesia, and the endodontic access was initiated. An EPT≠80 indicated a need to wait an additional time. We retested the tooth being treated using EPT at 2-minute intervals until EPT=80 or when a maximum of 20 minutes had passed since administering 2 IANBs. According to Whitcomb et al., waiting 10-15 minutes after administering the IANB should be adequate time to allow the onset of pulpal anesthesia in molars. Once EPT=80, the reading was reconfirmed in order to get a consecutive EPT=80 a minute after the initial reading. Participants who did not demonstrate *total* soft tissue and/or pulpal anesthesia within 20 minutes would be categorized as a failure and further managed

according to the best clinical practice (additional block/supplementary injections) so that the endodontic treatment could continue appropriately. After confirming soft tissue anesthesia and 2 consecutive EPT=80, the endodontic treatment could begin.

Upon the completion of the pulpotomy, the patient was shown the same Visual Analog Scale to re-assess their level of comfort. However, any discomfort recognized during the pulpal access or pulpotomy paused the procedure, and the VAS was shown immediately. Patients who indicated moderate or severe pain (VAS scores of 4 or higher) elicited from the tooth undergoing treatment upon pulpal access or a complete pulpotomy were categorized as an anesthesia failure (lack of profoundness) and appropriately managed as previously described. Patients who indicated no pain or mild pain (VAS scores of 3 or lower) were categorized as an anesthesia success (obtained profoundness), and the endodontic treatment continued. When co-residents rendered the clinical endodontic treatment, they recorded and reported these failures to the student researcher after appropriately treating their patient. The student researcher charted 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, VAS scores after both cold testing (baseline) and pulpotomy, and any other conditions that may have led to a "failed" profoundness of anesthesia.

STUDY PROCEDURES

1. Reviewed medical history as a standard of care for endodontic treatment (about 3-5 minutes)
2. Standard of care dental exam with sensibility testing that established baseline EPT reading and VAS score (about 5-10 minutes)

3. Reviewed inclusion/exclusion criteria using data collected in steps 1 and 2 for a standard of care to ensure that the subject qualified to continue with the study (about 3 minutes)
4. Performed consenting procedures for both the Non-surgical Root Canal Therapy (NSRCT) and the research study (about 5-10 minutes)
5. A trained research assistant prepared the cartridges of the type of anesthetic formulation (buffered vs. unbuffered) determined by the randomization scheme in a separate room immediately prior to it being administered. The assistant made a record using a unique identifying code for the type given to each patient. The Onpharma Onset protocol was used when indicated. The assistant "prepared" the unbuffered cartridges in the same amount of time as required for the buffered cartridges, as well as "puncturing" the unbuffered cartridges with the Onset pen so that each cartridge had a uniform appearance (about 3 minutes)
6. Applied 20% topical benzocaine jelly (Ultradent Products Inc, South Jordan, UT) after thoroughly drying the tissues surrounding the inferior alveolar nerve block (IANB) injection site, buccal vestibule, and lingual vestibule of the treatment tooth (about 1 minute)
7. The student researcher administered the 2 IANBs (about 2 minutes) and then started the timer immediately
8. The patient was regularly re-assessed for soft tissue anesthesia (as previously described)
    a. If within 10 minutes the patient had confirmed soft tissue anesthesia, then the IANBs were considered successful, and 1 cartridge of the respective

anesthetic formulation was supplementarily administered via apical buccal and lingual infiltrations (documented exact time elapsed)

   b. If at 10 minutes the patient did not have any indications of soft tissue anesthesia, then IANBs would be considered missed, and the patient would be withdrawn from the study. Administer additional local anesthetic as clinically appropriate

9. Tested the treatment tooth using EPT in 2-minute intervals (starting at 2 minutes post-supplementary infiltrations)
   a. If within 20 minutes post-IANBs pulpal anesthesia was confirmed with 2 consecutive EPT=80, initiated NSRCT (document exact time elapsed)
   b. If at 20 minutes post-IANBs pulpal anesthesia was not confirmed with 2 consecutive EPT=80, anesthesia was considered a failure, and additional local anesthetic was administered as clinically appropriate
10. All pertinent data, including the patient's VAS comfort assessment after pulp chamber access/pulpotomy, were recorded and analyzed with the help a professional statistician for statistical significance.

STATISTICAL ANALYSIS

The buffered anesthetic and unbuffered anesthetic groups were compared for differences in the percentage of subjects who achieved profound pulpal anesthesia using chi-square tests. The time needed to achieve profound pulpal anesthesia using buffered anesthetics and unbuffered anesthetics was compared using Kaplan-Meier survival curves and log-rank tests. A 5% significance level was used for all tests. Comparisons of the VAS results were made using a

Wilcoxon Rank Sum test. Up to 60 subjects were randomized to ensure that 40 evaluable subjects could complete the study. With a sample size of 20 subjects per group, the study had an 80% power to detect a difference between 90% and 50% of subjects who achieved profound pulpal anesthesia. Calculations were based on a chi-square test with a two-sided 5% significance level. Sample size calculations were performed using PASS 2019 (NCSS, LLC. Kaysville, UT). All calculations were derived with professional assistance.