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Effect of a new local anesthetic buffering device on pain reduction during nerve block injections

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The purpose of this double-blind, split-mouth, randomized human clinical study was to evaluate the effectiveness of a new sodium bicarbonate local anesthetic buffering device (Onset) in reducing pain associated with dental injections. Twenty patients were given bilateral inferior alveolar (IA) and long buccal (LB) nerve block injections and asked to quantify the pain experienced during injection on a visual analog scale (0, no pain; 10, worst possible pain). One side of the mouth received standard-of-care injections of 2% lidocaine with 1:100,000 epinephrine. On the opposite side, after the buffering device was used to mix the components within the anesthetic carpule, patients received injections of 2% lidocaine with 1:100,000 epinephrine buffered 9:1 with 8.4% sodium bicarbonate. The mean pain scores were 2.7 (SD, 1.3) for buffered and 2.7 (SD, 1.9) for unbuffered IA injections. The mean pain scores were 2.0 (SD, 1.4) for buffered and 2.7 (SD, 1.8) for unbuffered LB injections. The data were analyzed with a paired *t* test ($\alpha = 0.05$), and no statistically significant difference was found between groups for IA ($P = 0.94$) or LB ($P = 0.17$) nerve block injections. In this study of patients receiving common dental nerve block injections, local anesthetic buffering technology did not significantly lessen pain compared to that experienced during a standard unbuffered injection.

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For many people, the anticipation of pain associated with dental care is a significant deterrent to seeking treatment. With the advent of modern local anesthesia materials and techniques, the dental practitioner can, in most cases, attain an effective level of anesthesia that allows the patient to remain comfortable for the duration of dental treatment. This reduction in pain has been reported to reduce the stress associated with dental encounters.[1-3] Despite these advances, some patients still avoid necessary dental treatment solely out of fear of the pain associated with dental anesthetic injections. It is logical, therefore, to propose that a reduction in the pain associated with these injections will reduce the fear of dental treatment, and patients will then be more likely to seek care.[1,2] Numerous theories, drugs, devices, and techniques have been applied in attempts to mitigate or eliminate pain from dental injection, including application of topical anesthesia, pressure or vibration of tissues, application of cold, and buffering of the local anesthetic solution.

Buffering of local anesthetic solutions has been researched thoroughly in the medical literature. Recent meta-analyses of the available research concluded that buffered local anesthetic solutions are associated with a statistically significant decrease in pain of infiltration compared to unbuffered local anesthetic solutions.[4,5] The majority of cases evaluated in these analyses involved intradermal injections.

Pain is a message to the brain that damage has occurred or is about to occur. The body responds with protective and avoidance behaviors so that healing can occur and future damage can be avoided. Nociceptors are the specialized sensory nerves that are responsible for detecting a painful stimulus and initiating a signal to the central nervous system, usually in response to an intense noxious stimulus.[6] The signal comes in the form of an action potential that is carried from the nociceptors through synaptic connections in the spinal cord for processing in the cerebral cortex. Once this signal reaches the cerebral cortex, the sensation of pain is experienced. Local anesthesia administered near the nociceptors inhibits depolarization of the nociceptors, thereby preventing a signal from being transmitted to the central nervous system. Vasoconstrictors such as epinephrine are frequently added to local anesthetic to reduce blood flow in the area of injection. This allows the local anesthetic to remain in the area of injection for a longer period of time and prolongs anesthesia.[6-9]

Local anesthetic solutions contain a mixture of charged and uncharged molecules. Charged local anesthetic molecules (RNH^+) achieve anesthesia by blocking intracellular sodium channel receptors inside the neuron, which prevents conduction of nerve impulses when a painful stimulus is applied, resulting in anesthesia. However, these charged local anesthetic molecules are unable to pass through the nerve cell membrane into the nociceptor to reach their intended targets. In contrast, the uncharged local anesthetic molecule (RN) can readily cross the cell membrane into the neuron but is unable to block sodium channel receptors. Anesthesia is attained when the uncharged form enters the nerve cell, then dissociates into a mixture of charged and uncharged molecules, resulting in intracellular charged molecules. Thus, the sodium channels are engaged by charged (RNH^+) molecules and anesthesia occurs.[6-9]

The percentage of charged to uncharged local anesthetic molecules present is pH dependent and determined by the Henderson-Hasselbalch equation. The Henderson-Hasselbalch equation states that when the negative logarithm of the acid dissociation constant (pK_a) of a molecule matches the pH of the solution in which it is dissolved, there will be a mixture of exactly half charged and half uncharged molecules. When the pH of the solution is less than the pK_a, more molecules are charged than uncharged; when the pH is greater than the pK_a, more molecules are uncharged than charged.[10]

Some commonly used dental anesthetics have the following pK_a values: lidocaine, 7.7; articaine, 7.8; and mepivacaine, 7.6.[11] The anesthetic solution in which these molecules are dissolved has an average pH

of 3.5 (range of 2.86-4.16).[12-14] Therefore, more than half of the molecules are of the charged variety and unable to cross the cell membrane. If the pH of the anesthetic solution is raised, a higher percentage of the local anesthetic molecules is in the uncharged state, and therefore more molecules are available to cross into the nerve cells and bring about anesthesia.[15,16]

The pain associated with an injection is mainly attributed to 3 factors—the pain from the physical trauma of the needle piercing the tissue, the expansion of the tissue as the anesthetic is injected, and the acidity of the local anesthetic solution itself as it is deposited into the tissues—all of which stimulate nociceptors.[17,18] Raising the pH of the local anesthetic solution would theoretically result in less direct activation of nociceptors by noxious stimuli and fewer pain signals sent to the brain. In addition, as already explained, the buffering of the local anesthetic allows more uncharged local anesthetic molecules to cross the cell membrane into the neuron. Theoretically, this should result in higher intracellular levels of the active form (RNH^+) after dissociation has occurred, which facilitates the blockage of voltage-gated sodium channels. The pain associated with the injection process would thus be reduced because the sensory nerves are anesthetized more quickly and effectively.[11,19]

Despite the evidence in the medical literature indicating that buffering is effective, this technique is rarely used in dental injections because vasoconstrictors such as epinephrine become unstable at an elevated pH. To achieve the desired effects and maintain the stability of the vasoconstrictor, the buffered mixture must be prepared immediately prior to its use.[4,20,21] Therefore, manufacturers are prevented from offering prebuffered solutions, and the technical sensitivity involved in mixing the buffer and the local anesthetic chairside has minimized its use in dentistry to date.[17]

The manufacturer of Onset (Onpharma, Inc.), a recently patented local anesthetic buffering technology, claims to have solved this issue. Onset reportedly provides the dentist with a quick, predictable, and easy way to titrate sodium bicarbonate with the local anesthetic of choice, claiming all the benefits that local anesthetic buffering has been reported to provide: decreased pain on injection, more profound anesthesia, decreased time of onset of local anesthesia, and no decrease in longevity of anesthesia.[20,22]

Limited clinical research has been done to specifically test the efficacy of the Onset device in reducing pain on injection.[12,23] In the present study, the null hypothesis was that there would be no difference in pain during inferior alveolar (IA) or long buccal (LB) nerve block injections with or without use of the new mixing device to buffer the anesthetic.

Materials and methods

The protocol and informed consent documents were approved by the Institutional Review Board at Wilford Hall Ambulatory Surgical Center, Joint Base San Antonio (JBSA), Lackland, Texas. Twenty adults (active-duty military or Department of Defense beneficiaries) who were aged 18 years or older and needed treatment requiring bilateral IA and LB nerve blocks participated in this study. All subjects were in good general health, classified according to the American Society of Anesthesiologists (ASA) Physical Status Classification System as ASA I or ASA II.[24] The baseline pain level of all patients was 0 (no pain).

A sample size of 20 subjects would provide 80% power to detect a 0.75-standard deviation difference when a paired *t* test and an α level of 0.05 were used to compare scores for the 2 treatments. Sample size was determined by a statistical software package (PASS 2002, NCSS, LLC).

The subjects were selected from a pool of patients at the Dunn Dental Clinic (JBSA) and entered into the study by dentist referral. Specifically, the dentist providing care decided that the patient required bilateral IA and LB nerve blocks to complete treatment. The dentist then briefly explained the research study to determine the patient's interest in meeting the principal investigator (PI) or alternate investigator (AI) to learn more about the study. If the patient was interested, the dentist invited the PI or AI to talk briefly with the patient about the study and scheduled the patient for the initial consent appointment and subsequent enrollment into the study. All subjects signed an informed consent document and HIPAA (Health Insurance Portability and Accountability Act) authorization before any study-related procedures were conducted. The PI and AI did not perform the informed consent procedure for their own patients, to preclude any misconceptions of coercion or undue influence on their patients to participate in the study.

A randomized, block, split-mouth design was used. Immediately prior to the data collection appointment, the PI used a micrometer and permanent marker to create lines on 2 unbuffered carpules containing a 1.7-mL solution of 2% lidocaine with 1:100,000 epinephrine (DENTSPLY International), dividing the solution into fourths. One of the 2 carpules was loaded in the Onset mixing pen, and the pen was set to buffer the anesthetic 9:1. The patient and PI were blinded to the type of anesthetic, buffered or unbuffered, used in each injection at time of treatment.

The unbuffered anesthetic solution contained 1.7 mL of 2% lidocaine with 1:100,000 epinephrine and was administered with a 27-gauge long needle. The buffered anesthetic solution contained a 9:1 ratio of 2% lidocaine with 1:100,000 epinephrine to 8.4% sodium bicarbonate, per the manufacturer's instructions.[25] With the Onset mixing tool, 0.17 mL of solution was extracted from the 1.7-mL carpule and replaced with 0.17 mL of 8.4% sodium bicarbonate. The buffered solution was also administered with a 27-gauge long needle. A new needle was used to inject each side of the patient's mouth to ensure a fresh, sharp cutting tip. The PI performed all injections in this study to standardize the flow rate and technique.

The predetermined sequence of treatment, based on a randomized block, dictated which anesthetic would be used first (buffered or unbuffered) and which side would be tested first (right or left). When the dental procedure was ready to commence, the assistant informed the PI which side of the mouth was to be tested first. Benzocaine 20% topical anesthetic gel (Topex, Sultan Healthcare) was used to prepare the sites to receive the IA and LB nerve block injections. The benzocaine gel was placed in a 1-mL syringe, and 0.1 mL was dispensed on a cotton-tipped applicator. The mucosa at the sites of injection was dried with a 2 × 2-cm gauze square, and the gel on the cotton-tipped applicator was applied to the mucosa for a period of 2 minutes.

Per the manufacturer's instructions, once the local anesthetic solution is buffered it should be injected immediately.[25] After 1 minute of topical anesthetic application, the PI informed the assistant that the injection would take place in 1 minute. The assistant then prepared the local anesthetic (buffered or unbuffered, depending on the predetermined sequence of injections) out of sight of the PI. When the 2 minutes of topical anesthetic application had expired, the assistant handed the PI the appropriate local anesthetic carpule. The PI and patient were unaware of which solution was used.

The PI loaded the carpule into a syringe, and three-fourths of a carpule (judged by the markings that divided the carpule into fourths) was administered during the IA nerve block over 15 seconds. The remaining fourth was administered during the LB nerve block over 5 seconds. The IA nerve block injection was given at the pterygotemporal depression. The LB nerve block injection was given between the distal mandibular alveolar crest and the external oblique ridge.

The patient's self-report of injection pain was immediately evaluated using a visual analog scale (VAS) that is often used to measure pain intensity.[2,17] The VAS is a 100-mm horizontal line with hash marks every 10 mm, labeled *0-10*. The words *no pain* were labeled under the 0 on the left end of the line and the words *worst possible pain* were labeled under the 10 on the right end. Immediately after each injection, the patient was instructed to mark a vertical line on the 100-mm line to indicate the level of discomfort experienced during the injection.

After 5 minutes, the process was repeated on the opposite side using the second carpule. Each patient recorded 4 VAS scores, corresponding to the 4 injections. The pain score was calculated by measuring the millimeter distance from the left end of the VAS with a digital caliper. A higher score translated to higher pain intensity experienced by the patient. The contents of the solutions were recorded in an electronic database (Excel, Microsoft Corporation) by the PI immediately after completion of the treatment.

Results

The participant pool was made up of 15 men and 5 women whose ages ranged from 27-81 years (mean, 46 years). Ten patients received injections on the right side first, and 10 received treatment on the left side first. Ten patients received injections with unbuffered local anesthesia first, and 10 received injections with buffered local anesthesia first.

The mean pain score for the IA injections was 2.7 (SD, 1.3) for buffered and 2.7 (SD, 1.9) for unbuffered lidocaine. For the LB injections, the mean pain score was 2.0 (SD, 1.4) for buffered and 2.7 (SD, 1.8) for unbuffered anesthetic. Data were analyzed with a paired *t* test to compare buffered and unbuffered VAS scores for each injection site. No statistically significant difference was found between groups for the IA ($P = 0.94$) or the LB ($P = 0.17$) nerve block injections.

Discussion

In this double-blind, split-mouth clinical study, a new sodium bicarbonate local anesthetic buffering device (Onset) did not significantly reduce pain experienced during IA and LB nerve block injections compared to unbuffered local anesthetic. Therefore, the null hypothesis was not rejected.

The effect of buffering local anesthetic solution on the pain experienced during injection has been thoroughly investigated in the medical literature. Davies completed a systematic review of research published between 1966 and 2001 on the effectiveness of sodium bicarbonate–buffered local anesthetic in reducing pain on injection.[5] In 22 prospective randomized controlled clinical trials that met the inclusion criteria, "buffering with sodium bicarbonate significantly reduces the pain of local anaesthetic injection."[5] A meta-analysis by Hanna et al specifically investigated the effect of buffering of local anesthetic on the pain experienced during intradermal injections.[4] In 12 studies that met their inclusion criteria, the authors concluded, "the use of buffered local anesthetics seems to be associated with a statistical decrease in pain of infiltration when compared with unbuffered local anesthetic."[4]

The effect of buffered anesthetic on pain from intraoral injections is more equivocal. A study by Bowles et al found that patients experienced less pain when buffered lidocaine was used with maxillary infiltrations.[26] Kashyap et al found that buffered lidocaine decreased pain on mandibular block injections, and Al-Sultan found buffered lidocaine decreased pain on injection prior to maxillary anterior periapical surgery.[27,28] However, Hobeich et al and Primosch & Robinson found no reduction in pain when buffered lidocaine was used instead of unbuffered lidocaine for maxillary infiltrations.[23,29] Using buffered 4% articaine, Shurtz et al also found no significant difference in pain on mandibular first molar infiltration injections.[30] In agreement with the present study, Whitcomb et al concluded that 2% lidocaine buffered with sodium bicarbonate did not result in less pain than unbuffered anesthetic during IA injections.[31]

Two studies have evaluated the effect of using lidocaine buffered with the Onset mixing pen on the pain of injection.[12,23] One study used a maxillary infiltration and the other an IA injection. Hobeich et al found that 2% lidocaine buffered with 5% or 10% sodium bicarbonate did not differ from nonbuffered solutions in injection pain associated with infiltrations of maxillary canines.[23] Malamed et al investigated the effect of alkalinizing 2% lidocaine with 8.4% sodium bicarbonate at a ratio of 9:1 on pain during IA nerve block injections.[12] Their study was designed in a fashion similar to that of the present study; they included 18 subjects and used a prospective, randomized, double-blind design. However, there were several key differences in study design. First, their study only tested pain during IA nerve block injections, while the current study tested IA and LB nerve block injections; second, their injections were delivered over 60 seconds, while in the current study the IA nerve block injection was delivered over 15 seconds; third, topical anesthetic was not used in their study, and the pain associated with penetration of the needle in and through the tissue was not considered in the assessment of injection pain, while the current study used topical anesthetic and investigated the pain associated with the total injection; and fourth, their injections were completed in the same site at 2 separate appointments, while the current study used a split-mouth design in which both injections were given at the same appointment, 1 on each side of the mouth. Malamed et

al found that patients verbally expressed a preference for buffered IA nerve block injections over unbuffered injections at a statistically significant level.[12] However, the difference in pain caused by the buffered and unbuffered injections, as recorded on the VAS, was not statistically significant. The different conclusions drawn from the previous study and the current one may be attributed to the pain associated with needle penetration of the tissue.

After data collection, the patients in the present study often volunteered that they could feel 2 different phases of the injection. They felt the original prick of the needle penetrating the skin and then felt the solution being deposited in the target area. Both of these events were described as being uncomfortable. Despite the use of topical anesthetic, the subjects seemed to remain acutely aware of this first painful sensation. The buffering of the local anesthetic solution appeared to have little to no effect on this aspect of the injection. Therefore, even if the pain associated with the deposition of local anesthetic solution were lessened by this buffering technology, the pain associated with the original entry of the needle into the tissue cannot be easily addressed and may overcome any perceived benefits of local anesthetic buffering.

A recent study by DiFelice et al evaluated the effect of an intraoral vibration device on reducing pain during injection.[32] As in the current study, the IA nerve block injection was used. However, the variable tested in that study (vibration) was present before the original penetration of the syringe in the tissue. The researchers concluded that the vibratory device decreased the total pain of injection. That study lends credence to the theory that, if dental injection pain is to be reduced, the initial pain associated with tissue penetration must be addressed in addition to the pain experienced during deposition of the local anesthetic solution at the target site.

Another possible explanation for the lack of effectiveness of the local anesthetic buffering technique in reducing pain may be the rate at which the injections were given in the present study. It has been established that the distention of the tissue from injection of the anesthetic solution is one cause of the perceived pain; when the solution is deposited over a longer period of time, less pain is experienced.[18] Scarfone et al investigated the pain associated with local anesthesia in relation to the rate of administration and buffering of local anesthetic solutions.[33] Their study did not involve intraoral injections but investigated intradermal injection sites. They concluded that the rate of administration had a greater impact on perceived pain during lidocaine infiltration than did buffering. These results suggest that rate of injection may be a greater modifying factor than use of buffered anesthetic in reducing injection pain.

Although in the present study the buffering technique was not found to have a significant effect on reducing pain during intraoral injection, it may be a valuable tool to increase the speed and efficacy with which dental treatment is delivered. The buffering technology of Onset is primarily advertised to decrease the time of onset of local anesthesia.[22] Faster onset of anesthesia may have particular value for IA nerve block injections, which have a delayed onset of action compared to most other infiltration injections. As was explained previously, an anesthetic solution with a higher pH would theoretically provide faster onset of anesthesia and make the patient more profoundly numb.[20]

The results of medical research evaluating the onset of anesthesia with buffered anesthetic solutions have been somewhat equivocal to date; some studies have shown that onset of anesthesia is faster with anesthetic formulations with higher pH, and others have found no difference.[16,34-38] The results of dental research have also been equivocal. Using manually mixed solutions, Whitcomb et al found that 2% lidocaine buffered with sodium bicarbonate did not provide a statistically significant decrease in the time of onset of anesthesia compared to the unbuffered control during an IA injection.[31] Shurtz et al, using buffered 4% articaine, found no significant difference in onset of anesthesia after mandibular first molar infiltration injections.[30] However, studies by Kashyap et al and Al-Sultan determined that buffering of local anesthetic solution decreased the time to onset of anesthesia.[27,28]

Using the Onset mixing pen, Malamed et al investigated the effect of buffered 2% lidocaine on the onset of anesthesia during IA blocks.[12] Their results demonstrated a statistically significant decrease in time needed to obtain anesthesia. According to the authors, "70% of the participants receiving alkalinized lidocaine with epinephrine achieved pulpal analgesia in 2 minutes or less. This normally takes 15 minutes…."[12] However, Hobeich et al found that 2% lidocaine buffered with 5% or 10% sodium bicarbonate in the Onset mixing pen did not differ from nonbuffered solutions in anesthetic onset with infiltrations of maxillary canines.[23] Additional research is recommended to evaluate the efficacy of the Onset system in reducing pain or decreasing onset of anesthesia associated with intraoral injections.

Conclusion

In this double-blind, split-mouth clinical study, local anesthetic buffered with the Onset system did not significantly reduce pain during IA and LB nerve block injections compared to unbuffered local anesthetic.

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Disclaimer

The authors have no financial, economic, commercial, or professional interests related to topics presented in this article. The views expressed in this study are those of the authors and do not reflect the official policy of the US Air Force, the Department of Defense, or the US government.

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Manufacturers

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