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INITIATOR

1. USU Principal Author/Presenter: Capt Andrew Comerci

2. Academic Title: Resident, Advanced Education in General Dentistry Residency (AEGD-2)

3. School/Department/Center: Air Force Postgraduate Dental School (AFPDS)

4. Phone: 210-671-9822

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CHAIR OR DEPARTMENT HEAD APPROVAL

1. Name: Kraig S. Vandewalle, Director, Dental Research

2. School/Dept.: AFPDS / AEGD-2

3. Date: 10 July 2014

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Chair/Department Head Approval: Kraig S. Vandewalle Date 10 July 2014

SERVICE DEAN APPROVAL

1. Name: Col Drew Fallis

2. School (if applicable): AFPDS

3. Date: 10 July 2014

4. __Higher approval clearance required (for University-, DoD- or US Gov't-level policy, communications systems or weapons issues review").

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Effect of a New Local Anesthetic Buffering Device on
Pain Reduction During Nerve Block Injections

Capt Andrew W. Comeroi

APPROVED:

Col [illegible] ~~Steven~~ C. Maller

LtCol Richard D. Townsend

Capt John D. Teepe

Col Craig S. Vandewalle

Date

APPROVED:

Col Drew W. Fallis
Dean, Air Force Postgraduate Dental School

UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES
AIR FORCE POSTGRADUATE DENTAL SCHOOL
2133 Pepperrell Street
Lackland AFB Texas, 78236-5345
http://www.usuhs.mil

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Andrew Comerci, Capt, USAF, DC
AEGD-2 Residency Program - Lackland
Uniformed Services University
10 July 2014

Effect of a New Local Anesthetic Buffering Device on Pain Reduction During Nerve Block Injections

ABSTRACT

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®, Onpharma) 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 using a visual analog scale (VAS). One side of the mouth received standard of care injections using 2% Lidocaine with 1:100,000 epinephrine. On the opposite side, injections were administered using 2% Lidocaine with 1:100,000 epinephrine buffered 9:1 with 8.4% sodium bicarbonate using the Onset® device to mix the components within the anesthetic carpule. A mean VAS score and standard deviation for the IA injection was 2.7 ± 1.3 for buffered and 2.7 ± 1.9 for unbuffered and for the LB injection was 2.0 ± 1.4 for buffered and 2.7 ± 1.8 for unbuffered. The data were analyzed with a paired t-test (alpha=0.05). No significant difference was found between groups for the IA (p=0.94) or the LB injections (p=0.17). Conclusion: Onpharma's Onset® local anesthetic buffering technology did not significantly reduce pain from common dental nerve block injections compared to the standard unbuffered injection.

INTRODUCTION

For many people, the anticipation of pain associated with dental care is a significant deterrent in 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 reducing 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] A litany of theories, drugs, devices and

techniques has been applied in an attempt to mitigate or eliminate pain from dental injection to include: application of topical anesthesia, tissue pressure/vibration, cold application, and buffering of the local anesthetic solution.

In dentistry, the effect of buffering local anesthetic solutions was first studied by Gros and Laewen in 1910 and then by Tainter et al. in 1939.[4,5] Since then, very limited dental research involving this topic as it relates to dental injections has been published.[5-7] However, it has been researched more thoroughly in the medical literature. Three recent meta-analyses of the available research concluded that buffered local anesthetic solutions are associated with a statistically significant decrease in pain of infiltration when compared to unbuffered local anesthetic solutions.[8-10] 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/or future damage can be avoided. Nociceptors are the specialized sensory nerves that are responsible for detecting this painful stimulus and initiating a signal to the central nervous system (CNS), usually in response to an intense noxious stimulus.[8] 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 CNS.

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, charged local anesthetic molecules (RNH+) 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 (RN) enters the nerve cell, then dissociates into a mixture of charged (RNH+) and uncharged (RN) molecules resulting in intracellular

charged (RNH+) molecules. Thus, the sodium channels are engaged by charged (RNH+) molecules and anesthesia occurs. Vasoconstrictors such as epinephrine are frequently added to local anesthetic to prolong anesthesia by reducing blood flow in the area of injection (vasoconstriction). This allows the local anesthetic to remain in the area of injection for a longer period of time and prolongs anesthesia.[11-14]

The percentage of charged vs. uncharged local anesthetic molecules present is pH dependent and determined by the Henderson-Hasselbalch equation. The Henderson-Hasselbalch equation states that when a molecule's pKa 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 below the pKa, more molecules are charged than uncharged and vice versa.[15] The pKa of lidocaine is 7.7, articaine 7.8 and mepivicaine 7.6.[16] The anesthetic solution that these molecules are dissolved in typically has an average pH of 3.5 with a range of 2.86 to 4.16.[4,17,18] Therefore, more than half of the molecules are of the charged variety (RNH+), and unable to cross the cell membrane. By raising the pH of the anesthetic solution, 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 have an effect on anesthesia.[19,20]

The pain associated with the injection is mainly attributed to two factors: the pain from the physical trauma of the needle piercing the tissue and the acidity of the local anesthetic solution itself as it is deposited into the tissues, both of which stimulate nociceptors.[21] Raising the pH of the local anesthetic solutions would result in less direct activation of nociceptors by noxious stimuli and fewer pain signals sent to the brain. In addition, as explained above, the buffering of the local anesthetic allows more uncharged local anesthetic molecules (RN) 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 is thus reduced because the sensory nerves are anesthetized more quickly and effectively. The result of these two factors is a less painful injection.[16,22]

Despite the evidence in the medical literature indicating that buffering is effective, this technique is rarely used in dental injections. One reason for this is the fact that vasoconstrictors such as epinephrine become unstable at an elevated pH, thus preventing local anesthetic manufacturers from buffering the

solutions. To achieve the desired effects and maintain the stability of the vasoconstrictor, the buffered mixture needs to be prepared immediately prior to its use.[9,23,24] Another barrier to buffering local anesthetic solutions has been the technical sensitivity involved in mixing the buffer and the local anesthetic chair side, thus minimizing its use in dentistry to date.[21]

Onset®, the recently patented local anesthetic buffering technology created by Onpharma (Los Gatos, CA), claims to have solved this issue (See Figure 1). It 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 upon injection, more profound anesthesia, and decreased time of onset of local anesthesia with no decrease in longevity of anesthesia.[23,25]

Onpharma's sodium bicarbonate is an FDA registered product that is manufactured according to current Good Manufacturing Practices for injectable prescription drugs (cGMP), at an FDA licensed drug manufacturing facility. Onpharma's sodium bicarbonate solution is in a category of drugs known as "Grandfathered." This product has a GRAS/E (Generally Recognized as Safe and Effective) indication for use. The National Drug Code number for their Sodium Bicarbonate Neutralizing Solution is 50509-100-03.[25] Limited clinical research has been done to specifically test Onset's efficacy in reducing pain upon injection. The null hypothesis to be tested was that there would be no difference in pain in the IA or LB injections with or without buffering of the anesthetic using the mixing device.

METHODS AND MATERIALS

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 DoD beneficiaries) 18 years or older, in good general health classified as ASA I or ASA II (according to the American Society of Anesthesiologists Physical Status Classification System), who needed treatment requiring bilateral inferior alveolar and long buccal nerve blocks participated in this study. Baseline pain levels of all patients was zero (no pain). A sample size of 20

subjects provided 80% power to detect a 0.75 standard deviation difference when using a paired t-test and an alpha level of 0.05 to compare the scores for the two treatments. Sample size was determined by the NCSS Statistical Software package (NCSS PASS 2002). The subjects were selected from a pool of patients at the Dunn Dental Clinic (JBSA - Lackland, TX) and entered into the study by dentist referral. Specifically, the dentist providing care decided that the patient required bilateral inferior alveolar and long buccal nerve blocks to complete treatment. The dentist then briefly explained the research study and determined if the patient was interested in meeting the principle 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 briefly talk 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 Authorization prior to any study-related procedures being conducted. The PI and AI did not consent their own patients to preclude any misconceptions of coercion or undue influence toward their patients to participate in the study.

A randomized block, split-mouth design was used. Immediately prior to the data collection appointment, the PI marked lines on two unbuffered carpules of 1.7mL solution of 2% lidocaine with 1:100,000 epinephrine (Dentsply Pharmaceutical, York, PA), using a micrometer and permanent marker, dividing the solution into fourths. One of the two carpules was loaded into 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 1.7mL of 2% Lidocaine with 1:100,000 epinephrine and was administered using 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 manufacturer's instructions. With the Onset® mixing tool, 0.17mL of solution was extracted from the 1.7mL carpule and replaced with 0.17mL of 8.4% sodium bicarbonate. The buffered solution was also administered using a 27-gauge long needle. A new needle was used to inject each side to ensure a fresh, sharp cutting tip. 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 Dental Products, Hackensack, NJ) was used to prepare the sites to receive the inferior alveolar and long buccal nerve block injections. The method of application was as follows: 1) the gel was placed in a 1mL syringe and 0.1mL was placed on a cotton tip applicator, 2) the mucosa at the sites of injection was dried with a 2x2 cm gauze square and 3) the gel on the cotton tip applicator was applied to the mucosa for a period of 2 minutes. Per manufacturer's instructions, once the local anesthetic solution is buffered it should be injected within a minute. After one minute of topical anesthetic application, the PI informed the assistant that the injection would take place in one minute. The assistant would then prepare the local anesthetic (buffered or unbuffered depending on the predetermined sequence of injections). This was done out of sight of the PI. When the two minutes 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 it into a syringe and three fourths of a carpule (judged by the markings that divided the carpule into fourths) was administered during the inferior alveolar nerve block over 15 seconds and the remaining fourth was administered during the long buccal nerve block over 5 seconds.

The PI performed all injections in this study to standardize the flow rate and technique. The inferior alveolar nerve block injection was given at the pterygotemporal depression. The long buccal 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 the visual analogue scale (VAS) that is often used to measure pain intensity. [2,8,21] The VAS is a 100 mm horizontal line with hash marks every 10mm labeled 0-10. "NO PAIN" was labeled under the "0" on the left end and "WORST POSSIBLE PAIN" was 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 waiting five minutes, the process was repeated on the opposite side using the second carpule. Four VAS scores were recorded corresponding to the four injections. The VAS pain score was calculated by measuring the millimeter distance from the left end of the scale using a digital caliper. A higher score translated to a higher pain intensity experienced by the patient. The contents of the solutions were entered into an electronic database (Excel, Microsoft, Redmond, WA) by the principle investigator immediately after completion of the treatment.

RESULTS

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

The mean VAS score and standard deviation for the IA injection was 2.7 ± 1.3 for buffered and 2.7 ± 1.9 for unbuffered and for the LB injection was 2.0 ± 1.4 for buffered and 2.7 ± 1.8 for unbuffered. Data were analyzed with a paired t-test, comparing buffered versus unbuffered VAS scores per injection site. No significant difference was found between groups for the IA ($p=0.94$) or the LB injections ($p=0.17$).

DISCUSSION

In this double blind, split mouth clinical study, the new sodium bicarbonate local anesthetic buffering device (Onset®, Onpharma) did not significantly reduce pain compared to unbuffered local anesthetic during inferior alveolar and long buccal nerve block injections. Therefore, the null hypothesis was not rejected.

The effect of the buffering of local anesthetic solution on pain upon injection has been thoroughly investigated in the medical literature. Davies, in 2003 completed a systematic review using research published between 1966 and 2001 evaluating the effect of sodium bicarbonate buffered local anesthetic on reducing pain upon injection.[10] Out of twenty-two prospective, randomized, controlled clinical trials that met the inclusion criteria, his analysis concluded that, "buffering with sodium bicarbonate significantly reduced the pain of local anesthetic injections." A meta-analysis by Hanna, et al. in 2009 specifically investigated the effect of buffering local anesthetic on pain experienced during intradermal injections. In the~~se~~ twelve studies that met inclusion criteria, the authors concluded that "the use of buffered local anesthetic seems to be associated with a statistical decrease in pain of infiltration when compared with unbuffered local anesthetic."[9] Cepeda et al. in 2010 compared pH-adjusted lidocaine with unadjusted lidocaine solutions in their meta-analysis. Their meta-analysis concluded that "increasing the pH of lidocaine reduced pain and improved patients' comfort and satisfaction."[8]

Based on the consensus of these three meta-analyses, buffering local anesthetic solutions with sodium bicarbonate should be an effective way to reduce pain upon injection. The results of the current clinical study appear to be in disagreement. A possible explanation for this difference is that intra-oral injection sites this may be more highly innervated than the majority of the extraoral dermal sites previously studied.[26] Injections intra-orally could therefore naturally be more painful and the change in pain upon injection may not be as apparent in the area brought on by an elevation in pH of the local anesthetic.

Very limited research is available evaluating the effect of buffered anesthetic on pain from intra-oral injections. With maxillary infiltrations, a study by Bowles et al. found less pain using buffered lidocaine, but Primosch and Robinson found no reduction in pain compared to unbuffered lidocaine.[5,6] In agreement with this study, Whitcomb et al. concluded that buffering 2% lidocaine with sodium bicarbonate did not result in less pain with inferior alveolar injections when compared with unbuffered anesthetic.[7] The researchers prepared the solutions manually in a 5-mL syringe using a higher concentration (4:1) of sodium bicarbonate. The subjects rated the pain separately for needle insertion, needle placement, and solution deposition. No significant difference in pain was noted at any phase of injection.

Only one study has been published evaluating the effect of buffering lidocaine with the Onset® mixing pen.[4] In 2013, Malamed et al. investigated the effect of alkalinizing 2% lidocaine with 8.4% sodium bicarbonate at a ratio of 9:1 on pain during inferior alveolar nerve block injections.[4] Their study was designed in a very similar fashion to the current study: eighteen subjects, prospective, randomized, double-blind design. However, there were several key differences in study design. First, the study only tested injection pain involving the inferior alveolar nerve block injections (the current study tested inferior alveolar and long buccal nerve block injections); second, the injections were delivered over 60 seconds (the current study delivered the inferior alveolar nerve block injection over 15 seconds); third, topical anesthetic was not used and the pain associated with penetration of the needle into and through the tissue was not considered in the assessment of injection pain (the current study used topical anesthetic and investigated the pain associated with the total injection); and fourth, the injections were completed in the same site at two separate appointments (the currently study used a split mouth design where both

injections were given at the same appointment, one on each side of the mouth). Malamed et al. found that with respect to inferior alveolar nerve block injections, patients verbally expressed a preference to buffered injections to unbuffered at a statistically significant level.[4] However, the difference in pain recorded on the visual analog scales was not statistically significant between the buffered and unbuffered injections. An explanation regarding the different conclusions drawn from this study and the current one may be attributed to the pain associated with the needle's penetration of the tissue.

After data collection, the patients in this study often volunteered that they could feel two 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 which 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 appears 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 is lessened with this buffering technology, the pain associated with this original entry of the needle into the tissue cannot be easily addressed and may overcome any perceived benefits that may be available in local anesthetic buffering.

A recent study by DiFelice et al. in 2014 evaluated the effect of an intra-oral vibration device on reducing pain upon injection.[27] As in the current study, the inferior alveolar nerve block injection was used. However, the variable being testing in that study (vibration) was present before the original penetration of the syringe into the tissue. The article concluded that the vibratory device decreased the total pain upon injection. This study lends credence to the theory that if we are to be effective in reducing dental injection pain, the initial pain associated with the tissue penetration needs to be addressed in addition to the pain experienced during the deposition of the local anesthetic solution at the target site.

Another possible explanation of the lack of effectiveness in reducing pain of the local anesthetic buffering technique demonstrated in this study may be due to the rate upon which the injections were given. It has been established that the distention of the tissue from the rate of injection of the anesthetic solution is one cause of the perceived pain. When the solution is deposited over a longer period of time, the pain experienced is less.[28] A study by Scarfone et al. published in 1997 investigated the pain

associated with local anesthesia as it related to the rate of administration and buffered local anesthetic solutions.[29] As in the other studies mentioned, this study did not involve intra-oral injections but investigated intradermal injection sites. It was 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 the buffering technique was not found in this study to have a significant effect on reducing pain during intra-oral injection, it may be a valuable tool to increase the speed and efficacy in which we can deliver dental treatment. The buffering technology of Onset® by Onpharma is also advertised to decrease the time of onset of local anesthesia. Faster onset of anesthesia may have particular value with inferior alveolar 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 have a faster onset of anesthesia and potentially would get the patient more profoundly numb.[23] Medical research to date evaluating the onset of anesthesia with buffered anesthetic solutions have been somewhat equivocal, with some studies showing faster onset with anesthetic formulations with higher pH[30-33] and others finding no difference.[20,34] Limited dental research has been published evaluating the speed of onset of buffered anesthesia. 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 inferior alveolar injection.[7] Using the Onset® mixing pen, Malamed et al. in 2013 investigated the effect of buffered 2% lidocaine on the onset of anesthesia. Their results demonstrated a statistically significant decrease in time to obtain anesthesia. According to the authors, “seventy percent of the participants receiving alkalinized lidocaine with epinephrine achieved pulpal anesthesia in 2 minutes or less. This normally takes 15 minutes.”[4] Additional research is recommended to evaluate the efficacy of the Onset® system in reducing pain or decreasing onset time of intra-oral injections.

CONCLUSION

In this double blind, split mouth clinical study, local anesthetic buffered using Onset® by Onpharma did not significantly reduce pain upon injection during inferior alveolar and long buccal nerve block injections compared to unbuffered local anesthetic.

DISCLOSURE

The authors have no connection to or financial interest in Onpharma's Onset®. The views expressed in this study are those of the authors and do not reflect the official policy of the United States Air Force, the Department of Defense, or the United States Government. The authors do not have any financial interest in the companies whose materials are discussed in this article.

REFERENCES

1. Hutchins HS, Young FA, Lackland DT, Fishburne CP. The effectiveness of topical anesthesia and vibration in alleviating the pain of oral injections. Anesth Prog 1997;44:87-89.
2. Kosaraju A, Vandewalle KS. A comparison of a refrigerant and a topical anesthetic gel as preinjection anesthetics: A clinical evaluation. J Amer Dent Assoc 2009;140:68-72.
3. Armfield JM, Migrom P. A clinician guide to patients afraid of dental injections and numbness. SAAD Digest 2011;27:33-39.
4. Malamed SF, Tavana S, Falkel M. Faster onset and more comfortable injection with alkalinized 2% lidocaine with epinephrine 1:100,000. Compend Contin Educ Dent 2013; 34(Spec No 1):10-20.
5. Primosch RE, Robinson L. Pain elicited during intraoral infiltration with buffered lidocaine. Amer J Dent 1996;9:5-10.
6. Bowles WH, Frysh H, Emmons R. Clinical evaluation of buffered local anesthetic. Gen Dent 1995;43:182-184.
7. Whitcomb M, Drum M, Reader A, Nusstein J, Beck MA. Prospective, randomized, double-blind study of the anesthetic efficacy of sodium bicarbonate buffered with 2% lidocaine with 1:100,000 epinephrine in inferior alveolar nerve blocks. Anesth Prog 2010;57:59-66.
8. Cepeda MS, Tzortzopoulou A, Thackrey M, Hudcova J, Gandhi PA, Schumann R. Adjusting the pH of lidocaine for reducing pain on injection. Cochrane Database Syst Rev 2010; (12):CD006581.
9. Hanna MN, Elhassan A, Veloso PM, Lesley M, Lissauer J, Richman JM, Wu CL. Efficacy of bicarbonate in decreasing pain on intradermal injection of local anesthetics: A meta-analysis. Reg Anesth Pain Med 2009;43:122-125.
10. Davies RJ. Buffering the pain of local anaesthetics: A systematic review. Emerg Med 2003;15:81-88.

11. Yagiela JA, Dowd FJ, Neidle EA. Pharmacology and the therapeutics for dentistry. 5th ed. St. Louis: Mosby; 2004:108-110.

12. Younis I, Bhutiani RP. Taking the 'ouch' out – effect of buffering commercial xylocaine on infiltration and procedure pain – a prospective, randomized, double-blind, controlled trial. Ann R Coll Surg Engl 2004;86:213-217.

13. Crose VW. Pain reduction in local anesthetic administration through pH buffering. J Indiana Dent Assoc 1991;70:24-27.

14. McGlone R, Bodenham A. Reducing the pain of intradermal lignocaine injection by pH buffering. Arch Emerg Med 1990;7:65-68.

15. Guyton AC, Hall JE. Textbook of medical physiology. 11th ed. St. Louis: Mosby;2006:383-387.

16. Malamed SF. Handbook of local anesthesia. 5th ed. St. Louis: Mosby, 2004:18,57.

17. Hondrum SO, Ezell JH. The relationship between pH and concentrations of antioxidants and vasoconstrictors in local anesthetic solutions. Anesth Prog 1996;43:85-91.

18. Crews JC, Clark RB. Effect of alkalinization on the pH of local anesthetic solutions. Anesth Analg 1987;66:1203.

19. Rose LF, Mealey BL, Genco RJ, Cohen DW. Periodontics: Medicine, surgery, and implants. St. Louis: Mosby;2004:370.

20. Christoph RA, Buchanan L, Begalia K, Schwartz S. Pain reduction in local anesthetic administration through pH buffering. Ann Emerg Med 1998;17:117-120.

21. Burns CA, Ferris G, Feng C, Cooper JZ, Brown MD. Decreasing the pain of local anesthesia: A prospective, double-blind comparison of buffered, premixed 1% lidocaine with epinephrine versus 1% lidocaine freshly mixed with epinephrine. J Am Acad Dermatol 2006;51:128-131.

22. Malamed SF, Falkel M. Advances in local anesthetics: pH buffering and dissolved CO_2. Dent Today 2012;31:88-93.

23. McKay W, Morris R, Mushlin P. Sodium bicarbonate attenuates pain on skin infiltration with lidocaine, with or without epinephrine. Anesth Analg 1987;66:572-574.

24. Colaric KB, Overton DT, Moore K. Pain reduction in lidocaine administration through buffering and warming. Am J Emerg Med 1998;16:353-356.

25. Onpharma. The onset approach. Los Gatos, CA: Onpharma. Available at: "www.onpharma.com". Accessed January 24, 2014.

26. Drake RL, Wayne V, Mitchell AWM. Gray's anatomy for students. St. Louis: Mosby; 2005:21-25.

27. DiFelice M, Maller S, Hancock R, Vandewalle K. Effects of a vibratory device on pain from anesthetic injections. Compend Contin Educ Dent 2014;34:2-5.

28. Palmon SC, Lloyd AT, Kirsch JR. The effect of needle gauge and lidocaine pH on pain during intradermal injection. Anesth Analg 1998;86:379-81.

29. Scarfone RJ, Jasani M, Gracely EJ. Pain of local anesthetics: Rate of administration and buffering. Ann Emerg Med 1998;31:36-40.

30. DiFazio CA, Carron H, Grosslight KR, Moscicki J, Bolding WR, Johns RA. Anesth Analg 1986;65:760-764.

31. Zahl K, Jordan A, McGroarty J, Sorensen B, Gotta AW. Peribulbar anesthesia – effect of bicarbonate on mixtures of lidocaine, bupivacaine, and hyaluronidase with or without epinephrine. Ophthalmology 1991;98:239-242.

32. Benson HT, Toleikis JR, Dixit P, Goodman I, Hill JA. Onset, intensity of blockade and somatosensory evoked potential changes of the lumbarsacral dermatomes after epidural anesthesia with alkalinized lidocaine. Anesth Analg 1993;76:328-332.

33. Sinnott CJ, Garfield JM, Thalhammer JG, Strichartz GR. Addition of sodium bicarbonate to lidocaine decreases the duration of peripheral nerve block in the rat. Anesth 2000;93:1045-1052.

34. Galindo A. pH-adjusted local anesthetics: clinical experience. Reg Anesth 1983;8:35-36.