Double-Blind Crossover Study to Compare Pain Experience During Inferior Alveolar Nerve Block Administration Using Buffered Two Percent Lidocaine in Children

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Abstract: ***Purpose:*** *Buffering of anesthetic solutions has been suggested to reduce pain on injection and onset of anesthesia. The purpose of this study was to assess the reduction in pain on injection during inferior alveolar nerve block administration in children.* ***Methods:*** *A double blind crossover study was designed where 30 six- to 12-year-old patients received two sessions of inferior alveolar nerve block scheduled one week apart. Two percent lidocaine with 1:200,000 epinephrine was given during one appointment, and a buffered solution was given during the other. Pain on injection was assessed using the sound, eye, and motor (SEM) scale, and the time to onset was assessed after gingival probing. The Heft-Parker visual analogue scale (HP-VAS) was self recorded by the patient after administration of local anesthesia.* ***Results:*** *When tested using Mann-Whitney analysis, no significant differences were found between the SEM scores (P=0.71) and HP-VAS scores (P=0.93) for the two solutions used. Student's t test was used to assess the difference in the onset of anesthesia, which was also found to be statistically insignificant (P=0.824).* ***Conclusion:*** *Buffered lidocaine did not reduce the pain on injection or time to onset of anesthesia for inferior alveolar nerve block in children.* (Pediatr Dent 2016;38(1):25-9) Received April 15, 2015 | Last Revision November 9, 2015 | Accepted November 10, 2015

KEYWORDS: BUFFERED LIDOCAINE, INFERIOR ALVEOLAR NERVE BLOCK, PEDIATRIC DENTAL ANESTHESIA

Reduction in pain is most important in pediatric dentistry, as it dictates the behavior of the patient for the rest of the appointment. Local anesthesia administration is a prerequisite for pain reduction while performing various restorative, endodontic, and minor surgical procedures in children. Ironically, administration of local anesthesia itself becomes a source of pain and anxiety for children. Pain caused during local anesthesia administration has been attributed to many factors, including the speed of injection, site of injection, and pH of the anesthetic solution.[1-3]

Commercially available local anesthetic solutions have a pH ranging from 3.5 to 5.5 and a shelf life of three to four years due to the addition of hydrochloric acid to these solutions to increase their solubility and stability.[4] This pH is much less than the physiological pH (7.35).[5] Thus, the administration of this acidic solution into the tissues leads to pain and burning sensation.

It has been suggested that alkalizing this acidic solution can lead to reduced pain caused during administration of local anesthesia. This can also reduce the time of onset of anesthesia by increasing the concentration of uncharged basic form and facilitating the penetration of lidocaine into the nerve cell.[3] Buffered lidocaine has been used in various fields of medicine and surgery to reduce the pain and onset of anesthesia.[6-11] Patients receiving buffered lidocaine experienced less pain during intradermal injections and also showed a preference for buffered solution when compared to unbuffered lidocaine.[7,8] Similar favorable results were obtained for periocular subcutaneous anesthesia[9] during local wound infiltrations[10] and for infiltration during intravenous catheter insertion.[11] There have been very few studies conducted to assess the use of buffered lidocaine for infiltration and block anesthesia during dental procedures.[3,12-15] Although these studies have shown patient preference for buffered lidocaine, the results have been heterogeneous as far as reduction in pain intensity is concerned.[12-16]

A computerized database search in PubMed® using the keywords buffered/alkalinized lidocaine and children was conducted. Twenty-seven articles were obtained, from which only eight articles pertained to the use of buffered lidocaine in children, and none were studied for dental anesthesia. The purpose of this study was to assess whether buffering of anesthetic solution reduced the pain and time to onset for inferior alveolar nerve block (**IANB**) in children.

Methods

This randomized double-blind crossover study was conducted in the Department of Pedodontics and Preventive Dentistry, ITS-Centre for Dental Studies and Research (**ITS-CDSR**), Ghaziabad, India. Approval from the Institutional Ethical Board of ITS-CDSR was obtained before conducting the research.

A pilot study on 10 patients was initially conducted, wherein the overall average standard deviation in pain scores for lidocaine and buffered lidocaine was calculated; next, the following formula was applied to calculate the sample size for a crossover design[17]:

$$ N = \frac{(Z\alpha + Z\beta)^2 \sigma^2}{2(\mu - \mu_0 - \delta)^2} = 30 $$

where α equals 0.05 (significance level), β equals 0.2 (1-power of the test), δ equals 0.05 (clinically meaningful difference), μ-μ_0 equals 0.7 (true difference between the two mean values), and σ^2 equals 4.07 (population variance).

A sample of 30 six- to 12-year-olds was selected from the outpatient Department of ITS-CDSR, Ghaziabad, India, who were indicated for at least two clinical sessions of

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operative procedures requiring inferior alveolar nerve block anesthesia. Only patients who exhibited Frankl's behavior rating grade three or four and did not require any sedation were selected. Patients with a history of medically comprising conditions, allergy to lidocaine, or any soft tissue lesion at the site of injection were excluded from the study. Patients were instructed not to consume analgesics for 24 hours before the appointment. Written informed consent was obtained from the parents before enrolling the patients in the study.

The patients were numbered in a serial fashion from one to 30. Fifteen random numbers were obtained using software (StatTrek random number generator, StatTrek.com, USA), and patients with these random numbers were selected to receive buffered lidocaine on the first appointment while others received unbuffered lidocaine. On the second appointment, which was scheduled after one week, the solutions were alternated.

Buffered lidocaine was freshly prepared by mixing sodium bicarbonate with lidocaine solution in a 1:10 ratio by volume. A 30-ml vial of commercially available two percent lidocaine hydrochloride with 1:200,000 epinephrine (Lox two percent, Neon Laboratories Ltd., Mumbia, India) was taken, and three ml of 8.4 percent sodium bicarbonate (Neon Laboratories Ltd.) was mixed into the vial to make the final preparation. The pH of the commercial solution was found to be 4.33, while the pH of the buffered solution was 7.32. Either solution, at a volume of 1.8 ml, was dispensed in a disposable two-ml syringe with a 27 gauge needle, which was used for all IANB injections. Calibration of a researcher for the sound, eye, and motor (**SEM**) scale[18] (Table 1) scale was done prior to the commencement of the study. Fifteen patients, not included in the study, were videographed during administration of IANB. Three videotapes with technical flaws were excluded, and 12 were used for standardization exercises. One researcher and one independent observer rated the SEM motor responses on these recorded videos. Next, the values for both the observers were calibrated until full agreement was achieved.

On the day of appointment, every patient was re-evaluated for all the inclusion and exclusion criteria. One researcher dispensed the syringe with the randomly selected anesthetic solution for all the patients. Two percent benzocaine gel was applied at the injection site for one minute before IANB administration. The second researcher, who was blinded to the type of solution, administered the IANB. A third researcher, who was precalibrated and blinded to the type of solution, recorded the SEM scale during anesthetic deposition from a distance of 1.5 meters. The onset of anesthesia was checked using subjective symptoms and gingival probing, which was initiated 30 seconds after injection and checked every 15 seconds until the patient reported absence of pain on probing.

The patient, who was also blinded to the type of anesthetic solution, was then asked to self assess the pain experience using Heft Parker-visual analogue scale (**HP-VAS**). The HP-VAS scale is a 170-mm scale divided into four categories. On this scale, the zero mm point indicated no pain. Mild, faint, or weak pain corresponded to marking between zero to 54 mm. Moderate pain was defined as greater than 54 mm and less than 114 mm. Strong, intense, and maximum pain was any marking above 114 mm. The patient was instructed to place a mark on the line that corresponded to his/her current assessment of pain.[19]

The data were recorded and subjected to statistical analysis using SPSS 16.0 software (IBM Corp., Armonk, N.Y., USA). Student's t test was used for analyzing the difference in onset time, and the Mann-Whitney test was used to analyze the differences in SEM and HP-VAS scores. The significance level was set at five percent. For the SEM scale score, interexaminer agreement was calculated to be 0.806.

| Table 1.	SOUND, EYE, AND MOTOR (SEM) SCORING CRITERIA[18]			
Parameter	Comfort	Mild discomfort	Moderate discomfort	Severe discomfort
Grade	1	2	3	4
Sound	No sound	Non-specific sound (probable pain)	Verbal complaint, louder sound	Verbal complaint, shouting, crying
Eye	No sign	Dilated eye without tear (anxiety sign)	Tears, sudden eye movements	Crying, tears all over the face
Motor	Relaxed body and hand status	Muscular contraction, contraction of hands	Sudden body and hand movements	Hand movements for defense, turning the head to the opposite side
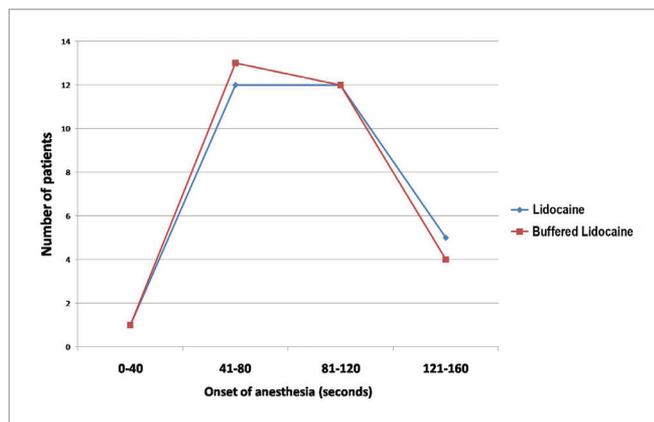
Figure 1. Variation in onset of anesthesia for both the solutions used.
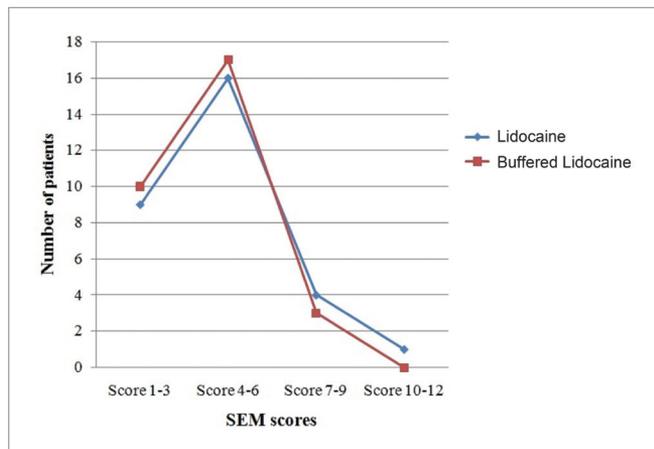

Figure 2. Number of patients with different sound, eye, and motor (SEM) scores for both types of solutions used.

Results

Thirty six- to 12-year-olds (12 males, 18 females; mean age equals 8.62 years old) participated in the study, and each received two IANB injections on two separate appointments. Thus, a total of 60 IANB injections were given.

Figure 1 shows the time to onset for both anesthetic agents. Mean (±standard deviation [**SD**]) time to onset of anesthesia for lidocaine was 86 (±27.8) seconds, while for buffered lidocaine it was 84.2 (±28.9) seconds. When tested using student's *t* test, the difference in the mean onset was not found to be statistically significant (*P*=0.824; Table 2).

Figure 2 shows the SEM scores for the patients in both the groups. Fifty-five percent of patients from both groups elicited SEM scores between four and six. Based on the results of the Mann-Whitney U test, the difference in SEM scores for the two types of anesthetic solutions was not found to be statistically significant (*P*=0.71) implying that there was no difference in the reaction to injection with either of the solutions (Table 2).

The Mann-Whitney U test results for HP-VAS scores also showed no difference between the two anesthetic solutions used (*P*=0.93), suggesting that the patients' experience with both solutions was similar (Table 2).

Table 3 shows the statistical analysis of all the parameters for both sexes and both age groups. The differences between the onset time (*P*=0.164, *P*=1.0), SEM scores (*P*=0.084, *P*=0.796) as well as HP-VAS scores (*P*=0.794, *P*=0.857) were not found to be significant for both males and females. Similarly, when the subjects were divided into two age groups (i.e., six to eight years old and nine to 12 years old), none of the age groups showed any difference between the two solutions for all the parameters tested (*P*>0.05).

Discussion

Different researchers have tried various additives like epinephrine, clonidine, dexmedetomidine, dexamethasone, and sodium bicarbonate[20] to improve the local anesthetic experience. Out of these, only epinephrine has received universal acceptance and is commercially added to local anesthetic solutions.[21] The addition of sodium bicarbonate has been suggested to raise the pH of lidocaine hydrochloride solution to around 7.4, which is almost equal to the pKa value of lidocaine. Thus, both the charged and uncharged forms will be present in equal quantity, facilitating the faster diffusion of anesthetic agent through tissue barriers leading to decreased pain on injection.[22] This can also reduce the time to onset of anesthesia by increasing the concentration of uncharged basic form and improving the penetration of lidocaine into the nerve cell.[3]

The pain caused during anesthetic deposition may manifest as a burning sensation and can be quite severe.[23,24] This pain is attributed to the increase in hydrogen ions in the local tissue environment caused by the acidity of lidocaine.[25] Adding sodium bicarbonate to the local anesthetic preparation in our study raised the pH of the formulation to 7.32 but did not result in significant reduction in pain during IANB injection in our patients. The self-reported scores were not different for both

Table 2. MEAN VALUES AND STATISTICAL RESULTS OF ONSET TIME, SOUND, EYE, AND MOTOR (SEM) SCORES AND HEFT PARKER - VISUAL ANALOGUE SCALE (HP-VAS) SCORES FOR CHILDREN RECEIVING INFERIOR ALVEOLAR NERVE BLOCK ANESTHESIA USING BUFFERED AND UNBUFFERED TWO PERCENT LIDOCAINE *

	Time to onset (seconds)		SEM scores		HP-VAS scores	
	Mean±SD	*t* test (significance 2-tailed)	Mean±SD	Mann-Whitney U test	Mean±SD	Mann-Whitney U test
Commercial unbuffered lidocaine (N=30)	86±27.8		4.84±1.8		39.5±18.2	
		P=0.824[NS]		*P*=0.71[NS]		*P*=0.93[NS]
Buffered lidocaine (N=30)	84.2±28.9		4.60±1.5		36.8±17.7	

* NS=nonsignificant, as *P*>0.05.

Table 3. AGE-WISE AND SEX-WISE STATISTICAL RESULTS OF ONSET TIME, SOUND, EYE, AND MOTOR (SEM) SCORES AND HEFT PARKER- VISUAL ANALOGUE SCALE (HP-VAS) SCORES FOR CHILDREN RECEIVING INFERIOR ALVEOLAR NERVE BLOCK ANESTHESIA USING BUFFERED AND UNBUFFERED TWO PERCENT LIDOCAINE *

	Onset time (seconds)			SEM score			HP VAS score		
	Mean (BL)	Mean (UL)	*P*-value (*t*-statistic)	Mean (BL)	Mean (UL)	*P*-value (Mann-Whitney)	Mean (BL)	Mean (UL)	*P*-value (Mann-Whitney)
Males (N=12)	95.4	91.6	0.614[NS]	4.5	5.1	0.084[NS]	37.6	34.2	0.794[NS]
Females (N=18)	80.2	80.2	1.0[NS]	4.6	4.7	0.796[NS]	42.5	41.4	0.857[NS]
Age 6-8 years (N=17)	79.4	90.0	0.076[NS]	5.1	5.3	0.496[NS]	42.9	34.9	0.178[NS]
Age 9-12 years (N=13)	86.9	86.5	0.954[NS]	3.9	4.3	0.276[NS]	37.5	43.3	0.196[NS]

* NS=nonignificant (*P*>0.05); BL=buffered lidocaine; UL=unbuffered lidocaine.

formulations, and the patients did not show a preference for any one type of solution. Similar conclusions were drawn by Whitcomb et al. and Balasco and Hobeich et al., who found that adding sodium bicarbonate did not reduce the pain on injection during either IANB or maxillary infiltration injections.[12-14]

However, a number of authors have reported reduction in pain on injection following buffering of lidocaine solution.[7,10,22] Malamed et al. reported more comfortable injection with alkalinized two percent lidocaine when used for IANB in adults.[3] Kashyap et al. also found alkalinized local anesthetic to be efficacious in reducing pain on injection when tested for inferior alveolar, lingual, and long buccal nerve blocks.[15]

An extensive review of the literature found that there was a paucity of studies evaluating the use of buffered lidocaine in children. Two studies by Richtsmeier et al. and Fatovich et al. that focused on children found no difference in the pain intensity between buffered and unbuffered lidocaine solution during skin infiltrations.[26,27] In the current study, we selected six- to 12-year-old children, as we do not give nerve blocks and use only infiltration anesthesia in children younger than six years old at our institution (ITS-CDSR, Ghaziabad).

Lugo Janer et al. suggested it was unlikely that the pain of infiltration was a simple function of the pH of the anesthetic solution.[28] Zaic et al. are of the opinion that diluting the anesthetic solution causes reduced pain.[29] It has been demonstrated that saline-modified anesthetic solution provides more comfort on injection than either buffered or unmodified lidocaine solution.[29,30]

The time to onset of anesthesia after IANB was found to be similar for both buffered and unbuffered lidocaine solution in the current study. Similarly, faster onset with buffering could not be demonstrated by Whitcomb et al.[12] and Hobeich et al.[13] for IANB and maxillary infiltrations, respectively. Although faster onset of anesthesia has been reported by Malamed et al.[3] for IANB and by Kashyap et al.[20] for inferior alveolar, lingual, and long buccal nerve blocks, whether these differences provide clinically meaningful results is still not clear.[20] Chow et al. had also found that alkalinizing a local anesthetic did not quicken the onset of a regional upper limb nerve blockade.[6]

As sodium bicarbonate is routinely used for intravenous infusions, its addition to anesthetic solutions is not associated with any adverse effects. None of our patients showed any adverse reactions to buffered lidocaine. Previous studies have also reported an absence of adverse events or toxicity in relation to buffered lidocaine, with the exception of one isolated case, which reported hematoma formation.[16]

The long-term physical and chemical stability of buffered lidocaine is unclear. Although some studies have shown that solution of buffered lidocaine in glass vials can be stored for up to seven days[31] and even up to 91 days,[32] freshly prepared buffered lidocaine solution was used in this study to eliminate any disparities in the results.

Conclusions

Based on this study's results, the following conclusions can be made:

1. Buffered two percent lidocaine with 1:200,000 epinephrine did not reduce the pain on injection during inferior alveolar nerve block in children compared with the unbuffered form.

2. Buffered lidocaine did not provide significant clinical advantage in relation to the onset time for inferior alveolar nerve blocks in children compared with the unbuffered form.

3. The self-assessed experience of the children during the injection was found to be similar with both the solutions.

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