Original Research
Pharmacology

Buffered 2% articaine in buccal infiltration of mandibular molars: a randomized triple-blind clinical trial

Sandro Alexander Lévano LOAYZA[a]
Thomas BARBIN[a]
Victor Augusto Benedicto dos SANTOS[a]
Francisco Carlos GROPPO[a]
Klinger de Souza AMORIM[a]
Daniel Felipe Fernandes PAIVA[a]
Sidney Raimundo FIGUEROBA[a]

[a]Universidade Estadual de Campinas – Unicamp, Piracicaba Dental School, Department of Biosciences, Piracicaba, SP, Brazil.

Abstract: This crossover study aimed to compare the anesthetic effects of buffered 2% articaine with 1:200,000 epinephrine with that of non-buffered 4% articaine with 1:200,000 epinephrine. Forty-seven volunteers were administered two doses of anesthesia in the buccal region of the second mandibular molars in two sessions using 1.8 mL of different local anesthetic solutions. The onset time and duration of pulp anesthesia, soft tissue pressure pain threshold, and the score of pain on puncture and burning during injection were evaluated. The operator, volunteers, and statistician were blinded. There were no significant differences in the parameters: onset of soft tissue anesthesia ($p = 0.80$), duration of soft tissue anesthesia ($p = 0.10$), onset of pulpal anesthesia in the second ($p = 0.28$) and first molars ($p = 0.45$), duration of pulp anesthesia of the second ($p = 0.60$) and first molars ($p = 0.30$), pain during puncture ($p = 0.82$) and injection ($p = 0.80$). No significant adverse events were observed. Buffered 2% articaine with 1:200,000 epinephrine did not differ from non-buffered 4% articaine with 1:200,000 epinephrine considering anesthetic success, safety, onset, duration of anesthesia, and pain on injection.

Keywords: Carticaine; Anesthesia, Local; Anesthetics, Local; Sodium Bicarbonate.

Declaration of Interests: The authors certify that they have no commercial or associative interest that represents a conflict of interest in connection with the manuscript.

Corresponding Author:
Sidney Raimundo Figueroba
E-mail: sfigueroba@uol.com.br

https://doi.org/10.1590/1807-3107bor-2023.vol37.0132

Submitted: April 3, 2023
Accepted for publication: September 13, 2023
Last revision: October 16, 2023

Introduction

Pain management remains one of the biggest issues in dentistry.[1] The most common pain originates inside the tooth, in the dental pulp, and can be triggered by several stimuli.[2] Over the years, a wide spectrum of local anesthetics has been developed to control pain, allowing selection and use based on individual patient needs and procedure type.[3]

Local anesthetics are injectable solutions that provide analgesia anywhere in the body by blocking voltage-gated sodium channels.[4] These hydrophilic molecules are unable to penetrate the neuron and must be converted to a lipophilic structure to facilitate their diffusion into tissues at a physiological pH of 7.4, which is considerably lower than the pKa of local anesthetics (pKa of articaine = 7.8), causing a delay in onset of action[5]. Epinephrine is added to the local anesthetic to provide blood vessel constriction at the injection site and prolong the duration of anesthesia.[6]

The combination of local anesthetic and vasoconstrictor has a pH of ~3.5.[7] Vasoconstrictors are much more susceptible to degradation, so antioxidants such as metabisulfite are added to the anesthetic solution,[8] but injecting acidic solutions can cause adverse effects.[9] The advantages of buffered local anesthetics have been widely reported, the primary ones being the reduction of pain and burning on injection, reduction of onset time, and greater anesthetic success.[7,8,10-13] Most studies reporting local anesthetic buffering include 2% lidocaine with 1:100,000 epinephrine and its buffered form.[8,12]

This study compared 4% articaine with 1:200,000 epinephrine with buffered 2% articaine with 1:200,000 epinephrine using the infiltrative anesthetic technique. We hypothesized that the buffered 2% formulation is an alternative to the non-buffered 4% formulation.

Methodology

Ethical review and informed consent

This study was a controlled, randomized, crossover, split-mouth, and triple-blind clinical trial. This study was approved by the Research Ethics Committee of the Piracicaba Dental School (FOP/UNICAMP) (number: 4,635,226) and registered in the Brazilian Registry of Clinical Research (RBR-6fsprpc). All the participants signed a written informed consent form.

Sample calculation and selection

Considering the results of the study by Amorim et al.[8] and the mean ± standard deviation of pain during injection of groups A (1 ± 1.8) and B (2.5 ± 2) on the visual analog scale (VAS) in centimeters (cm), the required sample size was at least 42 volunteers to attain a statistical power of 95% with a significance level of 5% and an effect size d of 0.81 (GPower 3.1), since it is a crossover study with an equal proportion for both samples (BioEstat 5.0 test).

Study design

The study sample consisted of undergraduate students from the second to the fifth year and graduate studies of both sexes, aged between 18 and 40 years old, all enrolled at the Piracicaba Dental School, who did not require dental intervention. The simple randomization was performed using Microsoft Office Excel 2016 Professional Plus. Only participants who met the following criteria were included: healthy individuals, previous experience with local anesthesia, no history of complications from local anesthesia, lower molars on both sides (absence of restorations), and responsive to the electrical stimulus "Pulp Tester" (PTE). Patients with the following conditions were excluded: pregnant and lactating women with systemic involvement that would contraindicate anesthesia. There was no modification of the research protocol with respect to eligibility criteria, outcomes, or analysis methodology and there was no sample loss in any selection step. All the participants were followed up as shown in Figure 1.

Anesthetic and materials used

The following preparations were used: 4% articaine hydrochloride with 1:100,000 and 1:200,000 epinephrine (DFL- Indústria e Comércio S.A., Rio de Janeiro, Brazil), Duflex carpule syringe (SSW White Artigos Dentários Ltda, Rio de Janeiro, RJ), and disposable short-jets 25 mm needle, 30G (GN Injecta Ind. Com. Mat. Med. Cirurg. Odont. e Descart. Ltda – Ibiporã, Brazil), 8.4% Samtec sodium bicarbonate injectable solution and Samtec distilled water for injection (Samtec Biotecnologia Ltda , Ribeirão Preto, Brazil). An electrical impulse emitting device called "Vitality Scanner 2006 Electronic Pulp Tester" (Analytic Technology, Redmond, USA) and SorriI Stesiometer Kit (Sorri-Bauru, Bauru, Brazil) were used.

Preparation and blinding of anesthetic solutions

To obtain buffered articaine hydrochloride, the 8.4% sodium bicarbonate ampoule was diluted to a working concentration of 1.344%, which then replaced 0.9 mL of the anesthetic solution in a 4% articaine cartridge with 1:100,000 epinephrine using a 1 mL disposable syringe. A cartridge of 1.8 mL anesthetic solution with 2% articaine, 1:200,000 epinephrine, and 0.67% sodium bicarbonate (solution A) was used. Although previous studies used a concentration of 0.84% sodium bicarbonate,[8,14] the concentration

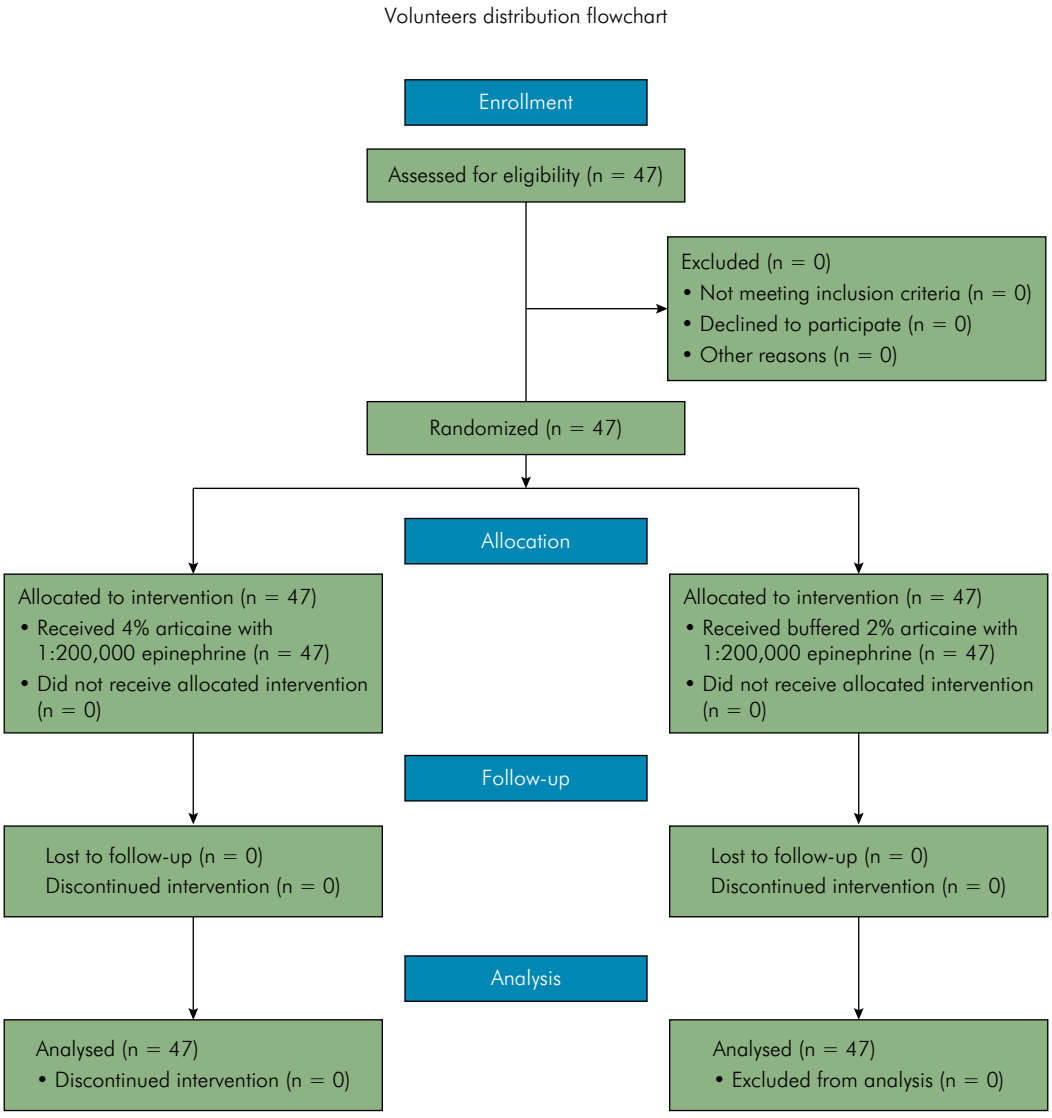

Figure 1. Flowchart of volunteer distribution.

of sodium bicarbonate was adapted to 0.67% to reach a final pH of 7.4. Solutions were prepared individually under aseptic conditions in a laminar flow hood with sterile and apyrogenic material, occurring only while performing the procedure to maintain stable content. A single researcher prepared the solutions in an place separate from the patient and the researcher who was applying the injection. The two solutions (commercial and buffered) were identified only by codes A and B, without any commercial identification, and were delivered directly to the researcher who performed the anesthesia. A commercial anesthetic solution of 4% articaine with 1:200,000 epinephrine (solution B) was used as a control.

Anesthetic procedure and assessment of anesthetic action

The interval between anesthesia sessions for each volunteer was at least one week to minimize the painful sensitization by the participants. The volume injected in each session was 1.8 mL. The anesthetic injection rate was 1 mL/min[15] and topical anesthesia was not used.

In the first session, the participants randomly received anesthesia with solution A (2% articaine

buffered at 1:200,000) or solution B administered by the infiltrative technique (buccal region of the mandibular second molar). In the second session, the remaining solution was administered on the opposite side using the same technique. Although the anesthetic was injected in the buccal region of the second molars (both sides), the first molars were evaluated to evaluate the extent of anesthesia.

Immediately after the anesthesia procedure, the evaluation of anesthetic onset was started with PTE, which causes a sensation described as tingling, pulsation, vibration, or pain, and the volunteers were instructed to raise their hands when they felt any of those sensations. The test was repeated for the following 30 s and then every minute until the absence of sensation with the application of the maximum stimulus of the PTE.

After no response was felt, the test was repeated every 10 min until a complete return to the baseline response threshold. Pulp onset time was defined as the period between the end of the anesthetic injection until no perception of the stimulus was felt by the volunteer at maximum intensity of the device (80 UI). The duration of pulp anesthesia was recorded as the time between the beginning of anesthesia and immediately before two responses from the electrical stimulus. The region of the anesthetized lower molar, the pulp, and the buccal and lingual gingiva were tested every 10 min.

Before anesthesia, the baseline threshold to painful stimuli in the buccal and lingual gingiva of the lower molar was determined and quantified as the pressure pain threshold (PPT). To evaluate the beginning and duration of anesthetic action in the soft tissues, an esthesiometer kit was used, which consisted of nylon filaments calibrated with a force of 300 gf applied against the gingiva until deflection. This was followed by the observation of any painful sensation by the volunteer. At the end of each session, the participants were asked to rate the pain after the anesthetic injection using the visual analog scale (VAS). Volunteers were instructed to mark their pain level on a vertical line anchored by 0, indicating no pain, in one end and 10, indicating the worst possible pain, in the other end. The distance between point 0 and the demarcation made by the volunteer was considered the pain intensity expressed as a numerical value. Subsequently, the volunteers completed a post-anesthesia questionnaire regarding discomfort and adverse events during the first and second sessions.

pH stability of the anesthetics

The pH of the solutions was measured using a pH meter (Labmeter, model PH2Os) in two groups, one at room temperature (25°C) and one stored in a refrigerator (4°C). Each group contained in triplicate: 4% articaine hydrochloride with 1:100,000 epinephrine, 4% articaine hydrochloride with 1:200,000 epinephrine, 2% articaine with 1:200,000 epinephrine, and 0.672% sodium bicarbonate. The pH of the solutions was also measured using a pH meter (Labmeter, model PH2), using 54 cartridges of the three local anesthetics, depending on the storage temperature for 24 h (0, 2, 4, 6, 8, 12, and 24 h), repeated for three days.

Data analysis

The data were blindly coded, grouped, and numerically analyzed using GraphPad Prism 7.0. The significance level was set at 5%. Data were subjected to distribution analysis (Shapiro-Wilk's test) and homoscedasticity (Bartlett test). Comparisons of anesthesia onset and duration between the two anesthetic formulations were assessed non-parametrically using the Wilcoxon test. Two-way ANOVA and Tukey's post-hoc tests were used to compare the pH of the solutions.

Results

After the data analysis, the researchers were informed that buffered 2% articaine corresponded to substance A and commercial 4% articaine to substance B. The study involved 47 volunteers distributed according to the Table 1. The recruitment period was from October 22, 2021 to January 14, 2022 and the assay from October 22, 2021 to January 21, 2022, following up for one week after each intervention. The sample was statistically calculated and representative of the population, balanced for gender and ethnicity.

The pH of the buffered solution was significantly higher ($p < 0.0001$) compared to the other solutions at

Table 1. Demographic characteristics of volunteers.

Variable	n	Age	Weight	Height
		mean (SD)	mean (SD)	mean (SD)
Male	16	24.2 (3.29)	78.4 (20.2)	1.75 (0.075)
Female	31	24.8 (4.48)	60.2 (9.72)	1.63 (0.0808)

SD: standard deviation.

Table 2. Onset time for gingival and pulpal anesthesia (minutes) and pain variability observed after application of the two solutions.

Variable	Sol A			Sol B			Wilcoxon's p
	1st quartile	median	3rd quartile	1st quartile	median	3rd quartile	
Onset time for gingival and pulpal anesthesia (minutes)							
Buccal*	0.5	0.5	1	0.5	0.5	1	0.8
Lingual*	1	1	2	0.5	0.5	0.5	NA
Teeth 37/47*	1	2	3	1	2	3	0.28
Teeth 36/46*	1.5	3	4.5	1	2	4	0.45
Pain (VAS)							
During puncture**	0	0.4	1.85	0.2	0.5	1.65	0.82
During Injection	0	0.1	1.2	0	0.6	1.35	0.8

*According to anesthesia latencies time; **according to Visual Analogic Scale pain score.

all evaluated time points. Conversely, the pH of the 4% articaine with 1:200,000 epinephrine solution was consistently lower than the others. The mean pH values for the 4% articaine with 1:200,000 epinephrine, 4% articaine with 1:100,000 epinephrine, and 2% articaine with 1:200,000 epinephrine solutions were 3.32, 3.57, and 7.35, respectively. The comparison between samples at room temperature (25 ± 2°C) and at 4°C showed no statistically significant differences in any time-points for articaine with 1:200,000 epinephrine and for buffered articaine.

Since there were no significant differences between the latencies of buccal gingiva anesthesia for solutions A and B, it was not possible to estimate the difference between the groups for lingual-gingival onset due to the small number of anesthetized individuals (Table 2). Pulpal anesthesia onset for both groups for teeth 37/47 and 36/46 is shown in Table 2. No statistically significant differences were observed between latencies of pulp anesthesia for solution A and B. The latencies of pulp anesthesia of teeth 36/46 obtained with solutions A and B did not differ significantly. In addition, Table 2 shows the level of pain measured using the VAS during puncture and injection. There were no statistically significant differences (Wilcoxon's test) in pain during puncture ($p = 0.82$) and injection between the groups.

The duration of buccal and lingual gingiva anesthesia is shown in Figure 2a. Non-anesthetized subjects were considered to have "zero" minutes of anesthesia. There were no statistically significant differences (Wilcoxon's test, $p = 0.10$) between the duration of buccal gingiva anesthesia for solutions A (45, 30–65 min) and B (50, 35–75 min). The duration of lingual-gingival anesthesia for solutions A and B had a median equal to zero. Quartiles were also equal to zero, not significantly different from each other (Wilcoxon's test, $p = 0.28$).

Figure 2b shows the buccal and lingual gingiva anesthesia over time induced by the two solutions. The log-rank test showed that the success of buccal gingiva anesthesia was higher ($p < 0.0001$) over time for solution B, although ~50% of the subjects were anesthetized for up to 60 min with both solutions. There were no statistically significant differences (log-rank, $p = 0.42$) between the two solutions for

lingual gingiva anesthesia. Therefore, the difference in success rate of both solutions was negligible.

The duration of pulpal anesthesia as a function of anesthetized teeth and groups is shown in Figure 3a. Non-anesthetized individuals were considered to have "zero" minutes of anesthesia. There were no statistically significant differences (Wilcoxon's test, p = 0.60) between the length of pulp anesthesia (median, 1st–3rd quartiles) by solutions A (20, 10–40 min) and B (20, 10–50 min) in the mandibular second molars. The duration (median, 1st– 3rd quartiles) of pulpal anesthesia also did not differ (Wilcoxon's test, p = 0.30) in the first molars between solutions A (0.0–10 minutes) and B (0.0–10 minutes).

The success of pulpal anesthesia over time for both the first and second molars is shown in Figure 3b.

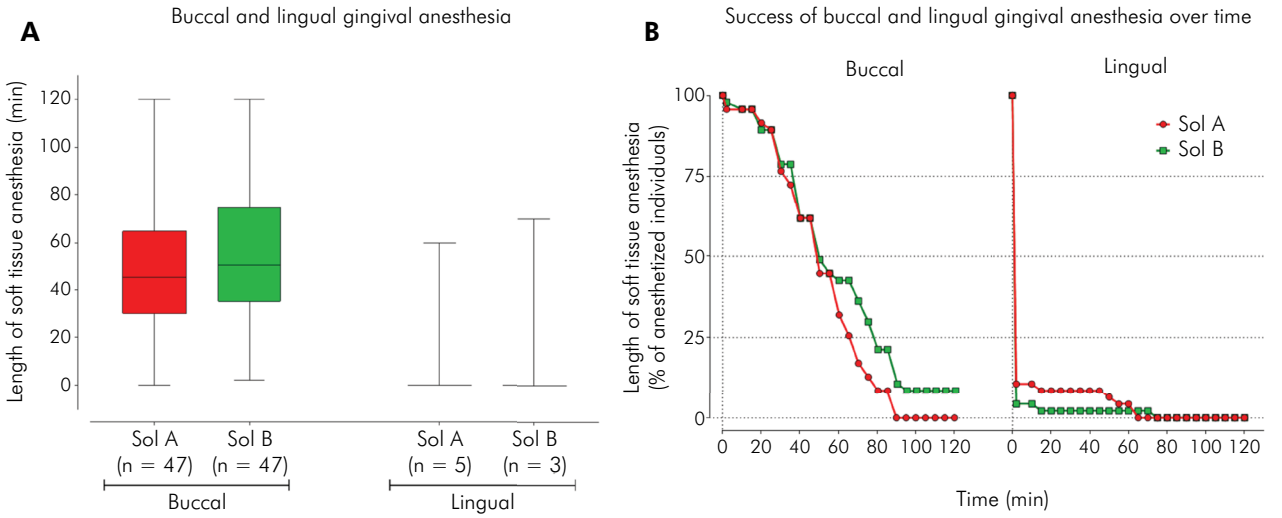

Figure 2. Soft tissue anesthesia duration and success in minutes. a. Buccal and lingual gingiva anesthesia of the groups. Central line = median; box = 1st and 3rd quartiles; whiskers = maximum and minimum values. b. Success (in %) of buccal and lingual gingiva anesthesia over time of the groups. The "n" refers only to the number of cases that had some effect (anesthesia).

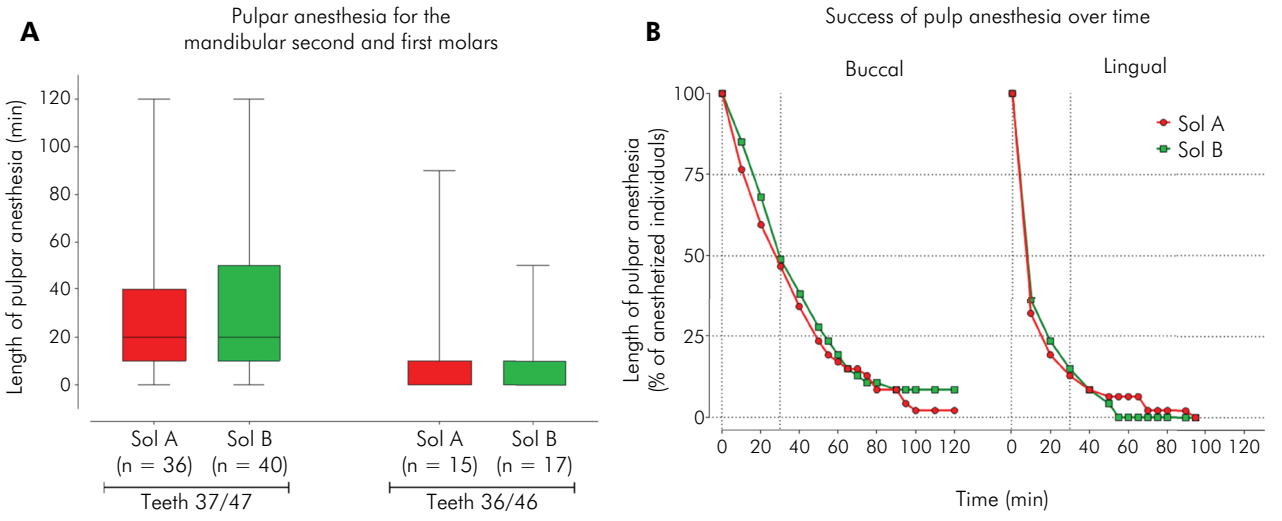

Figure 3. Duration and success of pulpal anesthesia in minutes. a. Pulpal anesthesia for the mandibular second and first molars of the groups. Central line = median; box = 1st and 3rd quartiles; whiskers = maximum and minimum values. b. Success (in %) of pulp anesthesia over time of the groups. The "n" refers only to the number of cases that had some effect (anesthesia).

Table 3. Absolute frequencies of adverse events observed after application of the two solutions.

Variables	Discomfort or pain after the end of the effect	Cold sore, edema, or gum pain	Swelling in test region	Total
Both	15	1	1	17
Solution A	13	1	3	17
Solution B	8	5	1	14
None	7	36	38	81
p-value (McNemar)	0.38	0.22	0.63	0.72

The log-rank test showed that the success of pulpal anesthesia of second molars did not differ ($p = 0.14$) between the two solutions over time. Anesthesia success for ~50% of the subjects was 30 minutes for both solutions. The success rate of pulpal anesthesia on first molars was between 13 and 15% at 30 min for both solutions, although the test was significant for solution A (log-rank, $p = 0.0053$).

The number of participants with no adverse events was higher than participants with adverse events (MacNemar test, $p > 0.0001$). There were no statistically significant differences ($p > 0.05$) between the two solutions for any of the events listed in Table 3.

Discussion

No serious adverse effects such as discomfort or pain after the end of the effect, canker soreness, swelling or pain in the gum, and swelling in the test region were observed in this study. We found no differences in the onset time between solutions, either in soft tissue or pulp, which is in concordance with Amorim et al.,[8] who also used articaine as a local anesthetic. However, Kattan et al.[10] show through a systematic review that there are significant differences between buffered and non-buffered local anesthetic even when lidocaine is used, with buffered anesthetic being more effective than non-buffered ones when used for mandibular or maxillary anesthesia in teeth with pulpal involvement.

A study comparing the use of 4% and 2% non-buffered articaine found no difference in onset time in soft tissues.[16,17] Although there are reports in the literature that the buffering of lidocaine accelerates the onset of anesthesia,[12,18,19] other studies did not observe differences in the onset time between the two,[20] as reported by Whitcomb et al., the failure observed must probably be due to the anesthetic technique used, the use of lidocaine hydrochloride, or the extent of the observed area.[21]

In this study, there were no differences in pulp and soft tissue onset times when buffered articaine was compared with the commercial solution. In addition, the action of articaine was maintained even with a 50% reduction in its concentration. There was no difference in soft tissues of 50% of the volunteers for 60 min regarding the extent of anesthesia. After this period, non-buffered articaine was better in 4% of the cases, which corroborates the study by Senes et al.,[16] who also found no significant difference in the extent of soft tissue anesthesia between 2 and 4% articaine using the inferior alveolar nerve blockage technique.

There was no difference over time regarding the duration of pulpal anesthesia. This result is similar to the study by Amorim et al.,[8] where the extent of anesthesia in soft tissue and pulp with the same concentrations of articaine in maxillary canines using the infiltrative technique did not differ. Hintze and Paessler,[22] using maxillary infiltrations with 2 and 4% articaine without buffering, found a shorter duration for 2% articaine than for 4% articaine.

Some studies have reported that buffered local anesthetic is less painful when injected because the pH of the solution is closer to physiological pH.[8,14,23] However, based on the VAS, there was no difference between buffered 2% articaine and 4% non-buffered articaine in pain at needle puncture and during injection.

Studies suggest that injection pain is not caused by the anesthetic but by the condition of the injection site

and technique.[20] Non-buffered articaine at its normal concentration of 4% did not differ in all analyzed variables compared with a solution of buffered articaine at 2% with 0.84% sodium bicarbonate, showing the same properties as the commercial anesthetic at a lower concentration.

Among the reported effects are discomfort or pain after the end of the effect, aphthous ulcers, edema or gum pain, and swelling in the test region. In addition, there was no difference between the tested solutions because of the low incidence of adverse effects. In a study carried out by Amorim et al,[8] one-third of the volunteers reported discomfort at the injection site and swelling that started after infiltration of buffered 2% articaine solution that lasted a maximum of 3 days. Studies comparing the level of pain in the maxilla and mandible show that stimuli in the anterior segment of the maxilla elicit a higher level of pain than in the posterior segment of the mandible,[24–26] which may have contributed to a lower level of pain when injecting 2% buffered articaine.

The adverse effects found in this study may be related to the higher pH, with an average of 8.14. A final pH above 7.6 after buffering can make the solution hypertonic and cause local edema.[15] Another study using an anesthetic formulation of lidocaine with a pH of 7.9 showed effects such as tissue damage and cellulitis.[27] When using a buffered lidocaine formulation with pH 7.5, no irritant effect was observed after injection.[21]

There were no changes in anesthetic stability of the either at room temperature or at 4°C. In this study, at time zero, anesthetic cartridges of 4% articaine with 1:200,000 epinephrine showed a lower pH than the solution containing 1:100,000 epinephrine, a result similar to the study by Amorim et al.[8] Commercial cartridges of local anesthetics containing epinephrine are up to 1000 times more acidic than physiological pH.[10] This pH reduction is intended to extend the shelf life of the solution and prevent early oxidation of the adrenaline.[18]

The main limitation of the present study was the use of a syringe for the buffering method, which is not very precise. The study was conducted in volunteers and the results may not be consistent with real clinical practice.

Conclusion

The buffered 2% articaine with 1:200,000 epinephrine solution did not differ from non-buffered 4% articaine with 1:200,000 epinephrine regarding anesthesia success, safety, onset, duration of anesthesia, and injection pain. Buffered 2% articaine may be a clinical alternative to 4% articaine for mandibular infiltrations.

Acknowledgements

This study was partially supported by a CNPq (National Board for Scientific and Technological Development) grant, protocol # nº88887.597593/2021-00.

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