

Epinephrine Concentration (1:100,000 or 1:200,000) Does Not Affect the Clinical Efficacy of 4% Articaine for Lower Third Molar Removal: A Double-Blind, Randomized, Crossover Study

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Purpose: This study compared the use of 4% articaine in association with 1:100,000 (10 µg/mL; A100) or 1:200,000 (5 µg/mL; A200) epinephrine in lower third molar removal.

Patients and Methods: Fifty healthy volunteers underwent removal of symmetrically positioned lower third molars, in 2 separate appointments, under local anesthesia with either A100 or A200, in a double-blind, randomized, and crossed manner. Latency, duration of postoperative analgesia, duration of anesthetic action on soft tissues, intraoperative bleeding, and hemodynamic parameters were evaluated.

Results: A100 and A200 presented very similar latency (1.64 ± 0.08 and 1.58 ± 0.08 minutes, respectively; $P > .05$). Identical volumes of both anesthetic solutions were used: 2.7 mL = 108 mg of articaine plus 27 µg (A100) or 13.5 µg (A200) of epinephrine. The 2 solutions provided similar duration of postoperative analgesia regardless of bone removal (around 200 minutes; $P > .05$). The 2 solutions also had a similar duration of anesthetic action on soft tissues (around 250 minutes; $P > .05$). The surgeon's rating of intraoperative bleeding was considered very close to minimal. Transient changes in hemodynamic parameters were observed, but these were neither clinically significant nor attributable to the type of anesthetic used ($P > .05$).

Conclusions: An epinephrine concentration of 1:100,000 or 1:200,000 in 4% articaine solution does not affect the clinical efficacy of this local anesthetic. It is possible to successfully use the 4% articaine formulation with a lower concentration of epinephrine (1:200,000 or 5 µg/mL) for lower third molar extraction with or without bone removal.

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A number of local anesthetic agents are available that provide rapid onset of surgical anesthesia and adequate duration of anesthetic effect.¹ Vasoconstrictors have been added to local anesthetic solutions to increase the quality and duration of anesthesia, avoid excessive intraoperative bleeding, and decrease systemic toxicity. Epinephrine has been widely used for this purpose in several countries.²⁻⁴

Whereas many studies exist on the most commonly used local anesthetics in lower third molar surgeries (eg, lidocaine, mepivacaine, bupivacaine),⁵⁻¹⁰ the dental literature on the use of articaine for this kind of surgery is limited.¹⁰⁻¹⁵ In a previous work,¹³ we demonstrated that 4% articaine with 1:100,000 epinephrine provided a longer period of analgesia and a tendency for a longer period of anesthesia on soft tissues compared with 2% mepivacaine with 1:100,000 epinephrine. Moreover, neither agent influenced hemodynamic parameters (arterial blood pressure, heart rate, and oxygen saturation) during these surgeries.¹³

Taking into account our findings¹³ and the paucity of studies comparing 4% articaine with 1:100,000 and 1:200,000 epinephrine,¹⁴⁻¹⁹ particularly in terms of postoperative pain and intraoperative bleeding control, the present study was undertaken to assess the clinical efficacy of 4% articaine in association with 2 different concentrations of epinephrine, 1:100,000 (A100) and 1:200,000 (A200), in a model of surgical removal of symmetrically positioned lower third molars.¹³

Patients and Methods

The Ethics Committee of our institution approved the study protocol (process 73/2005). All patients provided written informed consent during the pre-treatment screening period before any study procedures were performed.

The study population comprised 50 patients age 18 years and older with 2 impacted lower third molars in similar positions, as observed on panoramic radiograph. Eligibility and exclusion criteria were as described previously.¹³

This was a double-blind study; that is, neither the surgeon nor the patients were aware of the local anesthetic being used at the 2 different appointments. Each patient required surgical treatment with the same magnitude of trauma on opposite sides of the mandibular jaw, which was performed in 2 visits scheduled 1 to 2 months apart.¹³ For local anesthesia, in the first appointment, the patients randomly received A100 or A200. In the second appointment, the local anesthetic not used previously was administered in a crossed manner. The same surgeon performed all surgeries and postoperative controls.

The patients received a regional anesthetic blockade of buccal, lingual, and inferior alveolar nerves with 1.8 mL of the anesthetic solution. Five minutes after this initial injection (anesthesia of inferior lip was already achieved), an additional 0.9 mL of the same anesthetic was infiltrated into the mucosa to guarantee hemostasis and anesthesia of the site. Immediately after this infiltration, removal of the lower third molars was initiated following standard surgical technique.¹³

For postoperative pain control, all patients received piroxicam 20 mg, administered once daily for 4 days. Rescue analgesic medication (paracetamol 750 mg) was available to all patients as needed throughout the study. The patients were instructed to not interrupt the use of the anti-inflammatory agent, even if they had taken rescue analgesic medication.¹³

The following parameters were assessed:

1. Total volume of anesthetic solution used during the surgery (in mL).
2. Onset of anesthetic agent action (latency, in minutes), as determined by the loss of sensibility of the inferior lip, the corresponding half of the tongue, and the mucosa as reported by the patient.¹³
3. Quality of the anesthesia provided by the local anesthetic during the surgery and evaluated by the surgeon, according to a modification of the method described by Sisk.²⁰ This was based on a 3-point category rating scale: 1 = no discomfort reported by the patient during the surgery; 2 = any discomfort reported by patient during the surgery, without the need for additional anesthesia; and 3 = any discomfort reported by patient during the surgery, with the need of additional anesthesia.
4. Difficulty of the surgery according to the surgical trauma, rated by the surgeon at the completion of each extraction, according to a 3-point category rating scale: 1 = easy; 2 = normal; 3 = complicated.²⁰
5. Duration of the surgery (in minutes), corresponding to the period between the first incision and the final suture.¹³
6. Duration of postoperative analgesia (in minutes), as determined by the difference between the time at the end of the surgery and that at ingestion of the first piroxicam capsule for pain relief.¹³
7. Duration of postoperative anesthesia, represented by the lack of sensibility of the mucosa, tongue, and inferior lip. Patients recorded the moment that the anesthetic had worn off.¹³
8. Intraoperative bleeding, rated by the surgeon according to a 3-point category rating scale

Table 1. OBJECTIVE AND SUBJECTIVE PARAMETERS RECORDED IN PATIENTS WHO UNDERWENT SURGICAL REMOVAL OF BOTH LOWER THIRD MOLARS, IN 2 DIFFERENT APPOINTMENTS, UNDER LOCAL ANESTHESIA WITH 4% ARTICAIN PLUS 1:100,000 OR 1:200,000 EPINEPHRINE USED IN A DOUBLE-BLIND, RANDOMIZED, CROSSED MANNER

Parameter	4% Articaine With 1:100,000 Epinephrine		4% Articaine With 1:200,000 Epinephrine	
	Without Osteotomy (n = 27)	With Osteotomy (n = 23)	Without Osteotomy (n = 27)	With Osteotomy (n = 23)
Quality of anesthesia	1.00 ± 0.00 ^a	1.04 ± 0.04 ^a	1.11 ± 0.08 ^a	1.17 ± 0.08 ^a
Difficulty of surgery	1.15 ± 0.07 ^b	2.26 ± 0.11 ^a	1.11 ± 0.06 ^b	2.22 ± 0.15 ^a
Duration of surgery (min)	10.31 ± 0.50 ^b	22.20 ± 2.12 ^a	10.28 ± 0.73 ^b	19.74 ± 1.69 ^a
Duration of postoperative analgesia (min)	200.69 ± 22.80 ^a	172.98 ± 27.00 ^a	200.95 ± 20.40 ^a	196.25 ± 18.60 ^a
Duration of postoperative anesthesia (min)	271.58 ± 19.20 ^a	242.45 ± 15.00 ^a	253.47 ± 22.20 ^a	240.83 ± 16.20 ^a

NOTE: Data are expressed as mean ± SEM. For experimental conditions, see Patients and Methods. Distinct lowercase letters indicate statistically significant difference in the same line ($P < .05$).

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- (1 = minimal bleeding; 2 = normal bleeding; 3 = excessive bleeding),²⁰ immediately after the following steps: injection of the first cartridge of articaine, tissue incision, flap reflection, bone removal (when this procedure was necessary), tooth extraction, cleaning of the operated site, and completion of suturing.
9. Incidence, type, and severity of adverse reactions observed by the surgeon or reported by the patient (eg, nervousness, dizziness, tremors, blurred eyes, or any indication of effects on the cardiovascular and central nervous systems) during the surgery and the first postoperative hour.¹³ Patients were also asked to take note of any reaction occurring after their discharge from the clinic and before their return for suture removal (postoperative day 7).
 10. Systolic, diastolic, and mean arterial pressure; heart rate; and oxygen saturation, measured before the surgery and immediately after the steps described in item 8. All of the measurements were automated and noninvasive, performed with a device for monitoring hemodynamic parameters (DX2010; Dixtal Biomédica Indústria Com Ltda, Marília/SP, Brazil).¹³

Paired *t* tests were used to compare the duration of surgeries and latency. Quantitative measures were submitted to statistical analysis using analysis of variance, followed by Tukey's test for multiple comparisons. Nonparametric measures, with abnormal distribution or expressed by scores, were analyzed by Wilcoxon (for repetitive or dependent measures) or Mann-Whitney (for independent measures) tests. Statistical significance was established at 5%. The results are presented as mean ± standard error of the mean (SEM).

Results

The study group comprised 50 healthy volunteers (18 males and 32 females) with a mean age of 21.8 ± 0.63 years (range, 18 to 40 years). The group was divided into 2 categories: surgeries requiring osteotomy (23 patients) and surgeries not requiring osteotomy (27 patients). All of the results except latency are expressed according to these 2 categories.

No statistically significant difference between the latency of A100 (1.64 ± 0.08 minutes) and A200 (1.58 ± 0.08 minutes) was found ($P > .05$).

The surgeon's rating of quality of anesthesia indicated that both local anesthetics were successful, irrespective of the necessity of bone removal ($P > .05$, Table 1). The mean scores attributed to quality of anesthesia were very close to 1, and a score of 3 was not attributed to any surgery, strongly suggesting that patients felt no discomfort during all of the surgeries with A100 or A200 administered at the same volume (2.7 mL).

No statistically significant difference in the surgeon's mean rating of surgical difficulty between either surgery in the same patient was observed, irrespective of the anesthetic agent used ($P > .05$). However, surgeries requiring bone removal were rated more difficult compared with surgeries not involving bone removal ($P < .05$; Table 1).

The mean duration of surgeries, postoperative analgesia, and postoperative anesthesia are also shown in Table 1. The surgeries with osteotomy, rated by the surgeon as the most traumatic operations, took twice as long as those without osteotomy ($P < .05$). The kind of local anesthetic used did not influence the duration of the surgeries ($P > .05$), and no interaction was found between the kind of surgery and the kind of anesthetic used ($P > .05$). The duration of postoperative analgesia (around 200

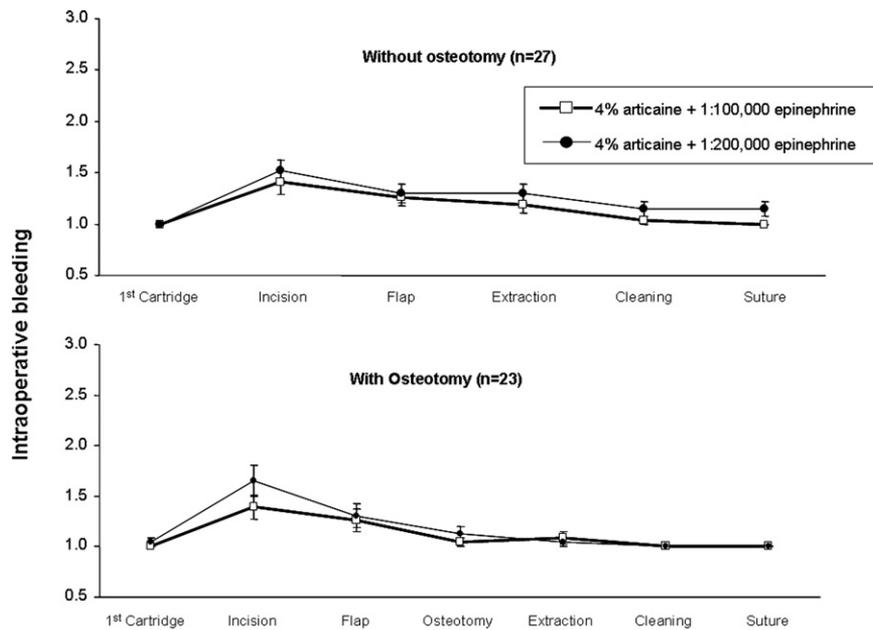


FIGURE 1. Surgeon's rating of intraoperative bleeding (1 = minimal bleeding; 2 = normal bleeding; 3 = excessive bleeding) in patients who underwent surgical removal of both lower third molars, in 2 different appointments, under local anesthesia with A100 or A200 used in a double-blind, randomized, and crossed manner. Data are presented as mean \pm SEM.

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minutes [or 3 hours, 20 minutes]) and the duration of anesthetic action on soft tissues (around 250 minutes [or 4 hours, 10 minutes]) evoked by A100 were not statistically different from those evoked by A200 whether or not the patient was subjected to osteotomy ($P > .05$).

Figure 1 indicates that both local anesthetics provided a minimum sustained level of intraoperative bleeding during almost all steps of the surgeries, according to the surgeon's evaluation. Slightly increased bleeding was observed only when tissue was first incised, but this difference was not statistically significant in surgeries with or without osteotomy ($P > .05$).

No adverse reactions due to the use of either anesthetic solution were observed by the surgeon or reported by the patients during the surgery or the first postoperative hour. Patients reported no reactions in the period from the end of the surgery to the removal of suture.

In terms of hemodynamic parameters, no hypertensive peak was observed in the measurement of systolic, diastolic, and mean arterial pressures during all steps of the surgeries. In addition, the type of anesthetic solution used did not influence the arterial pressure during the surgeries with or without osteotomy ($P > .05$; Fig 2). Heart rate varied during the surgical procedures ($P < .05$) but was not influenced by the local anesthetic used ($P > .05$; Fig 3). In surgeries without osteotomy, a significant increase in heart rate occurred immediately after tissue incision

and flap reflection ($P < .05$). In surgeries with osteotomy, a significant increase in heart rate occurred immediately after tissue incision, flap reflection, and bone removal ($P < .05$). The heart rate returned to basal levels after tooth removal.

In terms of oxygen saturation, a peak increase occurred immediately after administration of the first cartridge of articaine ($P < .05$) that remained constant until the end of surgery in the procedures done without osteotomy (data not shown). No statistically significant difference in relation to oxygen saturation was observed during the surgeries with osteotomy ($P > .05$). The kind of local anesthetic did not influence the oximetry results ($P > .05$).

Discussion

The present study provides further characterization of the clinical properties of 4% articaine associated with 2 different concentrations of epinephrine. Our results strongly suggest that 4% articaine with 1:100,000 epinephrine (A100) and 1:200,000 epinephrine (A200) are equally effective in lower third molar extraction, with or without bone removal, taking into account the following characteristics: anesthetic properties, intraoperative bleeding control, and lack of influence on hemodynamic parameters.

In our study, the similar latency between A100 and A200 after the administration of 1.8 mL of both solutions corroborates the findings of Costa et al,¹⁶ Tofoli

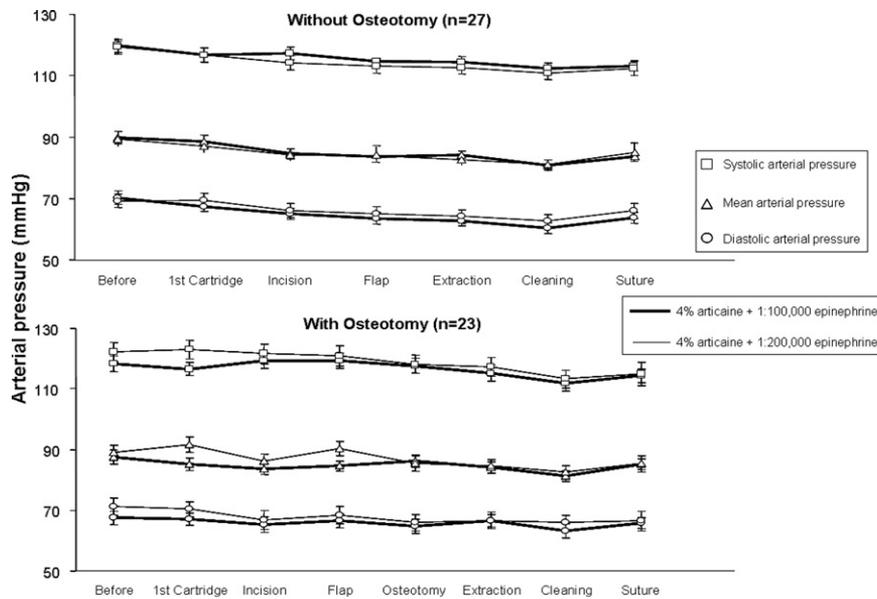


FIGURE 2. Measurements of systolic, diastolic, and mean arterial pressure (mm Hg) in patients who underwent surgical removal of both lower third molars, in 2 different appointments, under local anesthesia with A100 or A200 used in a double-blind, randomized, and crossed manner. Data are presented as mean ± SEM.

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et al,¹⁷ and Moore et al.¹⁹ However, our results differ from those of Lemay et al,²¹ who found latency values for A200 superior to those for A100. The results for A100 confirm our previous data¹³ and those of other authors,^{21,22} who have reported latency between 1.4 and 3.6 minutes after the inferior alveolar nerve

blockade. Although our values of latency for A100 and A200 (approximately 1.5 minutes) disagree with those of Tofoli et al¹⁷ (approximately 7 minutes) and Moore et al¹⁹ (approximately 5 minutes) and are close to those of Lemay et al²¹ (2 to 3 minutes), it is worth mentioning that this comparison must be made with

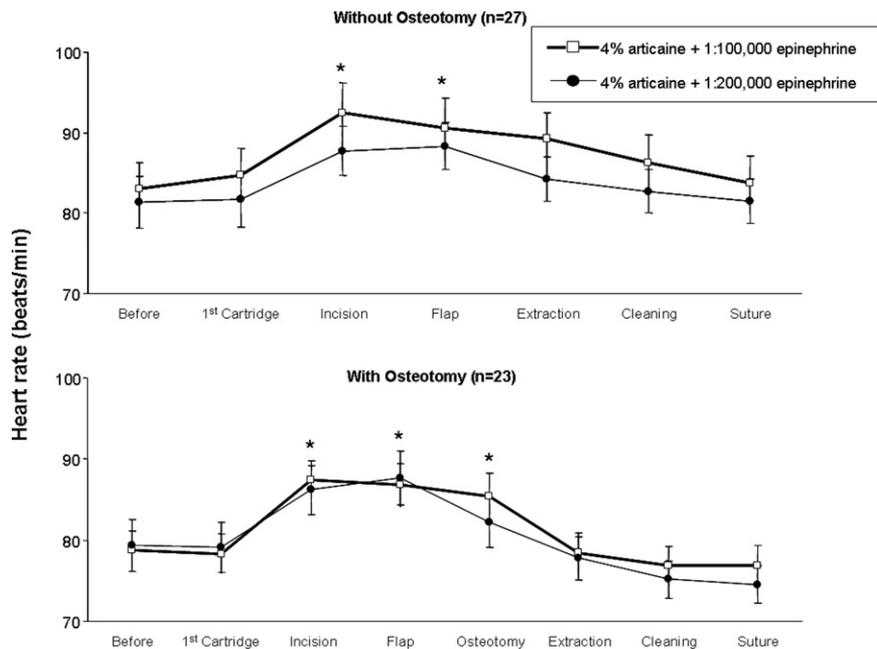


FIGURE 3. Measurements of heart rate (beats/minute) in patients who underwent surgical removal of both lower third molars, in 2 different appointments, under local anesthesia with A100 or A200 used in a double-blind, randomized, and crossed manner. Data are presented as mean ± SEM. Asterisks indicate significant differences compared with baseline values ($P < .05$). There were no differences at any surgical phase between the 2 local anesthetic solutions.

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caution, because those authors used a pulp tester to verify the anesthesia induced by the inferior alveolar nerve blockade, whereas we considered the loss of sensibility of the inferior lip, the corresponding half of the tongue, and the mucosa. Moore et al¹⁹ reported that the time to onset of 4% articaine solution without epinephrine (Aw/o) was similar to that of A100 and A200. In that work, however, only data for subjects who had achieved profound anesthesia (A200 = 54.8%; A100 = 47.6%; Aw/o = 25.8%) were available to calculate onset. The overall mean onset time for the 3 drug formulations was 4.4 min, which excludes data for unsuccessful anesthesia, and these values represent a more clinically meaningful estimate of the effective formulations containing epinephrine. Moore et al postulated that because the Aw/o formulation had an unsatisfactory success rate, the onset values shown do not represent clinical reality.¹⁹

All of the patients were anesthetized with 2.7 mL of A100 or A200. No patient required additional injections during the surgical procedures, even in more traumatic and longer surgeries involving osteotomy. Knoll-Köhler et al¹⁴ performed the same kind of surgery but with a greater volume (4 mL) of both anesthetic solutions. Also of note is the clinical trial reported by Hersh et al¹⁸ that compared the pharmacokinetics and cardiovascular effects of local anesthesia with 11.9 mL of A100 and A200 (near-maximum recommended dose of articaine, 7 cartridges, or 476 mg). Plasma concentrations of articaine over time were identical for A100 and A200, demonstrating that the 1:200,000 epinephrine concentration is as adequate as the 1:100,000 concentration in delaying the systemic absorption of articaine, and that the maximum recommended dose of articaine need not be altered in the A200 formulation from that recommended for the A100 formulation.¹⁸

The duration of surgery was similar in all patients regardless of whether A100 or A200 was used. However, the degree of difficulty of the surgical procedure and the local trauma involved varied among patients, depending on whether or not removal of bone tissue was necessary to extract the lower third molars. Thus, the establishment of 2 categories (with or without osteotomy) was necessary to guarantee that the sole variable in each category would be the local anesthetic used in the surgeries. This allowed the comparison of the efficacy of both agents in less traumatic and more traumatic surgeries.

Our data demonstrate that the postoperative analgesia and anesthesia provided by A100 or A200 were also very similar, confirming our previous findings in the same surgical model for A100.¹³ Thus, equal efficacy of A100 and A200 in terms of postoperative analgesia is demonstrated. The long period of analgesia finds explanation in a study by Oertel et al,²³ who

reported that the concentration of articaine in the alveolus of a tooth after extraction was about 100 times higher than in systemic circulation. This saturable local articaine metabolism has been considered as possibly contributing to the observed duration of the local anesthetic effect, despite articaine's very short systemic half-life. Moreover, the long duration of postoperative analgesia evoked by articaine may be explained by its ability to readily diffuse through tissues due to the presence of a thiophene group in the molecule, which increases its liposolubility.²⁴ In addition, our postoperative anesthesia values corroborate those of Cowan,²² Tofoli et al,¹⁷ and Lemay et al²¹; however, they are in disagreement with previous observations that the duration of the anesthetic effect is related to the concentration of vasoconstrictor in the anesthetic solution.^{3,25}

It is widely known that adding a vasoconstrictor agent to local anesthetic solutions reduces bleeding during oral surgery^{2,4,26} and contributes to a shorter duration of these procedures.²⁶ Our work was the first to compare A100 and A200 in terms of the level of intraoperative bleeding during lower third molar removal. We found that the concentrations of epinephrine in 4% articaine solution that we tested did not influence the control of intraoperative bleeding, which was near minimum in all of the surgeries with or without osteotomy. This factor certainly optimized the view of the operative field and contributed to the uniformity in the duration of surgeries (around 10 minutes for those without osteotomy and around 20 minutes for those with osteotomy). Our results differ from those of Buckley et al,²⁷ who found that 2% lidocaine with 1:50,000 epinephrine was more effective in controlling bleeding than 2% lidocaine with 1:100,000 epinephrine. However, it is important to point out that Buckley et al²⁷ evaluated bleeding associated with periodontal surgery, whereas in the present study we evaluated bleeding associated with lower third molar extraction.

No adverse reactions were observed by the surgeon or reported by the patients for both local anesthetics during surgery or in first postoperative hour. This finding corroborates the low allergenic potential of articaine compared with other anesthetic agents, due in part to the lack of metabolites derived from the benzenic ring, present in all of the other local amide anesthetics. The low toxicity of articaine also can be explained by the presence of an ester group in its molecule, which allows for quick metabolism by serum esterases.^{23,24} Moreover, a recent report by Siebrands and Friederich²⁸ indicates that articaine at clinically relevant concentrations does not inhibit human ether-a-go-go-related gene (hERG) potassium channels, which are potential targets involved in car-

diotoxic side effects of various pharmacologic agents, including local amide anesthetics.²⁸

In this study and in a previous study by our group,¹³ paresthesias were not observed. It is obvious that the limited number (120) of inferior alveolar nerve blockades in both studies must be taken into account. One of the most controversial aspects of articaine administration is its potential to cause paresthesias after inferior alveolar nerve blockade,^{29,30} which leads some researchers to support the opinion that 4% articaine should not be routinely used in this anesthetic application.^{30,31} Other authors attribute this adverse effect to the higher concentration of articaine (4%) compared with other local anesthetics (eg, 2% lidocaine in association with epinephrine). Interestingly, Haas and Lennon²⁹ also observed the same side effect for prilocaine, which is also available in the same concentration as articaine. It may be possible to decrease the risk of paresthesias by using a lower concentration of articaine to block the inferior alveolar nerve. In Germany, a 2% formulation in association with 1:200,000 epinephrine has recently become available for dental use and has proven to be as effective as A200 in teeth extractions with infiltration anesthesia.³² Recent *in vitro* findings showed that 2% and 4% articaine are more effective than 2% or 4% lidocaine and 3% mepivacaine for sensorial nerve blockade in rats; there was no significant difference between 2% or 4% articaine efficacy.³³ These recent laboratory data,³³ along with recent clinical findings,³² hold promise for future work comparing the efficacy of both articaine solutions in lower third molar removal and other oral procedures.

The administration of local anesthetic in patients subjected to restorative dental treatment is important, to avoid increases in arterial pressure.³⁴ In our study, the cardiovascular parameters analyzed were arterial pressure levels (systolic, diastolic, and mean), heart rate, and oxygen saturation. No consistent changes in arterial pressure or oxygen saturation were observed at the different steps of the surgical procedure compared with baseline, irrespective of either the use of both local anesthetics or the surgical trauma. These findings corroborate those reported by Knoll-Köhler et al,¹⁴ who used the same experimental model and found that the amount of epinephrine in A100 or A200 solutions had no effect on hemodynamic parameters. Our results are in agreement with those of Mestre Aspa et al,¹⁰ Knoll-Köhler et al,¹⁴ and Gortzak et al³⁴ with the use of 4% articaine with 1:100,000 epinephrine in lower third molar removal.

Transient increases and decreases in blood pressure and oxygen saturation were observed, but these were not clinically significant, nor were the differences between treatment groups statistically significant. Mestre Aspa et al,¹⁰ using the same local anesthetics used in this

investigation, found no statistical differences in blood pressure and oxygen saturation values attributable to the type of local anesthetic. It is important to note that our results were obtained when identical volumes of both anesthetic agents were used (2.7 mL). These volumes were lower than those used by Mestre Aspa et al,¹⁰ who administered 3.6 mL or less in 17 of their 45 patients and 3.6 to 5.4 mL in the remaining 28 patients. Hersh et al¹⁸ found more short-term cardiovascular effects with the A100 formulation than with the A200 formulation, as evidenced by the greater increase in heart rate and systolic blood pressure immediately after completion of the injection. The enhanced alpha-adrenergic and beta1-adrenergic effects exhibited by the larger volumes of local anesthetic solution (11.9 mL, 7 cartridges) administered in their study, especially with the A100 formulation (119 μ g epinephrine) compared with the A200 formulation (59.5 μ g epinephrine), most likely contributed to this difference.¹⁸ Troullos et al³⁵ demonstrated that administration of 8 cartridges of 2% lidocaine with 1:100,000 epinephrine (144 μ g epinephrine) in patients undergoing the surgical removal of 4 impacted third molars significantly increased hemodynamic parameters. They also found a significant rise (more than 27-fold) in plasma epinephrine levels.³⁵ Consequently, we can conclude that the small therapeutic volume of A100 or A200 that we used in our study (2.7 mL) seems to have relatively transient cardiovascular effects in healthy people due to the small amount of epinephrine contained in both solutions (27 and 13.5 μ g, respectively).

The only cardiovascular parameter that showed statistically significant variations was heart rate during some steps of the surgery, which is inherent to the surgical procedure demonstrating the stress on the patient, as also reported by Montebugnoli et al.³⁶ These variations were not influenced by the local anesthetic used and were not clinically significant, mainly because our patients were young and had no systemic disease.

On accidental intravascular injection of a local anesthetic, blood immediately enters the local anesthetic cartridge, mandating that the injection be stopped immediately. We experienced no cases of intravascular injection in our study. It is worth mentioning that Daublander et al³⁷ reported that A200 has less sympathomimetic effects than A100 for dental procedures. Despite the fact that the aspiration procedure can avoid intravascular injection, false-negative results are not uncommon.³⁸ Adverse reactions may occur, due mainly to the amount of vasoconstrictor in the local anesthetic solution. Healthy patients can tolerate these abrupt increases in vasoconstrictor serum concentration, but patients with cardiovascular disease may not be able to⁴; thus, less vasoconstrictor in the solution could be safer. Consequently, our results with experiments that enrolled subjects undergoing actual clinical procedures and other recently pub-

lished works^{18,19} strongly suggest the use of A200 instead of A100 for lower third molar removal.

In conclusion, epinephrine concentration (1:100,000 or 1:200,000) in 4% articaine solution does not influence the clinical efficacy of this local anesthetic in terms of anesthetic properties (latency, postoperative analgesia, postoperative anesthesia, and quality of anesthesia), intraoperative bleeding, and hemodynamic parameters in patients undergoing lower third molar removal. Therefore, it is possible to successfully use the 4% articaine formulation with a lower concentration of epinephrine (1:200,000, or 5 µg/mL) for lower third molar extraction with or without bone removal.

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