

Clinical study of hemodynamic changes comparing 4% articaine hydrochloride with 1:100,000 and 1:200,000 epinephrine

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Objective. To evaluate hemodynamic changes with the use of 4% articaine and 2 different concentrations of epinephrine (1:100,000 and 1:200,000) in the surgical removal of symmetrically positioned lower third molars.

Study Design. A prospective, randomized, double-blind clinical trial was carried out involving 42 patients each undergoing 2 surgeries on separate occasions under local anesthesia with 4% articaine and either epinephrine 1:100,000 or 1:200,000. The following parameters were assessed at 4 different moments: systolic, diastolic, and mean blood pressure; heart rate; oxygen saturation; rate pressure product (RPP); and pressure rate quotient (PRQ).

Results. The concentration of epinephrine did not affect diastolic blood pressure or oxygen saturation during the surgeries. Significant differences between were detected for heart rate, RPP, and PRQ ($P < .05$).

Conclusions. The epinephrine concentration (1:100,000 or 1:200,000) in a 4% articaine solution influences hemodynamic parameters without perceptible clinical changes in healthy patients undergoing lower third molar removal. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;116:e14-e22)

Pain control through a truncal block of the inferior alveolar nerve is one of the most widely used locoregional anesthetic techniques in oral surgery, affording comfort and safety to both the patient and operator when used correctly.¹ The choice of anesthetic solution should be based on 3 main clinical considerations: anesthetic potency, latency (time to the onset of anesthesia), and duration of the anesthetic effect.²

A number of local anesthetic agents provide the rapid onset of surgical anesthesia and adequate duration of the anesthetic effect.³ Vasoconstrictors are added to local anesthetic solutions to increase the quality and duration of the anesthesia, avoid excessive intraoperative bleeding and decrease systemic toxicity. Epinephrine has been widely used for this purpose in several countries.^{1,4,5}

Sung et al.⁶ found that the administration of progressive doses of epinephrine at concentrations lower than those used in dental practice gives rise to increases in myocardial yield and oxygen consumption. On the other hand, it is known that pain during dental treat-

ment can trigger the release of endogenous catecholamines, which, in turn, can give rise to hemodynamic changes, such as an increase in blood pressure and heart rate, and may even produce arrhythmia.⁷ A significant increase (5-12 mm Hg) in systolic blood pressure has been reported in patients subjected to root scaling and planing when using anesthesia with a vasoconstrictor.⁸ There is controversy regarding the use of epinephrine with local anesthetic solutions in patients with a history of cardiovascular problems, although the administration of a local anesthetic with a vasoconstrictor for the avoidance of patient pain and discomfort during dental treatment appears to be safe.^{9,10}

Articaine was synthesized by Rusching et al. in 1969 under the name carticine and first marketed in Germany in 1976. By 1983, the drug was available in practically all of Europe and Canada; it was not approved in the USA until March 2000 and only in its presentation as a 4% solution with 1:100,000 epinephrine.¹ Its pharmacologic characteristics are the main advantages over other local anesthetics and include the substitution of the aromatic ring with a

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Statement of Clinical Relevance

Even though the epinephrine concentration influences hemodynamic parameters with a 4% articaine solution, no clinical changes are noted during third molar extraction in healthy patients.

thiophenic ring, which increases the liposolubility and potency (1.5-fold greater than that of lidocaine) of the drug. Moreover, articaine is the only amide local anesthetic containing an ester group in its molecular structure, which allows the metabolism of the drug by both plasma esterases and liver microsomal enzymes.¹¹ The clinical advantages of articaine include the duration of its anesthetic effect—surpassed only by ultralong-acting anesthetics, such as bupivacaine, etidocaine, and ropivacaine—and its superior diffusion through bone tissue.^{12,13}

There are a large number of studies on the most commonly used local anesthetics in lower third molar surgeries (e.g., lidocaine, mepivacaine, bupivacaine).^{1,14-19} However, the dental literature on the use of articaine for this kind of surgery is limited.²⁰⁻²⁵ One study found that 4% articaine with 1:100,000 epinephrine provides a longer period of analgesia and a tendency toward a longer period of anesthesia on soft tissues compared with 2% mepivacaine with 1:100,000 epinephrine. Moreover, neither agent exerted an influence over hemodynamic parameters (blood pressure, heart rate, and oxygen saturation) during surgery.²¹

It has recently been shown that a 4% articaine solution with 1:200,000 adrenaline provides a degree of pulp anesthesia similar to that of 4% articaine with 1:100,000 adrenaline.²⁶ Although most information on the cardiovascular response to dental local anesthesia with articaine is limited to healthy patients,^{22,27-29} these data may still be of value to cardiologists, primary care physicians, surgeons, and dentists regarding the selection of a preferred local anesthetic for patients with cardiovascular conditions. On the other hand, no significant hemodynamic changes in patients with controlled hypertension have been attributed to 4% articaine with 1:200,000 adrenaline when <3 local anesthetic carpules are administered.⁷ Few studies have compared 4% articaine with 1:100,000 adrenaline and 1:200,000 epinephrine,^{22-26,29-32} particularly in terms of controlling postoperative pain and intraoperative bleeding.

The present study was undertaken to evaluate hemodynamic changes with the use of 4% articaine and 2 different concentrations of epinephrine (1:100,000 and 1:200,000) in the surgical removal of symmetrically positioned lower third molars.

MATERIALS AND METHODS

The protocol of the present study received approval from the Institutional Ethics Committee (CEP/UPE: 001.0.097.000-08). The subjects were selected from a pool of patients admitted for regular dental treatment from January 2009 to December 2010. All participants signed a term of informed consent.

A prospective, randomized, double-blind clinical trial was carried out. The split-mouth design was employed, with the right and left quadrants of the mouth constituting the experimental units and randomly assigned to 2 treatment groups. The fact that each patient served as his or her own control (crossover design) enhanced the statistical power of the study.^{33,34}

The sample size was estimated with the use of the PC-Size program (version 1.01), with data for independent samples used for comparison purposes. The difference in heart rate reported for different evaluation periods in the study carried out by Frabetti et al.³⁵ was used as the parameter, because the results were statistically significant ($P < .05$). With an alpha value of 5% and a beta value of 80%, it was determined that 42 patients would be needed for the study.

Forty-two healthy nonsmoking patients (33 men and 11 women aged 18-31 years; mean age $21.83 \pm$ SD 5.57 years) scheduled for the surgical removal of bilateral symmetrically positioned impacted lower third molars were enrolled in the study. The subjects had no known immune impairment or contraindications for oral surgery and were not taking any medication. The eligibility criteria included absence of systemic illness and no signs of inflammation or infection at the extraction sites. Exclusion criteria included a medical history of cardiovascular or kidney disease, gastrointestinal bleeding or ulceration, allergic reaction to local anesthetic, allergy to aspirin, ibuprofen, or any similar drugs, and pregnancy or current lactation.^{14,36} Instructions for not using antidepressants, diuretics, or aspirin in the days before the surgeries were given to the patients, because these drugs could cause hemorrhaging or other blood problems and would therefore interfere with the results of the present investigation. Patients were also given instructions not to take any other pain medication before the removal of the third molars. Orthopantomographic radiograms were taken to ensure the similarity of the tooth inclinations based on the Winter classification³⁷ and the Pell and Gregory classification.³⁸

The randomization process was carried out based on items 8-10 of the CONSORT statement 2001 checklist for randomized controlled clinical trials (Cochrane Collaboration, Manchester, U.K.).³⁹ Allocation to the 2 groups was performed by selecting from a set of sequentially numbered opaque sealed envelopes containing either of the 2 interventions: 4% articaine with 1:100,000 epinephrine (A100) or 4% articaine with 1:200,000 epinephrine (A200). Each impacted lower third molar (right and left sides) had an equal chance of being assigned to 1 of the 2 groups. The randomization process also determined which side would undergo the first surgery and which would undergo the second sur-

gery. During the entire double-blind study, randomization was conducted by the same researcher with ample research experience.

The preoperative treatment protocol for all patients included the prescription of 8 mg dexamethasone and 1 g amoxicillin taken orally 1 hour before surgery. The surgeon ensured that all patients knew how to take the prescribed medication. Dental extraction was carried out in a relaxed atmosphere, with no anxiolytic premedication. On the day of the extraction, the patients had a light breakfast and were instructed to take their usual medication at that time. The consumption of alcohol or coffee was to be avoided beginning the night before.

Each patient was operated on by the same senior oral-maxillofacial surgeon, using the same surgical technique on both sides to minimize discrepancies in the handling of the tissues. Extraoral antiseptics was performed with a 2.0% chlorhexidine solution, and intraoral antiseptics was performed with a 0.12% chlorhexidine rinse. The patient then received a regional anesthetic block of the buccal, lingual, and inferior alveolar nerves with 1.8 mL of the anesthetic solution. After 5 minutes, 0.9 mL of the same anesthetic was injected into the mucosa to ensure hemostasis and anesthesia of the site. An additional amount of anesthetic solution was injected when the patient complained of pain during the surgery; however, such patients were excluded from the sample. The materials and instruments routinely required for this type of surgery were used, and standardized technique was performed. Briefly, an L-shaped incision was made and a mucoperiosteal flap was raised. When osteotomy and tooth sectioning were performed on one side, the other side received the same treatment to standardize the surgical trauma. All procedures were performed under abundant irrigation with sterilized 0.9% physiologic solution. The closure of the mucoperiosteal flap was performed with 3-0 silk. The duration of the surgical procedure was counted from incision until tooth removal. Surgical procedures exceeding 30 minutes were excluded from the analysis. Moreover, when surgery on one side exceeded the other side by >10 minutes, the patient was excluded. One impacted lower third molar was removed on the first surgical visit, and the contralateral lower third molar was removed on the second surgical visit, which was scheduled for 3 weeks later.

In the first 48 hours following surgery, the patients were authorized to take analgesics (acetaminophen 750 mg 4 times daily) only in case of pain. Acetaminophen was also used as the rescue drug. The patients were instructed to eat only soft food and abstain from mouth

washing for the first 24 hours and from brushing and flossing around the surgical area until the removal of the suture (14 days after surgery). For plaque control, the patients used a 0.12% chlorhexidine mouth rinse for 1 minute twice a day for 2 weeks after surgery.

Systolic, diastolic, and mean blood pressure, heart rate, and oxygen saturation were assessed before (T0) and during the surgery (T1 and T2) as well as after suturing (T3). Two measurements were made during surgery: one immediately after the regional anesthetic block (T1) and another 5 minutes later (T2). The rate pressure product (RPP) and pressure rate quotient (PRQ) were also evaluated. The RPP is derived by multiplying systolic blood pressure and heart rate and is a good indicator of oxygen consumption by the myocardium in nonanesthetized patients. The PRQ is calculated by dividing mean blood pressure by heart rate and it is used as an indicator of cardiac ischemia.^{19,22,40} All of the measurements were automated, noninvasive, and performed with the aid of equipment for monitoring hemodynamic parameters (OX-P10 Monitoring System; EMAI, São Paulo, Brazil).

A dataset was generated and analyzed using the Statistical Package for the Social Sciences (SPSS v. 13). Descriptive (measures of central tendency and dispersion) and inferential (with a 5% level of significance) statistics were performed. The Kolmogorov-Smirnov test was used to determine normal or heterogeneous distribution of the data, and appropriate parametric or nonparametric tests were then employed. The parametric test was the paired-sample *t* test.

RESULTS

The demographic and baseline characteristics of the sample are summarized in Table I. A total of 50 individuals participated in the survey. However, 8 were excluded from the sample: 3 had an additional amount of anesthetic solution injected, the surgical time exceeded 30 minutes for 2 patients, and 3 failed to return for surgery on the contralateral side. Thus, 42 participants remained, with 42 impacted lower third molars allocated to the A100 group and the 42 contralateral impacted lower third molars allocated to the A200 group. The split-mouth design allowed the standardization of the surgical technique, because each patient participated in both groups.

The mean duration of surgery from the time of administration of A100 until the completion of the suturing of the surgical wound was 14.61 ± 2.58 minutes, which was not statistically different from that observed after the administration of A200 (14.97 ± 2.16 min; $P > .05$).

No adverse reactions due to the use of either concentration of epinephrine were observed by the surgeon or reported by the patients during the surgery or the first

Table 1. Demographic characteristics at screening examination

Variable	Value
No. of subjects (both surgical procedures completed)	42
Age (y)	
Mean \pm SD	21.83 \pm 5.57
Range	18-31
Gender (male/female)	30/12
Weight (kg)	
Mean \pm SD	59.83 \pm 14.37
Range	40-118
Vital signs at screening appointment	
Heart rate (beats/min)	84.07 \pm 12.56
Systolic blood pressure (mm Hg)	120.46 \pm 9.09
Diastolic blood pressure (mm Hg)	78.81 \pm 8.73
SpO ₂	97.52 \pm 1.80
RPP	9742.26 \pm 2,037.98
PRQ	1.14 \pm 0.17

SPO₂, oxygen saturation; RPP, rate pressure product; PRQ, pressure rate quotient.

postoperative hour. Moreover, the patients reported no reactions in the period from the end of the surgery to the removal of the suture.

In terms of hemodynamic parameters, no hypertensive peak was observed in systolic, diastolic, or mean blood pressure at any evaluation time. Moreover, the concentration of epinephrine exerted no influence over diastolic or systolic blood pressure ($P > .05$; Figures 1 and 2) during surgery. In both groups, heart rate varied during the surgical procedure, with a rise in value following the administration of the local anesthetic solution and a return to near baseline levels after suturing; however, the difference was statistically significant only at 5 minutes after the administration of the anesthetic (T2; $P < .05$; Figure 3). A peak increase in oxygen saturation occurred immediately after the administration of both local anesthetic solutions, which remained increased until the end of surgery. The concentration of epinephrine also exerted no influence over the oximetry results ($P > .05$; Figure 4). RPP increased from T1 to T2 with both solutions, with a decrease in values at T3. A statistically significant difference between solutions was detected only at 5 minutes after administration (T2; $P < .05$; Figure 5). PRQ decreased with A100 and increased with A200 at T1, which was the only moment with a statistically significant difference between protocols ($P < .05$). Both groups had diminished values at T2 and T3, with no statistically significant difference between groups ($P > .05$; Figure 6).

DISCUSSION

To investigate the therapeutic efficacy of an anesthetic drug, every effort should be made to standardize the procedure. A crossover study design is useful in elim-

inating variations in inflammatory response stemming from individual differences. The surgical technique and surgeon should be the same in all procedures, and the patients should be meticulously selected to ensure the similarity of the trauma caused in both surgeries. Therefore, the experimental model of the bilateral surgical removal of impacted lower third molars was used for evaluation of the anesthetic agents in the present study.⁴¹ However, most studies addressing the effects of anesthetic solutions in third molar surgery are performed without the split-mouth design, which hinders the comparison of results.

No adverse reactions were observed by the surgeon or reported by the patients with either local anesthetic solution. This finding corroborates earlier studies that report the low allergenic potential of articaine compared with other anesthetic agents, partly due to the lack of metabolites derived from the benzenic ring in all other local amide anesthetics.^{21,24} The low toxicity of articaine may also be explained by the presence of an ester group in its molecule, which allows rapid metabolism by serum esterases.^{11,27} However, some authors report adverse events after the use of articaine with epinephrine, such as headache, edema of lips, face and eyelids, trismus, soreness, swelling, and paresthesia.^{11,42-44}

The present study provides further characterization of hemodynamic changes with the use of 4% articaine associated with 2 different concentrations of epinephrine. The results strongly suggest that 4% articaine with epinephrine at 1:100,000 (A100) and 1:200,000 (A200) is equally effective in lower third molar extraction and that neither protocol exerts a significant influence over hemodynamic parameters, as previously reported by Santos et al.

All patients were anesthetized with 2.7 mL A100 or A200, as in the study by Santos et al.²⁴ Knoll-Köhler et al.²² performed the same kind of surgery, but with a greater volume of both anesthetic solutions (4 mL). Also of note is the clinical trial reported by Hersh et al.,²⁹ who compared the pharmacokinetics and cardiovascular effects of local anesthesia with 11.9 mL A100 and A200 [near the maximum recommended dose of articaine (7 cartridges or 476 mg)]. Plasma concentrations of articaine over time were identical with both 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.²⁹

A large number of hemodynamic studies have been carried out with patients subjected to a local anesthetic injection with a vasoconstrictor.^{7-10,19,21-25,28,29,35,40,45-51}

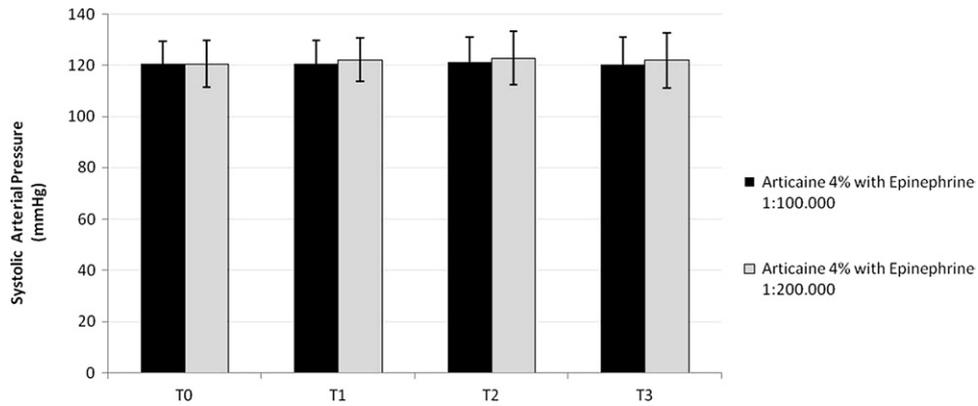


Fig. 1. Mean (and SD) systolic blood pressure (mm Hg) in patients under 4% articaine with 1:100,000 and 1:200,000 epinephrine at 4 different evaluation times.

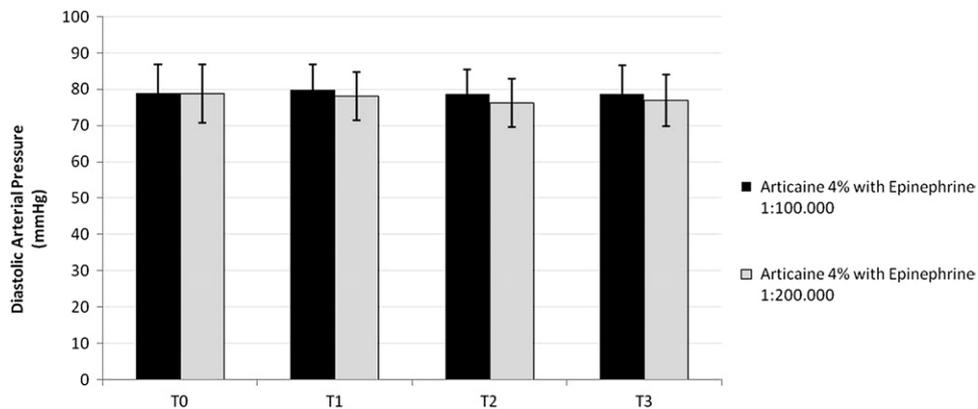


Fig. 2. Mean (and SD) diastolic blood pressure (mm Hg) in patients under 4% articaine with 1:100,000 and 1:200,000 epinephrine at 4 different evaluation times.

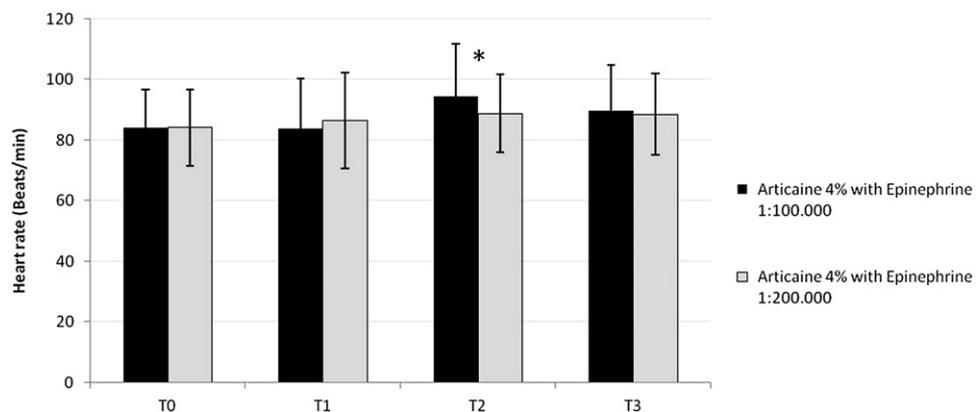


Fig. 3. Mean (and SD) heart rate (beats/min) in patients under 4% articaine with 1:100,000 and 1:200,000 epinephrine at 4 different evaluation times. Asterisk indicates significant difference between groups ($P < .05$).

Some involve subjects with no history of disease and found no significant changes in either blood pressure (systolic and diastolic) or heart rate. However, some authors have suggested that such changes are dependent on the dose of the vasoconstrictor injected.⁵² Therefore, it is clear that important variations are to be expected if the

injection technique is not performed carefully and the solution is accidentally injected into a blood vessel.⁵³

The administration of a local anesthetic in patients subjected to restorative dental treatment is important to avoid an increase in blood pressure.⁴⁹ In the present study, the cardiovascular parameters analyzed were

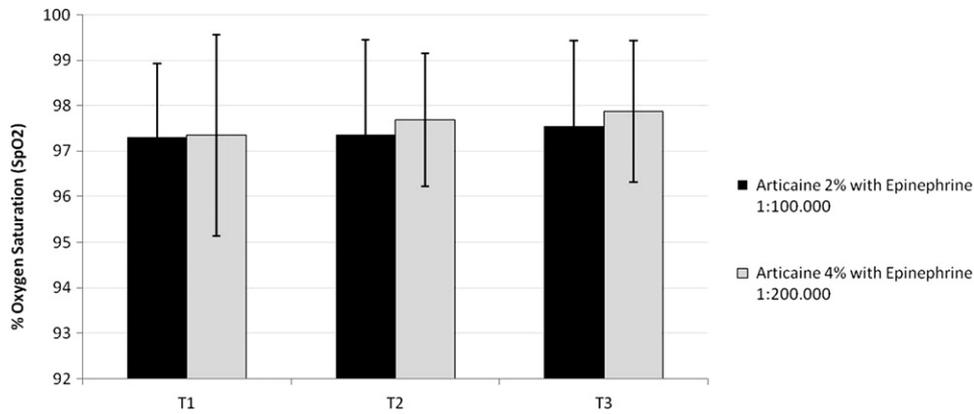


Fig. 4. Mean (and SD) percentage of oxygen saturation (SpO₂) in patients under 4% articaine with 1:100,000 and 1:200,000 epinephrine at 4 different evaluation times.

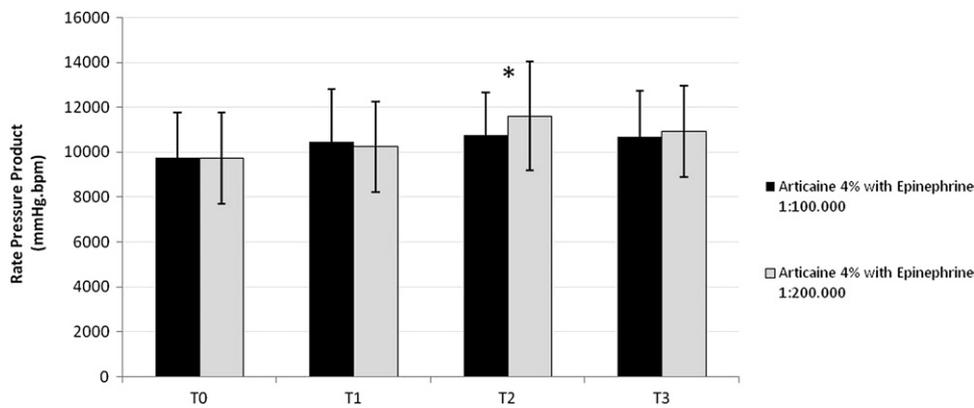


Fig. 5. Mean (and SD) rate pressure product (mm Hg·beats/min) in patients under 4% articaine with 1:100,000 and 1:200,000 epinephrine at 4 different evaluation times. Asterisk indicates significant difference between groups ($P < .05$).

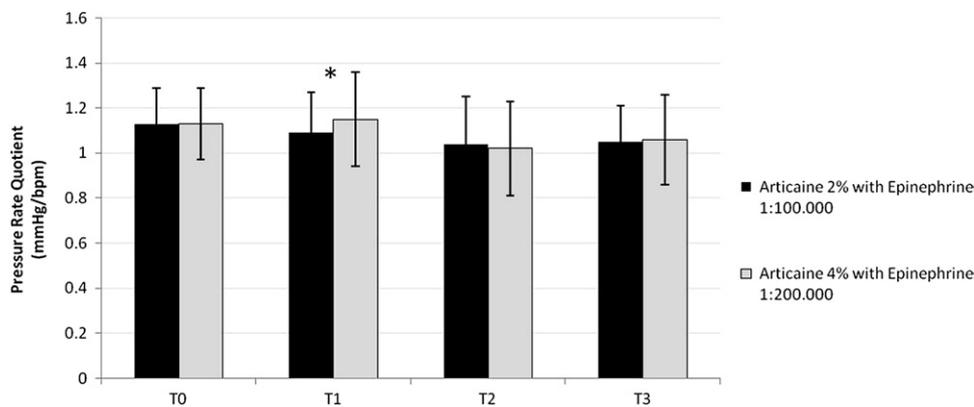


Fig. 6. Mean (and SD) pressure rate quotient (mm Hg/beat) in patients under 4% articaine with 1:100,000 and 1:200,000 epinephrine at 4 different evaluation times; Asterisk indicates significant difference between groups ($P < .05$).

blood pressure levels (systolic, diastolic, and mean), heart rate, oxygen saturation, RPP, and PRQ. Although statistically significant changes occurred in heart rate (T2), RPP (T2), and PRQ (T3), it can be stated that no consistent changes in blood pressure or oxygen saturation were observed at the different moments of the

surgical procedure compared with baseline values (Figures 1-6). These findings corroborate those reported by Knoll-Köhler et al.²² and Santos et al.,²⁴ who used the same experimental model and found that the amount of epinephrine in A100 or A200 solutions had no effect on hemodynamic parameters. The results are also in agree-

ment with those reported by Mestre Aspa et al.,¹⁹ Knoll-Köhler et al.,²² Santos et al.,²⁴ and Gortzak et al.,⁴⁹ who investigated the use of 4% articaine with 1:100,000 epinephrine in lower third molar extraction.

Dionne et al.⁵⁴ found that, after the administration of 5.4 mL 2% lidocaine with 1:100,000 epinephrine, taking care to avoid intravascular injection, heart rate increased in 19% of cases and cardiac output increased as much as 30%. According to Silvestre et al.,^{7,55} the use or nonuse of a vasoconstrictor with the local anesthetic solution exerts no effect upon blood pressure in normotensive or hypertensive patients. The fact that the anesthetic solution was limited to 2.7 mL may explain the absence of hemodynamic alterations in the present study, as was also done in the study by Santos et al.

Hersh et al.²⁹ reported 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 the study cited, especially with the A100 formulation (119 µg epinephrine) compared with the A200 formulation (59.5 µg epinephrine), most likely contributed to this difference.²⁹ Troullos et al.⁵⁶ demonstrated that administration of 8 cartridges of 2% lidocaine with 1:100,000 epinephrine (144 µg epinephrine) significantly increased hemodynamic parameters in patients undergoing the surgical removal of 4 impacted third molars. The authors also found a significant increase (>27-fold) in plasma epinephrine levels. Consequently, one may conclude that the small therapeutic volume of A100 and A200 used in the present study (2.7 mL) seems to have relatively transient cardiovascular effects in healthy people owing to the small amount of epinephrine contained in both solutions (27 and 13.5 µg, respectively), as reported in the study by Santos et al.

Regarding RPP, a relationship is thought to exist between this parameter and cardiac ischemia.^{19,22,40} In the present study, RPP behaved differently at all evaluation times with both anesthetic solutions. Mestre Aspa et al.¹⁹ report an increased value before an injection of the anesthetic solution, followed by a drop immediately after the administration of lidocaine and articaine. The present findings are in disagreement with this, because the RPP value rose following the administration of the anesthetic (T1 and T2) and diminished after suturing.

PRQ is the most widely parameter used as an indicator of cardiac ischemia.^{19,22,40,57} PRQ <1 is associated to subendocardial ischemia.¹⁹ Myocardial ischemia occurs when blood flow to the heart is decreased

by a partial or complete blockage of an artery, which reduces the oxygen supply in the heart. The classic symptoms of acute myocardial infarction include sudden chest pain (typically radiating to the left arm or left side of the neck), shortness of breath, nausea, vomiting, palpitations, sweating, and anxiety (often described as a sense of impending doom).⁵⁸

In the present study, a statistically significant difference in PRQ was found between A100 and A200 only after the administration of the local anesthetic (T1). This finding is in disagreement with that described by Mestre Aspa et al.,¹⁹ who found no significant differences between the anesthetic solution used or the surgical phase involved. According to Campbell and Langston,⁴⁰ only patients with simultaneously abnormal RPP and PRQ values are at a significant risk of suffering cardiac ischemia, which would, moreover, have to be confirmed electrocardiographically. However, the use of PRQ is not an indicator of myocardial ischemia in humans.⁵⁹ Accordingly, it would be advisable to monitor all patients with known cardiovascular disease or arterial hypertension scheduled for oral surgery or potentially painful procedures.¹⁹ Therefore, because the only significant differences were the effect on PRQ at T1 and RPP at T2, no perceptible clinical changes were noticed during the surgeries.

Daublander et al.³¹ reported that A200 has fewer sympathomimetic effects than A100 in dental procedures. Despite the fact that the aspiration procedure can avoid intravascular injection, false-negative results are not uncommon.⁴⁶ Adverse reactions may occur, owing 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.⁵ Therefore, less vasoconstrictor in the solution could be safer. Consequently, the results of the present investigation involving subjects undergoing actual clinical procedures as well as the findings of other recently published studies^{7,10,24-26,29} strongly suggest the use of A200 rather than A100 in lower third molar extraction.

According to a number of authors, oral surgery implies important patient stress, triggering the release of a considerable amount of endogenous catecholamines, which would be responsible for the small hemodynamic fluctuations observed rather than the epinephrine habitually associated in the local anesthetic solution used.^{19,54,60} However, in a study on blood pressure fluctuations in hypertensive patients during different oral surgical procedures, Meiller et al.⁶¹ found no such correlation between patient stress and changes in hemodynamic variables. This may explain the fact that the use of A200 led to significantly higher RPP and PRQ values at some evaluation times, but this did not

appear to be related to the concentration of epinephrine in the solution.

It is worth mentioning that none of the present results were influenced by the type or concentration of the vasoconstrictor substance associated to the local anesthetics employed, as both contained 1:100,000 epinephrine. Many authors state that the amount of epinephrine administered with the local anesthetic formulation exerts a cumulative effect with plasma catecholamine levels, although this phenomenon would not suffice to induce hemodynamic changes in young healthy individuals, such as those in the present study. However, in patients with cardiovascular disease, the risk of complications attributable to this mechanism increases. Systematic monitoring of such patients is therefore advisable.^{19,22,23,35,40,54,57}

CONCLUSION

In summary, the epinephrine concentration (1:100,000 or 1:200,000) in a 4% articaine solution influences hemodynamic parameters in healthy patients undergoing lower third molar removal. However, PRQ and RPP alterations do not mean that clinical changes occur.

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