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## A comparison of the clinical anesthetic efficacy of 4% articaine and 0.5% bupivacaine (both with 1:200,000 epinephrine) for lower third molar removal

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**Objective:** This study compared the clinical efficacy of 4% articaine (A200) and 0.5% bupivacaine (B200), both with 1:200,000 epinephrine, for lower third molar removal.

**Study design:** Fifty patients underwent removal of symmetrically positioned lower third molars, in 2 separate appointments, under local anesthesia either with A200 or B200, in a double-blind, randomized, and crossover manner. Time to onset, duration of postoperative analgesia, duration of anesthetic action on soft tissues, intraoperative bleeding, and hemodynamic parameters were evaluated.

**Results:** A statistically significant difference between the time to onset of A200 ( $1.66 \pm 0.13$  minutes) and B200 ( $2.51 \pm 0.21$  minutes) was found ( $P < .05$ ). There was no statistically significant difference in the duration of analgesia, whether the patient was subjected to osteotomy or not, regardless of the local anesthetic used (3 to 4 hours;  $P > .05$ ). However, when patients received B200 they experienced a statistically significant longer period of anesthesia on the soft tissues as compared with when they had received A200 (around 5 hours and 4 hours, respectively,  $P < .05$ ). The surgeon's rating of intraoperative bleeding was considered very close to minimal for both anesthetics. In the surgeries with osteotomy, the comparison between A200 and B200 showed statistically significant differences in the diastolic (64 mm Hg and 68 mm Hg, respectively,  $P = .001$ ) and mean arterial pressure (86 mm Hg and 89 mm Hg, respectively,  $P = .031$ ) when data from all the surgical phases were pooled. Additionally, the mouth opening at the suture removal was statistically different for A200 and B200 solutions ( $91.90\% \pm 3.00\%$  and  $88.57\% \pm 2.38\%$  of the preoperative measure, respectively) when surgeries required bone removal ( $P < .05$ ).

**Conclusions:** In comparison with 0.5% bupivacaine, 4% articaine (both with 1:200,000 epinephrine) provided a shorter time to onset and comparable hemostasis and postoperative pain control with a shorter duration of soft tissue anesthesia in lower third molar removal. (*Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008;106:19-28)

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Postoperative pain is a common phenomenon after surgery, due to surgical trauma and the release of pain mediators.<sup>1-3</sup> Regarding the surgical removal of lower third molars, the maximum intensity of pain occurs in the first hours after the end of the surgery, when the local anesthetic has worn off.<sup>1,2,4</sup> Postoperative pain control is frequently performed with the administration of short-acting local anesthetics and oral analgesics. Theoretically, pain control can be increased by using a local anesthetic with a more prolonged action.<sup>1-3,5-8</sup>

Bupivacaine, an amide-type local anesthetic, is a well-known long-acting local anesthetic. Its use in rou-

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tine oral surgery is especially justified for lengthy surgical procedures or oral surgical extraction associated with predicted postoperative pain and discomfort.<sup>2,9</sup> A number of authors have reported its potent cardiac toxic effects, even in small doses.<sup>9,10</sup>

Taking into account our previous results with the use of articaine for lower third molar surgeries<sup>11-13</sup> and the lack of studies comparing articaine and bupivacaine, the aim of this work was to assess the clinical efficacy of 4% articaine (A200) and 0.5% bupivacaine (B200), both with 1:200,000 epinephrine, in the model of surgical removal of symmetrically positioned lower third molars.<sup>11-14</sup>

## MATERIAL AND METHODS

The institutional Ethics Committee approved the protocol and the informed consent document of this study (#75/2006). All patients provided written informed consent during the pretreatment screening period before any study procedures were performed.

The study population comprised 50 patients aged 18 years or over, with both lower third molars in similar positions, as observed in panoramic radiographies. All the subjects were in good health, and none was taking any medication that would alter pain perception, as determined by oral questioning and written health history.<sup>9,15</sup> Eligibility and exclusion criteria were detailed previously,<sup>11-14,16</sup> including histories of allergies to ester containing drugs or products.

This was a double-blind study, that is, neither the surgeon nor the patients were aware of the local anesthetic being used at the two different appointments, since the labels of both anesthetics were pulled off and the cartridges were coded by someone not directly involved in data collection prior to the patient visit. Each patient required surgical treatment with the same magnitude of trauma on opposite sides of the mandibular jaw, which was performed in two visits 1 to 2 months apart.<sup>11-14,16</sup> The ipsilateral maxillary third molars were removed only 2 months after the end of this study. For local anesthesia, in the first appointment, the patients randomly received A200 or B200 solutions. In the second appointment, the local anesthetic not used previously was then administered in a crossover manner. The same surgeon (FPMG) performed all 100 surgeries and postoperative evaluations.

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. Additional volume of the solution would be infiltrated if the patient complained

of pain during the surgery. The removal of lower third molars followed a standard surgical technique.<sup>11-14,16</sup>

For postoperative pain control, all patients received 20 mg piroxicam,<sup>11,16</sup> which was administered once daily for 4 days. Rescue analgesic medication was available to any patient as needed throughout the study; for this purpose, 750 mg paracetamol was provided to all patients. Patients were instructed not to interrupt the use of the anti-inflammatory, even if they had taken rescue analgesic medication.<sup>11-14,16</sup>

The parameters evaluated were as follows:

1. The total volume of anesthetic solution used during the surgery (in mL).<sup>11,13</sup>
2. The onset of anesthetic agent action (in minutes), determined by the loss of sensibility of the inferior lip, the corresponding half of the tongue and the mucosa.<sup>11,13</sup>
3. The quality of the anesthesia provided by the local anesthetic during the surgery and evaluated by the surgeon. 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 of additional anesthesia; and 3 = any discomfort reported by patient during the surgery, with the need of additional anesthesia.<sup>13</sup>
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.<sup>13</sup>
5. Duration of the surgery after anesthetic administration (in minutes), which corresponded to the period between the first incision and the last suture.<sup>11-14,16</sup>
6. Duration of postoperative analgesia (in minutes), which was determined by the difference between the time at the end of the surgery and that for the ingestion of the first piroxicam capsule for pain relief.<sup>11,13</sup>
7. Duration of postoperative anesthesia on soft tissues, represented by the lack of sensibility of the mucosa, tongue and inferior lip. Patients recorded the moment that all soft tissue sensation returned to normal.<sup>11,13</sup>
8. Intraoperative bleeding, rated by the surgeon according to a 3-point category rating scale (1 = minimal bleeding; 2 = normal bleeding; 3 = excessive bleeding),<sup>13</sup> right after the following steps: injection of the first cartridge of local anesthetic solution, tissue incision, flap reflection, bone removal (when this procedure was necessary), tooth extraction, cleaning of the operated site and end of the suture.

**Table I.** 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% articaine or 0.5% bupivacaine (both with 1:200,000 epinephrine) used in a double-blind, randomized, and crossover manner

Parameter	4% Articaine with 1:200,000 epinephrine		0.5% Bupivacaine with 1:200,000 epinephrine	
	With osteotomy (n = 28)	Without osteotomy (n = 22)	With osteotomy (n = 28)	Without osteotomy (n = 22)
Quality of anesthesia	1.25 ± 0.14 <sup>a</sup>	1.05 ± 0.05 <sup>a</sup>	1.61 ± 0.19 <sup>a</sup>	1.23 ± 0.14 <sup>a</sup>
Difficulty of surgery	2.18 ± 0.13 <sup>a</sup>	1.36 ± 0.15 <sup>b</sup>	2.36 ± 0.12 <sup>a</sup>	1.23 ± 0.12 <sup>b</sup>
Duration of surgery, min	19.54 ± 1.08 <sup>a</sup>	12.37 ± 0.75 <sup>b</sup>	22.88 ± 1.78 <sup>c</sup>	13.28 ± 0.87 <sup>d</sup>
Duration of postoperative analgesia, min	193.14 ± 24.56 <sup>a</sup>	195.68 ± 27.74 <sup>a</sup>	226.21 ± 60.25 <sup>a</sup>	281.72 ± 68.62 <sup>a</sup>
Duration of postoperative anesthesia, min	245.10 ± 16.60 <sup>a</sup>	260.31 ± 20.49 <sup>a</sup>	310.92 ± 49.86 <sup>b</sup>	319.68 ± 34.26 <sup>b</sup>
Quality of wound healing	1.25 ± 0.09 <sup>a</sup>	1.05 ± 0.05 <sup>a</sup>	1.39 ± 0.11 <sup>a</sup>	1.14 ± 0.08 <sup>a</sup>

Data are the mean ± SEM. Distinct lowercase letters indicate statistically significant difference in the same line (*P* < .05).

9. Incidence, type and severity of adverse reactions observed by the surgeon or reported by the patient (e.g., 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. Patients were also asked to take note of any reaction occurring after their discharge from the clinic and before their return for suture removal.<sup>11-14,16</sup>
10. Systolic, diastolic and mean arterial pressure, heart rate and oxygen saturation,<sup>11-13</sup> measured in the following moments: before the surgery and immediately after the steps described in the item 8. All of the measurements were automated and noninvasive, and were performed with a device for monitoring hemodynamic parameters (DX2010, Dixtal Biomédica Ind e Com Ltda, Marília/SP, Brazil).
11. Mouth opening (distance, in mm, between the mesial-incisal corners of the upper and lower right central incisors at maximum opening of the jaws) before the surgery and at the moment of suture removal (7 days postoperatively). The postoperative ability to open the mouth was expressed as a percentage of preoperative measure.<sup>11-14,16</sup>
12. Quality of wound healing, rated by the surgeon according to a 3-point category rating scale (1 = normal healing; 2 = delayed healing; 3 = complicated healing due to alveolitis) at the moment of suture removal (7 days postoperatively).<sup>13</sup>
13. Subjective pain evaluation, with the aid of a 100-mm-length visual analogue scale (VAS), with 0 anchored by “no pain” and 100 anchored by “worst pain imaginable.”<sup>11-14,16</sup> Subjects recorded the intensity of postoperative pain at the moment that the anesthetic had worn off, and then 24 and 48 hours later.
14. Time to first rescue analgesic medication (paracetamol), total amount of rescue analgesic medica-

tion (in mg) ingested during the postoperative period, and percentage of patients who needed rescue medication.<sup>11-13,16</sup>

Paired *t* tests were used to compare duration of surgeries and time to onset. 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. Fisher’s exact analysis was used to compare the percentages of patients in each group requiring additional infiltration anesthesia. Statistical significance was established at 5%. The results were presented as the mean ± standard error of mean (SEM).

**RESULTS**

The study comprised 50 healthy volunteers (21 males and 29 females), with a mean age of 21.84 ± 0.65 years (range 18 to 35), who were divided into 2 categories: surgeries requiring osteotomy (28 patients), and surgeries not requiring osteotomy (22 patients). Hence, all the results except time to onset are expressed according to these 2 categories.

A statistically significant difference between the time to onset of A200 (1.66 ± 0.13 minutes) and B200 (2.51 ± 0.21 minutes) was found (*P* < .05).

The surgeon’s rating of quality of anesthesia indicated that both local anesthetics produced adequate surgical anesthesia, irrespective of the necessity of bone removal (*P* > .05, Table I). Although the mean scores attributed to quality of anesthesia were very close to 1 with the use of A200 and B200, the percentage of people who required complementary anesthetic infiltration was significantly higher (*P* < .05) for B200 (14%) than for A200 (2%). Thus, the volume of B200

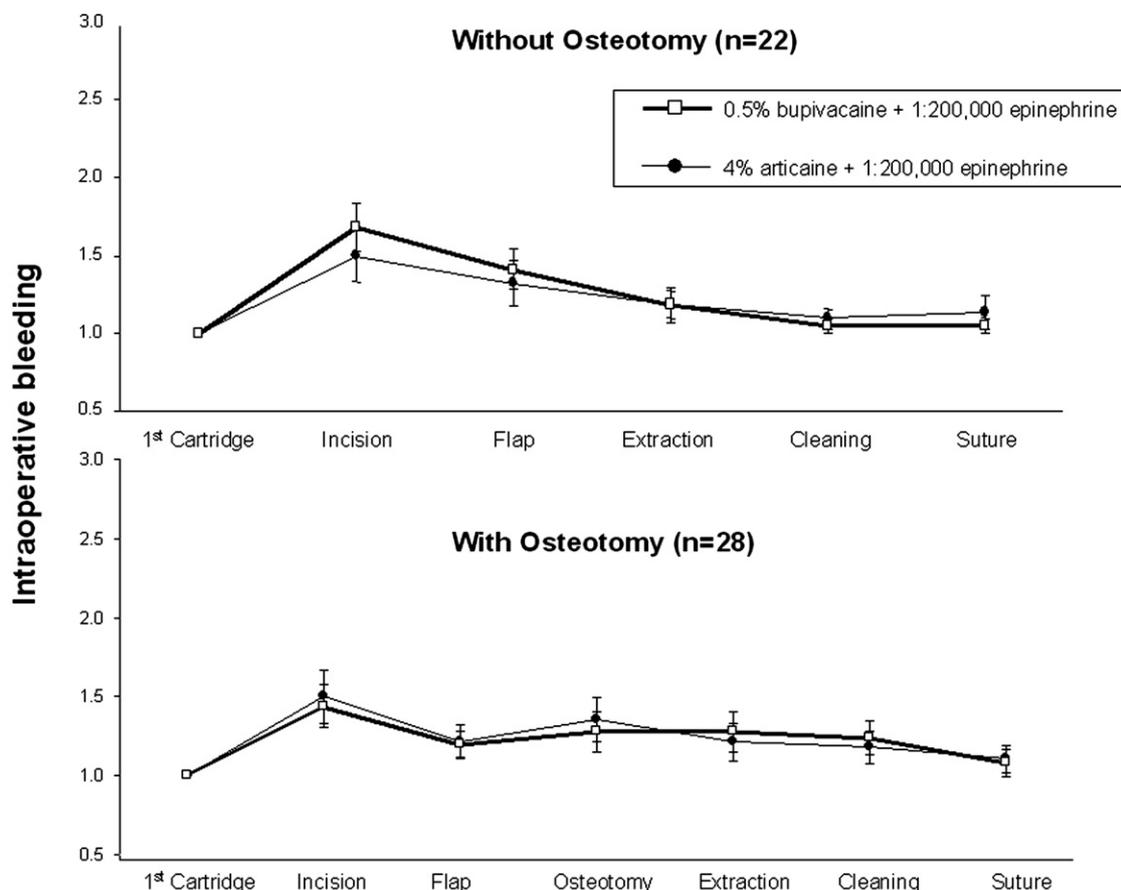


Fig. 1. Surgeon's rating of intraoperative bleeding (1 = minimal bleeding; 2 = normal bleeding; 3 = excessive bleeding) in patients who underwent surgical removal of both lower third molars, in 2 different appointments, under local anesthesia with 4% articaine or 0.5% bupivacaine (both with 1:200,000 epinephrine) used in a double-blind, randomized, and crossover manner. Data are presented as a mean  $\pm$  SEM.

administered during surgeries was greater than that of A200 ( $2.90 \pm 0.07$  mL and  $2.72 \pm 0.02$  mL, respectively), although no statistically significant difference could be observed ( $P > .05$ ).

No difference in the surgeon's mean rating of surgical difficulty of both surgeries in the same patient was observed, irrespective of the anesthetic agent employed ( $P > .05$ ). However, those surgeries requiring bone removal were rated more difficult as compared with those without this procedure ( $P < .05$ , Table I), regardless of the local anesthetic solution employed.

The mean duration of surgeries, postoperative analgesia, and postoperative anesthesia are also shown in Table I. The surgeries with osteotomy, rated by the surgeon as the most traumatic ones, lasted considerably longer than those without osteotomy ( $P < .05$ ). The type of local anesthetic used also influenced the duration of the surgeries ( $P < .05$ ), and there was interaction between the kind of surgery and the type of anesthetic employed ( $P < .05$ ).

Despite the apparent difference between the duration of postoperative analgesia evoked by A200 (around 194 minutes or 3 hours) and B200 (around 250 minutes or 4 hours), there was no statistically significant difference in this parameter whether the patient was subjected to osteotomy or not ( $P > .05$ ), probably due to the high variation of response among patients as revealed by the SEM. However, patients who received B200 experienced a statistically significantly longer period of anesthesia as compared with when they received A200 (around 315 minutes or 5 hours and around 250 minutes or 4 hours, respectively,  $P < .05$ ).

Both local anesthetics provided a minimum sustained level of intraoperative bleeding during almost all steps of the surgeries, according to the surgeon's evaluation. A discrete increase of bleeding level was only observed when tissue was first incised, but it was not statistically significant in either surgery with or without osteotomy (Fig. 1,  $P > .05$ ).

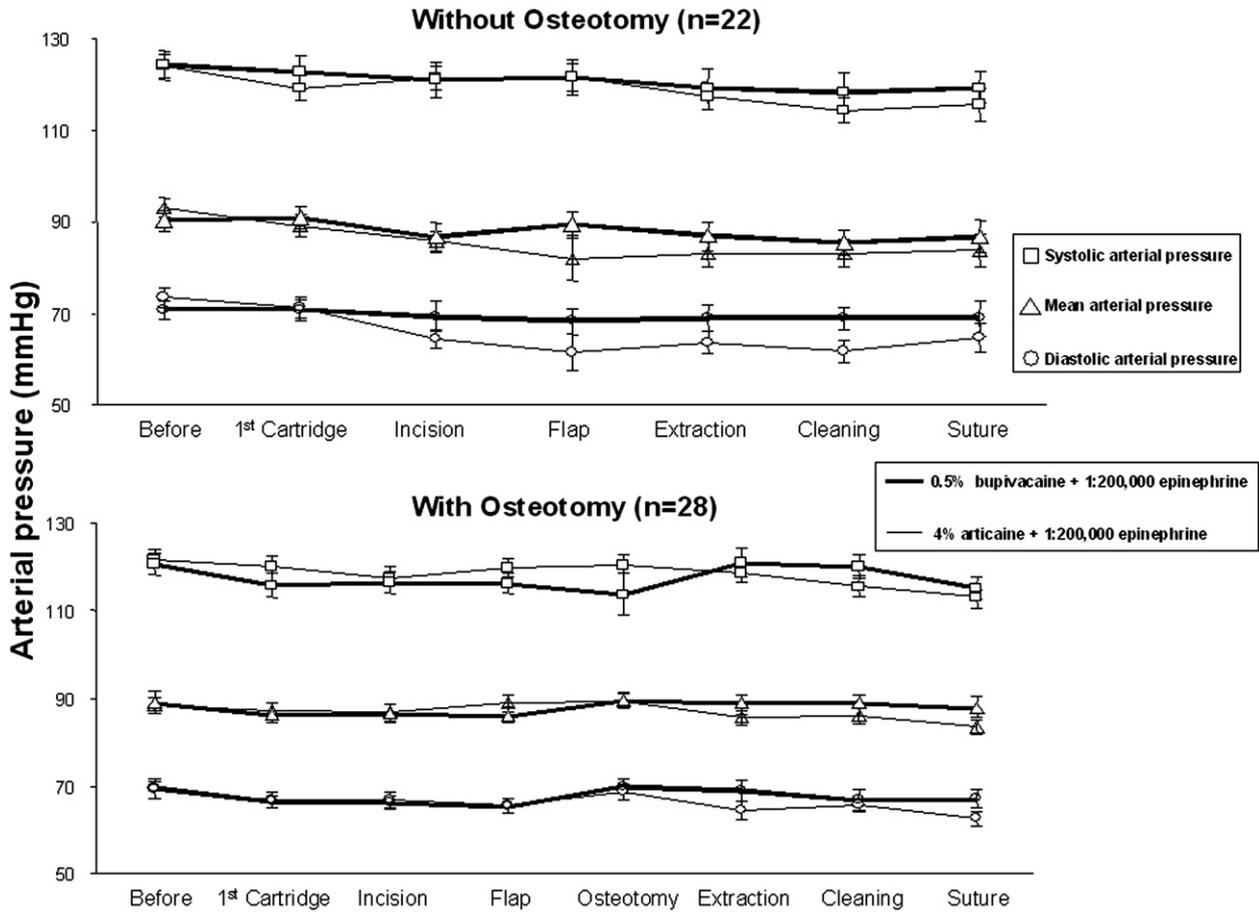


Fig. 2. Measurements of systolic, diastolic, and mean arterial pressure (mm Hg) in patients who underwent surgical removal of both lower third molars, in 2 different appointments, under local anesthesia with 4% articaine or 0.5% bupivacaine (both with 1:200,000 epinephrine) used in a double-blind, randomized and crossover manner. Data are presented as a mean  $\pm$  SEM.

Concerning the adverse reactions, after the use of A200, 1 patient vomited at the end of surgery, and 2 patients reported dizziness when surgeries were performed with the use of B200 (one right after the injection of the first cartridge of anesthetic solution and the other one during suture).

Regarding the hemodynamic parameters, the kind of anesthetic solution did not influence the level of systolic, diastolic, and mean arterial pressure during the surgeries without osteotomy when the different surgical phases were assessed individually or pooled ( $P > .05$ , Fig. 2). In the surgeries with osteotomy, however, the comparison between A200 and B200 showed statistically significant differences in the diastolic (64 mm Hg and 68 mm Hg, respectively,  $P = .001$ ) and mean arterial pressure (86 mm Hg and 89 mm Hg, respectively,  $P = .031$ ) when data from all the surgical phases were pooled (data not shown).

The values concerning heart rate varied during the surgical procedures with and without osteotomy ( $P$

$< .05$ , Fig. 3), and were not influenced by the local anesthetic used ( $P > .05$ , Fig. 3). No statistically significant difference in relation to oxygen saturation was observed during the surgeries with or without osteotomy ( $P > .05$ , Fig. 4). The kind of local anesthetic did not influence the results of oxymetry ( $P > .05$ , Fig. 4).

The mouth opening at the suture removal was  $97.72\% \pm 2.68\%$  and  $100.80\% \pm 2.55\%$  of the preoperative measure for A200 and B200, respectively ( $P > .05$ ), for patients subjected to surgeries without osteotomy. However, when surgeries required osteotomy, the mouth opening at the suture removal was statistically different for A200 and B200 solutions ( $91.90\% \pm 3.00\%$  and  $88.57\% \pm 2.38\%$  of the preoperative measure, respectively,  $P < .05$ ).

The surgeon's rating of quality of wound healing was similar for both local anesthetics, irrespective of the necessity of bone removal ( $P > .05$ , Table I).

The percentage of patients taking rescue analgesic

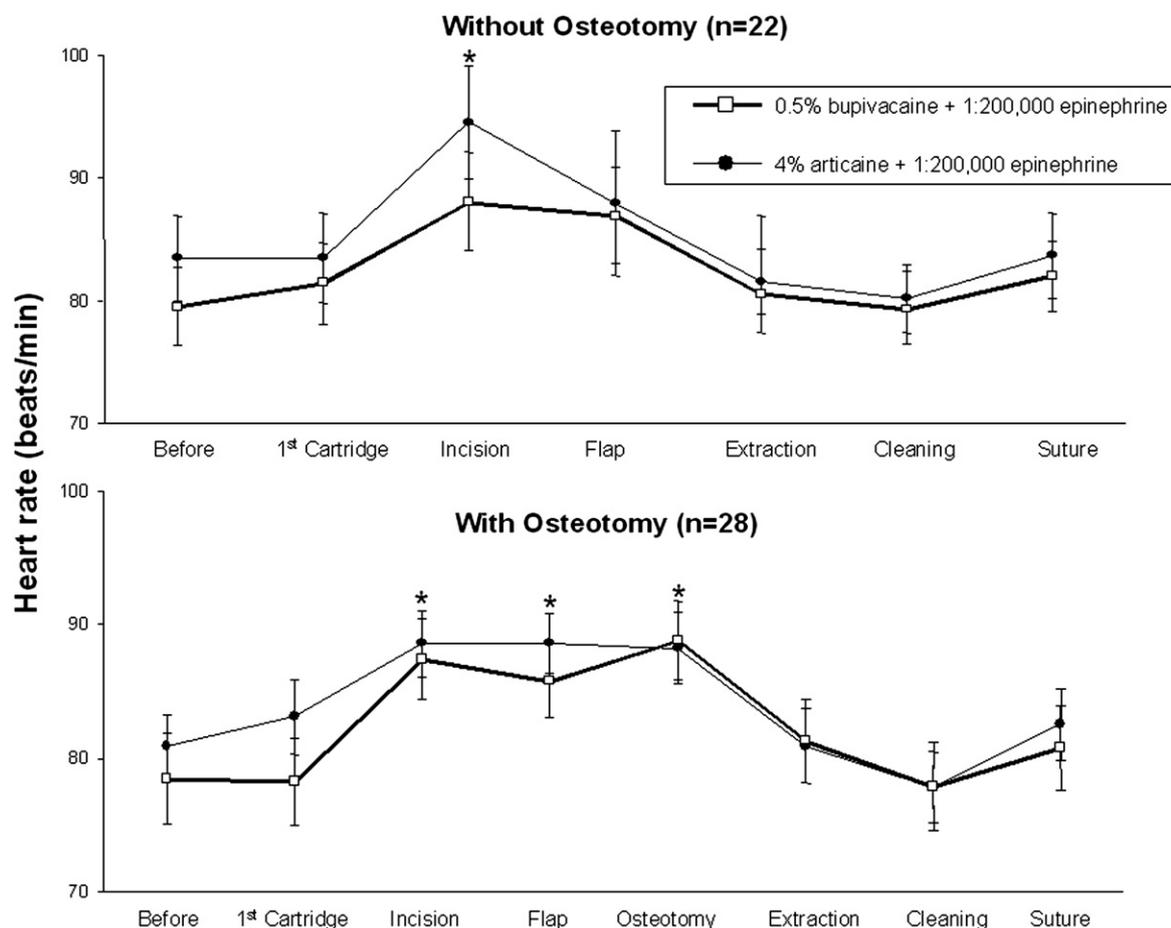


Fig. 3. Measurements of heart rate (beats/min) in patients who underwent surgical removal of both lower third molars, in 2 different appointments, under local anesthesia with 4% articaine or 0.5% bupivacaine (both with 1:200,000 epinephrine) used in a double-blind, randomized and crossover manner. Data are presented as a mean  $\pm$  SEM. Asterisks indicate significant differences compared with baseline values. There were no differences at any time point between the 2 local anesthetic solutions.

medication (paracetamol) and the total amount of this drug were similar in all groups ( $P > .05$ , Table II). In addition, there was no significant difference in the time to ingestion of the first rescue medication when A200 or B200 was used in the surgeries, irrespective of the necessity of bone removal ( $P > .05$ , Table II).

## DISCUSSION

The present study compares the clinical properties of 2 local anesthetics, 4% articaine (A200) and 0.5% bupivacaine (B200), both with 1:200,000 epinephrine. Our results suggest that A200 may be a more desirable local anesthetic to use in some patients compared with B200 because of its shorter time to onset, its shorter duration of soft tissue anesthesia, and comparable intraoperative bleeding control and postoperative analgesic effects as well as possibly somewhat better pain control during the surgical procedure itself. In addition,

the hemodynamic variables were found to be more stable with A200 than with B200, although the differences in mean arterial and systolic blood pressure were quite small and really not clinically significant for the healthy patients who participated in this study.

The results for time to onset of A200 confirm our previous data<sup>13</sup> and those of other authors.<sup>17-19</sup> In addition, the time to onset of B200 is within the range of 1.9 to 2.6 minutes of onset times previously established.<sup>20-22</sup> However, it differs from the results of Fernandez et al.,<sup>15</sup> who reported time to onset of  $6.53 \pm 0.68$  minutes for the same solution. This difference may be justified because in that study, subjects were asked to pinch their lip on the side of the injection to determine if the lip was profoundly numb. Nevertheless, in our study the time to onset was determined at the moment that patients reported an initial loss of sensibility of the inferior lip, the corresponding half of the

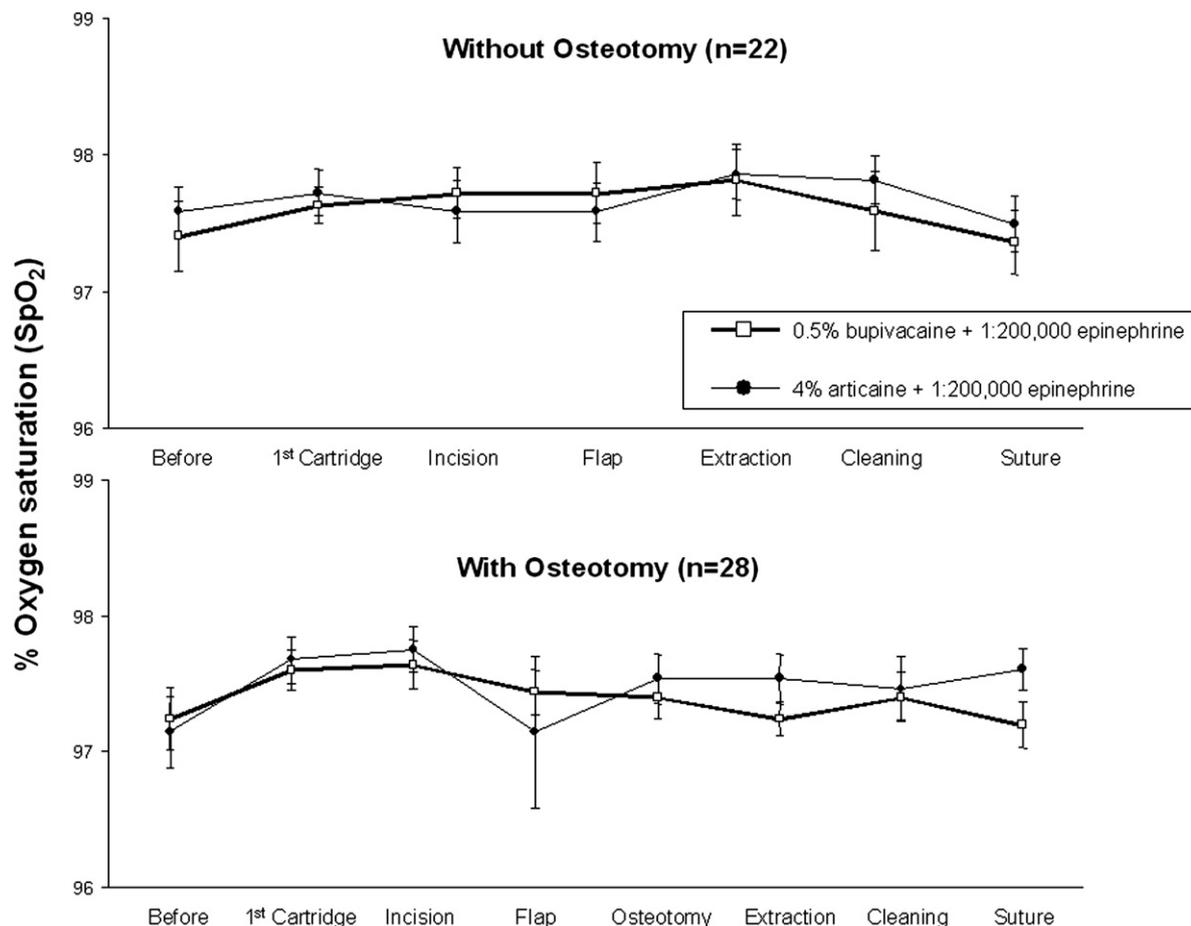


Fig. 4. Measurements of percentage oxygen saturation (SpO<sub>2</sub>) in patients who underwent surgical removal of both lower third molars, in 2 different appointments, under local anesthesia with 4% articaine or 0.5% bupivacaine (both with 1:200,000 epinephrine) used in a double-blind, randomized and crossover manner. Data are presented as a mean ± SEM.

**Table II.** Consumption of rescue analgesic medication (paracetamol) recorded for comparison of postoperative courses after removal of lower third molars under local anesthesia with 4% articaine or 0.5% bupivacaine (both with 1:200,000 epinephrine) used in a double-blind, randomized, and crossover manner

Parameter	4% Articaine with 1:200,000 epinephrine		0.5% Bupivacaine with 1:200,000 epinephrine	
	With osteotomy (n = 28)	Without osteotomy (n = 22)	With osteotomy (n = 28)	Without osteotomy (n = 22)
Patients taking rescue medication, n (%)	12 (42.85)	11 (50.00)	15 (53.57)	12 (54.54)
Time to first rescue medication, h	9.52 ± 3.10	10.37 ± 4.84	9.43 ± 2.33	6.25 ± 1.02
Total amount of rescue medication, mg	776.79 ± 243.66	784.09 ± 211.50	830.36 ± 269.88	1193.18 ± 324.04

Data are the mean ± SEM. There were no differences between the 2 local anesthetic solutions.

tongue, and the mucosa. It is worth mentioning that in the study by Moore et al.,<sup>19</sup> the time to onset showed by 4% articaine solution without epinephrine was similar to that of this local anesthetic with 1:100,000 (A100) and 1:200,000 (A200) epinephrine.

The difference between the time to onset of A200

and B200 could be explained by the lower pKa of A200 (7.8) than that of B200 (8.1). It is well known that the closer the anesthetic pKa is to the pH of the local environment where it is injected, the faster is its onset of action. Therefore, at a tissue pH of 7.4 bupivacaine would initially have fewer anesthetic molecules avail-

able in the free-base form to diffuse through the nerve membrane as compared with articaine; the result is a slower onset of action for the former solution in comparison with the latter.<sup>23</sup>

Despite the lack of a statistically significant difference between the volumes of A200 and B200 used, 7 patients (14%) felt discomfort during the surgeries in which B200 solution was used, thus requiring the infiltration of additional volume of this anesthetic agent. In contrast, it is worth mentioning that only one of the patients (2%) required complementary infiltration of anesthetic solution during the surgeries in which A200 was administered. This situation may explain the significantly longer duration of the surgeries with the use of B200 than that with A200, since 7 patients (14%) required additional anesthesia when operated under anesthesia with B200. In addition, the duration of the surgeries directly depended on whether or not removal of bone tissue was necessary to extract the lower third molars. This might account for the greater degree of trismus and perceived better result with the articaine as well as the increased volumes of bupivacaine necessary to complete the case. Considering that surgeries requiring osteotomy represented a higher degree of difficulty and gave rise to increased local trauma as compared with those without osteotomy, the establishment of 2 categories (with or without osteotomy) was crucial to guarantee that the sole variable in each category would be the local anesthetic used in the surgeries. This approach allowed the comparison of the clinical efficacy of both agents in less traumatic and more traumatic surgeries.

Our results also showed that there was no statistically significant difference between the values of mouth opening in both preoperative periods (data not shown), which demonstrates that all patients recovered totally after the first surgery, regardless of the local anesthetic employed. Additionally, there was no significant difference between the pre- and postoperative values of mouth opening for A200 and B200 for the less traumatic surgeries. However, for surgeries with osteotomy, a reduced postoperative ability to open the mouth was observed when patients received B200 as compared with A200, which may be attributed to the longer duration of the surgeries when B200 was used, rather than an anesthetic substance influence on the function of masticatory muscles.

Although it is well known that a bupivacaine solution prolongs the analgesic period for inferior alveolar nerve block anesthesia,<sup>2,15,24</sup> no difference concerning this parameter could be observed between A200 and B200 in our study. Moreover, the analgesic duration either with A200 or B200 did not extend long enough to cover the whole time of postoperative discomfort, which could be confirmed by the need to consume piroxicam

after the surgeries as well as data regarding the percentage of patients who needed rescue medication, the time to the first rescue analgesic medication, and the total amount of this drug ingested during the postoperative period. Thus, the use of piroxicam allied to the consumption of rescue analgesic medication was necessary to the relief of postoperative pain.

Bupivacaine's longer duration of action is in part because of protein binding.<sup>15,23</sup> Nevertheless, there is little advantage to having lip numbness for extended periods of time. Difficulty in eating, speaking, and possibility of soft tissue trauma are viewed as nuisances by the patient.<sup>2,15</sup> Fernandez et al.<sup>15</sup> reported anesthesia duration of  $411 \pm 14.5$  minutes after the alveolar nerve blockade with 1 cartridge of B200 solution, which is a longer period than that observed in our study both with and without osteotomy. Actually, this is an intriguing issue because although a greater volume of the same anesthetic was administered in our work, the anesthesia duration was shorter (mean of 315 minutes) than that found by those authors. The long period of analgesia for A200 finds explanation in a study by Oertel et al.,<sup>25</sup> 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.<sup>26</sup> While it is true that an extended duration of soft tissue anesthesia (lip, tongue, and cheeks) is definitely a quality of life detriment in pretty much all patients undergoing nonsurgical dental procedures, this is not always the case with those undergoing surgery especially if there was significant soft tissue trauma. While the differences in analgesic duration were not significant between articaine and bupivacaine (and as we stated the large variability contributed to that) there is certainly a strong trend in our data of extended analgesia when patients received bupivacaine.

As far as bleeding control is concerned, the results obtained in this study for A200 corroborate the findings of a previous work by our group.<sup>13</sup> Both solutions exhibited a good control of intraoperative bleeding since scores were very close to minimum in all of the surgeries, with or without osteotomy. However, in periodontal surgeries where more intraoperative bleeding is anticipated, articaine solutions containing 1:100,000 epinephrine have recently been shown to provide a clearer surgical field with

less blood loss than the same local anesthetic containing a 1:200,000 concentration.<sup>27</sup>

In this study and in 2 previous works by our group<sup>11,13</sup> paresthesia was not observed. It is obvious that the limited number (170) of inferior alveolar nerve blockades in such studies must be taken into account. One of the most controversial aspects of articaine administration is its potential to cause paresthesia after inferior alveolar nerve blockade,<sup>28-30</sup> which leads some researchers to support the opinion that 4% articaine should not be routinely employed in this anesthetic technique.<sup>29-31</sup> Other authors attribute this adverse effect to the higher concentration of articaine (4%) in comparison with other local anesthetics (e.g., 2% lidocaine in association with epinephrine). Interestingly, Haas and Lennon<sup>28</sup> 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 paresthesia 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, which proved as effective as A200 in teeth extractions with infiltration anesthesia.<sup>32</sup> Recent *in vitro* findings showed that 2% and 4% articaine were 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.<sup>33</sup> These recent laboratory data,<sup>33</sup> along with the recent clinical findings<sup>32</sup> are very promising for future works comparing the efficacy of both articaine solutions in lower third molar removal and other oral procedures.

No consistent changes in 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. Statistically significant variations in heart rate were detected during some steps of the surgery, which is inherent to the surgical procedure, revealing the stressful situation to the patient as also reported by Montebugnoli et al.<sup>34</sup> These oscillations were not influenced by the local anesthetic employed. The present results of heart rate variations confirm the data we observed in a previous work by our group in the same surgical model.<sup>13</sup> Regarding arterial pressure, B200 evoked higher values than A200 during more traumatic surgeries with osteotomy both for diastolic and mean arterial pressure when data from all the surgical phases were pooled. It is worth mentioning that the aforementioned oscillations in heart rate and blood pressure were not clinically significant, mainly because our patients were young and with no systemic disease. Healthy patients may tolerate these increases, but it may not occur in patients with cardiovascular disease. Cardiotoxic effects reported for B200 are very well documented in the literature.<sup>35</sup> In contrast, a recent report suggested that A200 may be an

acceptable option for patients with long QT syndrome.<sup>36</sup> It is important to stress that with articaine and other local anesthetic solutions in general, 1:100,000 and 1:50,000 epinephrine concentrations are associated with greater cardiovascular stimulation than 1:200,000 epinephrine formulations, especially when larger local anesthetic volumes are administered.<sup>37,38</sup> Hersh et al.<sup>39</sup> found more short-term cardiovascular effects with A100 than A200, as evidenced by the greater increase in heart rate and systolic blood pressure immediately after the completion of the injection. The enhanced alpha-adrenergic and beta-1-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 µg epinephrine) as compared with the A200 formulation (59.5 µg epinephrine) most likely contributed to this difference. Troullos et al.<sup>40</sup> demonstrated that 8 cartridges of 2% lidocaine with 1:100,000 epinephrine (144 µg epinephrine) in patients undergoing the surgical removal of 4 impacted third molars significantly increased hemodynamic parameters. They also found a remarkable rise in plasma epinephrine levels of more than 27-fold. Therefore, one can conclude that since patients received a small amount of epinephrine when anesthetized with A200 or B200 (around 13.5 µg), any cardiovascular effect may be attributable to the local anesthetic itself.

## CONCLUSION

In comparison with 0.5% bupivacaine, 4% articaine (both with 1:200,000 epinephrine) provided a shorter time to onset, and comparable hemostasis and postoperative pain control, with a shorter duration of soft tissue anesthesia in lower third molar removal. Fewer patients required supplemental intraoperative injections when operated with 4% articaine.

## REFERENCES

1. Seymour RA, Walton JG. Pain control after third molar surgery. *Int J Oral Surg* 1984;13(6):475-85.
2. Markovic AB, Todorovic L. Postoperative analgesia after lower third molar surgery: contribution of the use of long-acting local anesthetics, low-power laser, and diclofenac. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006;102(5):e4-8.
3. Dionne RA, Campbell RA, Cooper SA, Hall DL, Buckingham B. Suppression of postoperative pain by preoperative administration of ibuprofen in comparison to placebo, acetaminophen, and acetaminophen plus codeine. *J Clin Pharmacol* 1983;23(1):37-43.
4. Koerner KR, Taylor SE. Pharmacologic considerations in the management of oral surgery patients in general dental practice. *Dent Clin North Am* 1994;38(2):237-54.
5. Fisher SE, Frame JW, Rout PG, McEntegart DJ. Factors affecting the onset and severity of pain following the surgical removal of unilateral impacted mandibular third molar teeth. *Br Dent J* 1988;164(11):351-4.
6. Davis VM Jr, Oakley J, Smith E. Comparison of the effectiveness of etidocaine and lidocaine as local anesthetic agents during oral surgery. *Anesth Prog* 1984;31(4):159-64.
7. Hyrkas T, Ylipaavaliemi P, Oikarinen VJ, Paakkari I. Effective

- postoperative pain prevention through administration of bupivacaine and diclofenac. *Anesth Prog* 1994;41(1):6-10.
8. Moore PA. Bupivacaine: a long-lasting local anesthetic for dentistry. *Oral Surg Oral Med Oral Pathol* 1984;58(4):369-74.
  9. Volpato MC, Ranali F, Ramacciato JC, Oliveira PC, Ambrosano GMB, Groppo FC. Anesthetic efficacy of bupivacaine solutions in inferior alveolar nerve block. *Anesth Prog* 2005;52(4):132-5.
  10. Bacsik CJ, Swift JQ, Hargreaves KM. Toxic systemic reactions of bupivacaine and etidocaine. *Oral Surg Oral Med Oral Pathol* 1995;79(1):18-23.
  11. Colombini BL, Modena KC, Calvo AM, Sakai VT, Giglio FP, Dionisio TJ, et al. Articaine and mepivacaine efficacy in postoperative analgesia for lower third molar removal: a double-blind, randomized, crossover study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006;102(2):169-74.
  12. Calvo AM, Sakai VT, Giglio FP, Modena KC, Colombini BL, Benetello V, et al. Analgesic and anti-inflammatory dose-response relationship of 7.5 and 15 mg meloxicam after lower third molar removal: a double-blind, randomized, crossover study. *Int J Oral Maxillofac Surg* 2007;36(1):26-31.
  13. Santos CF, Modena KCS, Giglio FPM, Sakai VT, Calvo AM, Colombini BL, et al. 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. *J Oral Maxillofac Surg* 2007;65(12):2445-52.
  14. Calvo AM, Sakai VT, Modena KCS, Colombini BL, Gallina MC, Dionisio TJ, et al. Comparison of the efficacy of etoricoxib and ibuprofen in pain and trismus control after lower third molar removal. *Rev Odontol UNICID* 2006;18(1):29-36.
  15. Fernandez C, Reader A, Beck M, Nusstein J. A prospective, randomized, double-blind comparison of bupivacaine and lidocaine for inferior alveolar nerve blocks. *J Endod* 2005;31(7):499-503.
  16. Benetello V, Sakamoto FC, Giglio FPM, Sakai VT, Calvo AM, Modena KCS, et al. The selective and non-selective cyclooxygenase inhibitors valdecoxib and piroxicam induce the same postoperative analgesia and control of trismus and swelling after lower third molar removal. *Braz J Med Biol Res* 2007;40(8):1133-40.
  17. Costa CG, Tortamano IP, Rocha RG, Franciscone CE, Tortamano N. Onset and duration periods of articaine and lidocaine on maxillary infiltration. *Quintessence Int* 2005;36(3):197-201.
  18. Tofoli GR, Ramacciato JC, de Oliveira PC, Volpato MC, Groppo FC, Ranali J. Comparison of effectiveness of 4% articaine associated with 1:100,000 or 1:200,000 epinephrine in inferior alveolar nerve block. *Anesth Prog* 2003;50(4):164-8.
  19. Moore PA, Boynes SG, Gersh EV, DeRossi SS, Sollecito TP, Goodson JM, et al. The anesthetic efficacy of 4 percent articaine 1:200,000 epinephrine: two controlled clinical trials. *J Am Dent Assoc* 2006;137(11):1572-81.
  20. Laskin JL, Wallace WR, DeLeo B. Use of bupivacaine hydrochloride in oral surgery: a clinical study. *Oral Surg* 1977;35(1):25-9.
  21. Moore PA, Dunsky JL. Bupivacaine anesthesia: a clinical trial for endodontic therapy. *Oral Surg Oral Med Oral Pathol* 1983;55(2):176-9.
  22. Dunsky JL, Moore PA. Long-acting local anesthetics: a comparison of bupivacaine and etidocaine hydrochloride in endodontics. *J Endod* 1984;10(9):457-60.
  23. Ruetsch YA, Böni T, Borgeat A. From cocaine to ropivacaine: the history of local anesthetic drugs. *Curr Top Med Chem* 2001;1(3):175-82.
  24. Nayyar MS, Yates C. Bupivacaine as pre-emptive analgesia in third molar surgery: randomized controlled trial. *Br J Oral Maxillofac Surg* 2006;44(6):501-3.
  25. Oertel R, Berndt A, Kirch W. Saturable in vitro metabolism of articaine by serum esterases: does it contribute to the persistence of the local anesthetic effect? *Reg Anesth* 1996;21(6):576-81.
  26. Vree TB, Gielen MJ. Clinical pharmacology and the use of articaine for local and regional anesthesia. *Best Pract Res Clin Anaesthesiol* 2005;19(2):293-308.
  27. Moore PA, Doll B, Delie RA, Hersh EV, Korostoff J, Johnson S, et al. Hemostatic and anesthetic efficacy of 4% articaine HCl with 1:200,000 epinephrine and 4% articaine HCl with 1:100,000 epinephrine when administered intraorally for periodontal surgery. *J Periodontol* 2007;78(2): 247-53.
  28. Haas DA, Lennon D. A 21-year retrospective study of reports of paresthesia following local anesthetic administration. *J Can Den Assoc* 1995;61(4):319-20,323-6,329-30.
  29. Hillerup S, Jensen R. Nerve injury caused by mandibular block analgesia. *Int J Oral Maxillofac Surg* 2006;35(5):437-43.
  30. Haas DA. Articaine and paresthesia: epidemiological studies. *J Am Coll Dent* 2006;73(3):5-10.
  31. Yagiela JA. Recent developments in local anesthesia an oral sedation. *Compend Contin Educ Dent* 2004;25(9):697-706.
  32. Hintze A, Paessler L. Comparative investigations on the efficacy of articaine 4% (epinephrine 1:200,000) and articaine 2% (epinephrine 1:200,000) in local infiltration anaesthesia in dentistry—a randomised double-blind study. *Clin Oral Investig* 2006;10(2):145-150.
  33. Potocnik I, Tomsic M, Sketelj J, Bajrovic FF. Articaine is more effective than lidocaine or mepivacaine in rat sensory nerve conduction block in vitro. *J Dent Res* 2006;85(2):162-6.
  34. Montebugnoli L, Servidio D, Miaton RA, et al. Heart rate variability: a sensitive parameter for detecting abnormal cardiocirculatory changes during a stressful dental procedure. *J Am Dent Assoc* 2004;135(12):1718-23.
  35. Naguib M, Magboul MM, Samarkandi AH, Attia M. Adverse effects and drug interactions associated with local and regional anaesthesia. *Drug Saf* 1998;18(4):221-50.
  36. Wynn RL. Articaine 4% with 1:200,000 epinephrine: an acceptable option for patients with QT syndrome. *Gen Dent* 2007;55(3):176-8.
  37. Knoll-Köhler E, Frie A, Becker J, Ohlendorf D. Changes in plasma epinephrine concentration after dental infiltration anesthesia with different doses of epinephrine. *J Dent Res* 1989;68(6):1098-101.
  38. Daublander M, Muller R, Lipp MD. The incidence of complications associated with local anesthesia in dentistry. *Anesth Prog* 1997;44(4):132-41.
  39. Hersh EV, Giannakopoulos H, Levin LM, Secreto S, Moore PA, Peterson C, et al. Pharmacokinetics and cardiovascular effects of high doses articaine with 1:100,000 and 1:200,000 epinephrine. *J Am Dent Assoc* 2006;137(11):1562-71.
  40. Troullos ES, Goldstein DS, Hargreaves KM, Dionne RA. Plasma epinephrine levels and cardiovascular response to high administered doses of epinephrine contained in local anesthesia. *Anesth Prog* 1987;34(1):10-3.
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