Original Article

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Comparison of the effects of articaine and bupivacaine in impacted mandibular third molar tooth surgery: a randomized, controlled trial

Berkay Tokuç, Fatih Mehmet Coşkunses

Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Kocaeli University, Kocaeli, Turkey

Background: The aim of this randomized, triple-blind trial was to determine the anesthetic, analgesic, and hemodynamic effects of articaine and bupivacaine in the extraction of impacted mandibular third molar teeth.
Methods: Twenty-six patients who underwent removal of bilaterally symmetric mandibular third molars were randomly assigned to articaine and bupivacaine groups in a split-mouth design. The onset of anesthetic action, intraoperative comfort, total amount of solution used, duration of postoperative anesthesia and analgesia, rescue analgesic use, postoperative pain, intraoperative bleeding, and hemodynamic parameters were evaluated.
Results: In the articaine group, the onset of anesthetic activity was faster, intraoperative comfort was greater, and effective anesthesia required less local anesthetic solution. The bupivacaine group showed a significantly longer duration of postoperative anesthesia and analgesia, in addition to lower visual analog scale values at 6 and 48 hours postoperatively. There were no significant differences between the two solutions regarding rescue analgesic medication use, intraoperative bleeding, or hemodynamics.
Conclusion: Articaine showed greater clinical efficacy than bupivacaine in intraoperative anesthesia, achieving faster onset of anesthetic action and greater patient comfort while also requiring less reinforcement during surgery. However, bupivacaine was superior in terms of postoperative anesthesia, reducing postoperative pain due to its residual anesthetic and analgesic effects. Both anesthetic solutions led to similar hemodynamics at low doses in mandibular third molar surgery

Keywords: Anesthesia; Articaine; Bupivacaine; Postoperative Pain; Third Molar; Tooth Extraction.

INTRODUCTION

Postoperative pain is induced by intraoperative trauma and the release of chemical mediators, such as histamine, serotonin, quinine, and arachidonic acid [1]. In post-operative pain control, the combination of short-acting local anesthetics and nonsteroidal anti-inflammatory drugs (NSAIDs) is used frequently; however, the application of long-acting local anesthetics is also effective in managing postoperative pain [2,3].

The administration of long-acting local anesthetics decreases pain level and duration, especially in the first 6–8 hours after oral administration [2,4–6]. Furthermore, some authors have claimed that long-acting local anesthetics decrease the total amount of analgesic use due to their residual analgesic effect [4,6]. This feature reduces postoperative pain, which is one of the main concerns in patients undergoing surgery [3].

Articaine is widely used in oral surgery, with a rapid

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Corresponding Author: Berkay Tokuç, Kocaeli University, Faculty of Dentistry, Department of Oral and Maxillofacial Surgery, Yuvacık/Başiskele, 41190 Kocaeli, Turkey
Tel: +00-90-262-344-2222 / 5030 Mobile: +00-90-537-546-3886 Fax: +00- 90-262-344-2109 E-mail: berkay_tokuc@hotmail.com

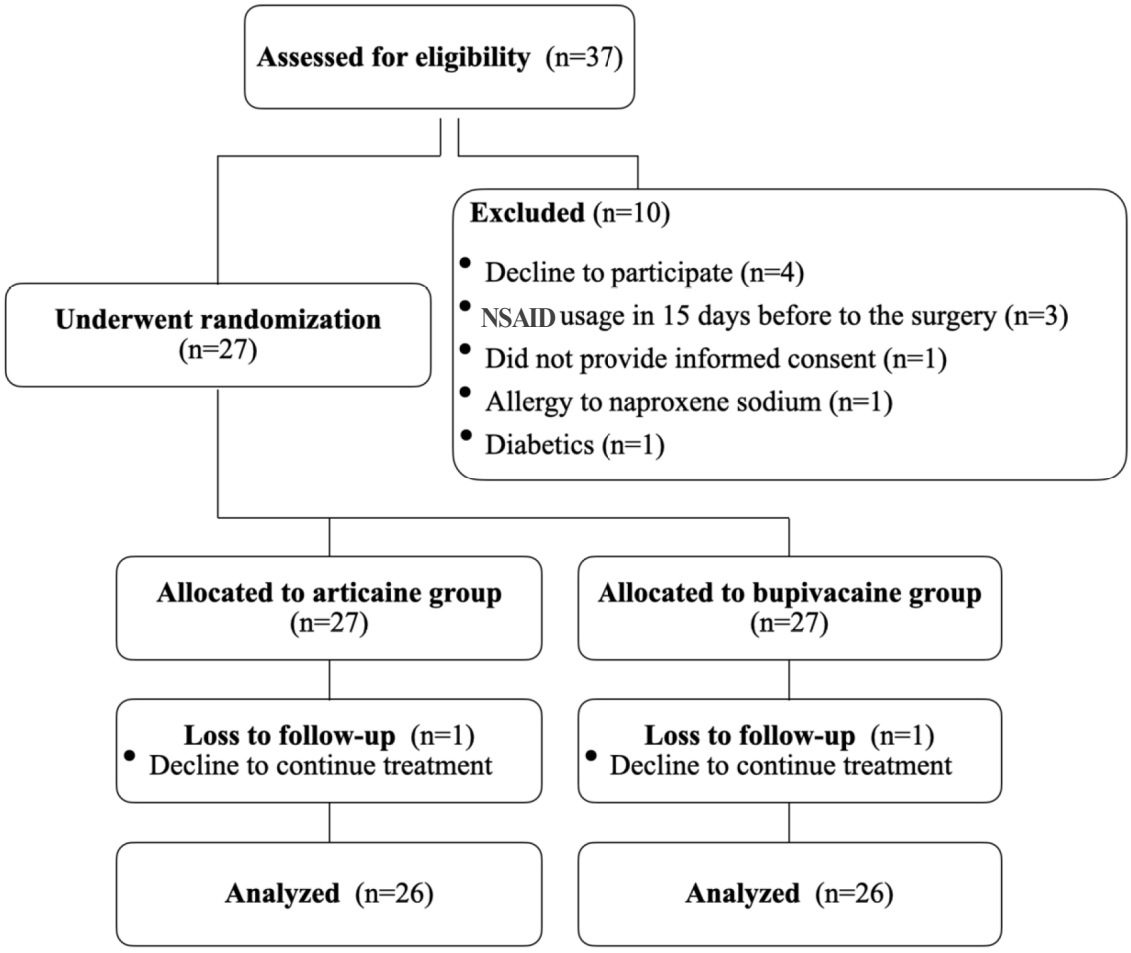

Fig. 1. Flow diagram of participant inclusion in the study. NSAID, nonsteroidal anti-inflammatory drug.

onset of action and low risk of side effects [7]. Bupivacaine is a potent, amide-type local anesthetic agent with a long duration of action and has a residual analgesic effect [4,7]. The long-term anesthetic and analgesic effects of bupivacaine yield a more comfortable postoperative period, but prolonged anesthesia in soft tissues can also be an unpleasant feeling for patients. Therefore, its use is recommended in operations of long duration or operations that are expected to cause severe pain in the early postoperative period [4,5,8].

Although many authors have compared the effects of local anesthetic agents in the literature, very few studies have compared the effects of articaine and bupivacaine in third molar surgery in a split-mouth design. The aim of this study was to determine the anesthetic, analgesic, and hemodynamic effects of articaine and bupivacaine in the extraction of symmetrically impacted mandibular third molar teeth.

METHODS

1. Patient selection and study design

The sample size was calculated using postoperative pain as the primary outcome. A power calculation was performed for a power of 80% and significance level of 5% using a two-sided unpaired t-test. Based on these data, at least 26 patients in each experimental group were required to detect a significant difference between the groups. Therefore, 27 patients were included in the study.

A randomized, triple-blinded study was performed in a consecutive series of 27 patients. The study included

26 patients: 6 (23.1%) men and 20 (76.9%) women. Their mean age was 22.1 years (range, 18–36 years) (Fig. 1).

This research was conducted in accordance with the Helsinki Declaration and was approved by the ethics committee of the Kocaeli University, School of Medicine, Kocaeli, Turkey (process no. 2018/338; Clinical Trials Registry Id Number: NCT04645888). The manuscript has been written according to the CONSORT guidelines for reporting RCTs (http://www.consort-statement.org). All patients received information about the study and signed informed consent forms.

The inclusion criteria were as follows: (1) age >18 years; (2) bilateral symmetric impacted mandibular third molars; and (3) American Society of Anesthesiology score of 1. The exclusion criteria were as follows: (1) presence of any systemic diseases, (2) allergy to articaine or bupivacaine, (3) allergy to NSAIDs, and (4) use of analgesic or anti-inflammatory drugs 15 days before the surgery.

This was a triple-blinded study; the patients, surgeon, and statistician were blinded to the group allocations. Operations were performed on each patient at two appointments separated by an interval of at least three weeks. The local anesthetic solutions were coded as numbers 1 and 2 by an independent body who was not involved in the study, and a random draw determined which local anesthetic solution would be applied at each appointment.

2. Surgical procedure

The same surgeon performed all surgeries, and the same person monitored all patients in this study. Both groups were blinded to the group allocations. Either 4% articaine with 1:200,000 epinephrine (Ultracain DS, Sanofi Aventis, Istanbul, Turkey) or 0.5% bupivacaine without epinephrine (Marcaine 0.5%, Astra Zeneca Ilaç, Istanbul, Turkey) was administered to the patients using the inferior alveolar nerve block technique at the first intervention. During the second surgery, another anesthetic solution was administered to the patients. A total of 2 ml of anesthetic solution was used in each surgery: patients received 1.5 ml of the anesthetic solution to anesthetize the inferior alveolar nerve and lingual nerve, and the remaining solution (0.5 ml) was administered to anesthetize the buccal nerve.

The mucoperiosteal flap was elevated with a horizontal incision and vertical incision from the mesial line angle of the mandibular second molar. Osteotomy and odontosection were performed, and the wound was closed using 3/0 silk suture for primary closure. The same procedures were performed on the other side after a washout period of three weeks. All patients were prescribed an antibiotic (amoxycillin-clavulanic acid, 1000 mg), an NSAID (naproxen sodium, 500 mg), and mouth rinse (0.12% chlorhexidine gluconate). Patients were instructed to use paracetamol in case of pain as a rescue medication during the postoperative period.

3. Data collection

Each patient's weight, height, and body mass index (BMI) were recorded. Before extraction, the teeth were classified according to Winter's classification [9]. The duration of surgery was recorded for both sides.

The onset of anesthetic action was determined by the first sign of numbness in the ipsilateral lower lip, tongue, and alveolar mucosa. The surgeon evaluated the quality of anesthesia using a three-point category rating scale [10], and intraoperative bleeding was rated using a 3-point category rating scale [11]. A modified Parant scale was used to determine the difficulty of the surgery [12]. The total amount of local anesthetic solution and the presence of any side effects during the operation were also recorded.

The duration of the postoperative anesthesia and postoperative analgesia was determined using the absence of sensitivity in the ipsilateral lower lip, tongue, and alveolar mucosa and the time from the end of the operation to the first naproxen sodium intake. Patients were instructed to indicate their pain 6, 12, 24, 48, and 72 hours and 7 days postoperatively using a visual analog scale (VAS) that ranged from 0 to 10. The time of the first rescue medication intake and total amount of rescue

Table 1. Baseline demographic characteristics of the patients

Variable	N
Patients	26
Gender n (%)	
Female	20 (76.9)
Male	6 (23.1)
Age (years; mean ± SD, range)	22.1 ± 4.00 (18-36)
Weight (kg; mean ± SD, range)	59.6 ± 14.0 (43-100)
Height (cm; mean ± SD, range)	167.9 ± 10.6 (153-194)
BMI (kg/m^2; mean±SD,range)	20.8 ± 2.8 (17.8-27.9)
Angulation of impacted teeth according to Winter classification n (%)	
Vertical	12 (46.2)
Mesioangular	9 (34.6)
Horizontal	4 (15.4)
Distoangular	1 (3.8)

BMI, body mass index; n, number.

medication were also recorded in the questionnaire by the patients.

The same patient monitor was used to determine systolic and diastolic blood pressure, cardiac rate, and blood oxygen saturation level at baseline (T1), 1 min after anesthesia (T2), and immediately after surgery (T3).

4. Statistical analysis

Statistical analyses were performed using SPSS 20.0 for Windows (SPSS, Inc., Chicago, IL, USA). Normality was tested using the Shapiro–Wilk test. The paired t-test was used to compare two normally distributed numerically dependent measurements, and the Wilcoxon test was used to compare two non-normally distributed numerically dependent measurements. The relationships between categorical variables were tested using the chi-squared test. Student's t-test and Mann–Whitney U test were performed to investigate the numerical variables in both groups. Statistical significance was set at $P < 0.05$.

RESULTS

A total of 26 healthy patients (6 men and 20 women) with a mean age of 22.1 years (range 18–36 years) were included in this study. Baseline demographic characteristics of the patients are shown in Table 1. The duration of surgery and difficulty of surgery according to the modified Parant scale were comparable between groups (P = 0.10 and P = 0.70, respectively) (Table 2).

Table 2. Comparison of groups in terms of the mean duration and difficulty of surgery based on the modified Parant scale

Study Group	Duration of surgery (min) (± SD)	Difficulty of surgery
Articaine	17.11 ± 6.88	3.34 ± 0.89
Bupivacaine	18.80 ± 6.38	3.30 ± 0.97

†Paired t-test, ‡Wilcoxon test, SD, standard deviation.

There was a statistically significant difference between the onset of anesthetic action of articaine and bupivacaine (P = 0.02). Intraoperative discomfort was significantly lower in the articaine group than in the bupivacaine group (P = 0.002). Thus, significantly larger quantities of bupivacaine than articaine were needed to provide effective anesthesia (P = 0.008) (Table 3).

The bupivacaine group had lower pain scores than the articaine group 6 and 48 hours postoperatively (P = 0.03 and P = 0.03, respectively) (Table 4).

The mean duration of postoperative anesthesia and analgesia was greater in the bupivacaine group than in the articaine group (P = 0.001 and P = 0.01, respectively) (Table 5).

The total rescue analgesic medication usage, percentage of patients taking this drug, and the time to the ingestion of the first rescue medication were comparable in both groups (P = 0.20, P = 0.69, and P = 0.60).

Hemodynamic changes including T0–T1, T0–T2, and T1–T2 values were comparable between groups for systolic blood pressure (T0–T1: P = 0.31, T0–T2: P = 0.53, T1–T2: P = 0.62), diastolic blood pressure (T0–T1: P = 0.97, T0–T2: P = 0.80, T1–T2: P = 0.96), heart rate (T0–T1: P=0.67, T0–T2: P = 0.81, T1–T2: P = 0.22), and blood oxygen saturation (T0–T1: P = 0.73, T0–T2: P = 0.76, T1–T2: P = 0.47). In addition, there were no statistically significant differences between the two groups in terms of the amount of intraoperative bleeding (P = 0.41).

Table 3. Comparison of intraoperative parameters, including onset of anesthetic action, total amount of anesthesia used, and intraoperative comfort

Intraoperative parameters	Articaine	Bupivacaine	P - value
Onset of action (sec) (±SD)	51.34 ± 23.64	74.03 ± 40.29	0.020†*
Total amount (ml) (±SD)	2.26 ± 0.66	2.84 ± 1.38	0.002†*
Intraoperative comfort	1.11 ± 0.32	1.53 ± 0.64	0.002†*
Intraoperative bleding	1.23 ± 0.60	1.46 ± 0.54	0.410‡

*P < .05 considered statistically significant.
†Wilcoxon test, ‡chi-square test, SD, standard deviation.

Table 4. Comparison of groups in terms of postoperative pain based on VAS scores

Postoperative pain	Articaine (± SD)	Bupivacaine (± SD)	P - value†
6th hour	3.23 ± 2.59	2.12 ± 2.40	0.030*
12th hour	1.76 ± 2.25	1.71 ± 2.42	0.720
24th hour	1.03 ± 1.17	1.10 ± 1.85	0.830
48th hour	0.63 ± 0.82	0.39 ± 0.49	0.030*
72th hour	0.91 ± 1.54	1.25 ± 2.28	0.370
7th day	0.68 ± 1.25	0.60 ± 1.33	0.660

*P < .05 considered statistically significant.
†Wilcoxon test, SD, standard deviation; VAS, visual analog scale.

Table 5. Comparison of postoperative parameters, including duration of postoperative anesthesia and analgesia, total amount of anesthesia used, percentage of patients taking rescue analgesic medication, and time to of first rescue analgesic medication

Postoperative parameters	Articaine	Bupivacaine	P - value
Duration of anesthesia (min) (± SD)	233.87 ± 51.22	426.37 ± 192.24	0.001†*
Duration of analgesia (min) (± SD)	186.30 ± 89.86	288.26 ± 221.75	0.010‡*
Total amount of rescue analgesic use (tablet [500 mg] per patient) (± SD)	1.50 ± 3.06	0.73 ± 1.11	0.200‡
Percentage of patients taking rescue analgesic (%) (± SD)	50	42.3	0.690††
Time to ingestion of first rescue analgesic (min) (± SD)	1531.33 ± 1771.42	2736.33 ± 3767.32	0.600††

*P < .05 considered statistically significant.
†Paired test, ‡Wilcoxon test, ††chi-square test, SD, standard deviation.

DISCUSSION

The present study compared the anesthetic, analgesic, and hemodynamic effects of articaine and bupivacaine in surgery for symmetrically impacted third molar tooth. This randomized, controlled, triple-blinded study was performed by a single surgeon to minimize discrepancies in operating techniques, type and duration of operations, and patient evaluations. The split-mouth design also diminished the variables related to patient differences.

The results of our study showed that articaine was superior in factors related to intraoperative anesthesia, such as the onset of anesthetic action, total amount of anesthesia used, and intraoperative comfort. In contrast, bupivacaine showed a better clinical effect in post-operative anesthesia; it increased the duration of postoperative anesthesia and analgesia while reducing postoperative pain. The effects of articaine and bupivacaine on the use of rescue analgesics and vital signs were similar.

Cardiotoxic effects of bupivacaine have been reported in the literature [13]. In the present study, systolic and diastolic blood pressure did not differ between the two

groups. Heart rate and blood oxygen saturation decreased in the postoperative period, but a statistically significant difference was not found between groups, which was in accordance with the results obtained in other studies [14,15]. One of the main reasons for this could be that the present and similar studies in the literature were performed in younger patients without systemic diseases [14,15-17]. Another reason may be the use of low doses of local anesthetics due to the extraction of only one impacted tooth. In support of this view, Troullos et al. [18] extracted four impacted third molar teeth simultaneously with 2% lidocaine, and a significant increase in all hemodynamic parameters was reported.

In this study, the onset of action in the articaine group was faster than that in the bupivacaine group, which is compatible with previous reports in the literature [8,14]. Anesthetic action starts faster when the pKa of local anesthetic agents is close to the pH of the tissue where they are injected. The pKa values of the tissue, bupivacaine, and articaine were 7.4, 8.1, and 7.8, respectively. Thus, articaine creates more free molecular forms in the tissue and diffuses better into the nerve membrane [7,19].

The duration of postoperative anesthesia was significantly higher in the bupivacaine group, with a mean duration of 426 minutes. Similar to this study, some researchers have presented results demonstrating that bupivacaine provides long-lasting anesthetic action [5,8, 14,15−17,20]. The possible causes are not only the high pKa of bupivacaine but also its high protein-binding capacity. Additionally, the rapid metabolism of articaine due to its degradation by hydrolysis may have caused an increase in the difference in the duration of postoperative anesthesia between articaine and bupivacaine in the present study [7,19].

The elimination of articaine is faster than that of bupivacaine because it is metabolized in both the plasma and liver. Therefore, the duration of postoperative analgesia with articaine is shorter than that of bupivacaine [8]. Chapman et al. [4] and Fernandez et al. [20] reported that the analgesic effect of bupivacaine was superior to that of lidocaine and mepivacaine. In the present study, bupivacaine was reported to have a longer duration of action. Many studies have compared bupivacaine with other local anesthetics, such as lidocaine, mepivacaine, and articaine, and have recommended the use of bupivacaine in long-term surgical procedures because of its residual analgesic effect [4,20,21]. The present study demonstrated that the total amount of rescue medication was lower and the time to ingestion of the first rescue analgesic was higher in the bupivacaine group, but no statistically significant difference was observed between the two solutions. Olmeda-Gaya et al. [2] used paracetamol as a rescue analgesic medication in their study, and the rescue analgesic consumption in the articaine group was greater than that in the bupivacaine group. In addition, the time to ingestion of the first rescue medication was shorter in the articaine group, but the difference was not significant, similar to the findings in our study. Thakare et al. [22] also reported that bupivacaine provides longer analgesia than articaine during the postoperative period.

The VAS is a universal method of pain measurement and is frequently used in the evaluation of postoperative pain in oral surgery [23,24]. In our study, the VAS was used to compare the postoperative efficacy of two local anesthetic agents. Bupivacaine is effective in reducing or delaying postoperative pain due to its residual analgesic effect and long duration of action. These findings coincide with those of most published studies; bupivacaine provides a more comfortable postoperative period because of its 8−12-h residual analgesic effect , which is the period with the highest level of pain after third molar tooth extraction [16,20,24]. Another study reported that pain was more severe in the articaine group and reached its highest level earlier (after 6 hours postoperatively) than in the bupivacaine group (after 12 hours postoperatively) [14]. In the present study, bupivacaine reduced pain more effectively than articaine at 6 and 48 hours postoperatively, but not at 12 and 24 hours postoperatively. The lack of a statistically significant difference between solutions might be due to the small

sample size of our study. Therefore, further clinical trials with larger sample sizes are required to confirm the efficacy of bupivacaine against postoperative pain in different timeframes.

In conclusion, articaine was more effective than bupivacaine in terms of the onset of anesthetic action, intraoperative comfort, and amount of solution used; however, bupivacaine was more effective than articaine in terms of postoperative comfort, as indicated by the VAS scores, and the mean duration of postoperative anesthesia and analgesia. Moreover, the hemodynamic parameters of both solutions were similar at the therapeutic doses. From a clinical perspective, articaine may be the best choice for optimal anesthesia when the main concern of the patient or dentist is intraoperative comfort (i.e., in circumstances involving patient anxiety and surgical difficulty), with the understanding that rescue analgesics will be required early. However, bupivacaine may be a better choice if the patient or dentist is most worried about postoperative pain management due to a patient's allergy to pain medications or the expectation of high postoperative surgical pain, as bupivacaine will provide adequate anesthesia and superior postoperative analgesia due to its longer action.

AUTHOR ORCIDs

Berkay Tokuç: https://orcid.org/0000-0002-1149-2886
Fatih Mehmet Coşkunses: https://orcid.org/0000-0001-8764-5992

AUTHOR CONTRIBUTIONS

Berkay Tokuç: Data curation, Formal analysis, Investigation, Resources, Validation, Writing - original draft
Fatih Mehmet Coşkunses: Conceptualization, Methodology, Project administration, Supervision, Visualization, Writing - review & editing

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ETHICS: The study was conducted in accordance with the World Medical Association Declaration of Helsinki and was approved by the ethics committee of the Kocaeli University School of Medicine, Kocaeli, Turkey (process no. 2018/338; Clinical Trials Registry: Primary Id Number: NCT04645888).

DATA AVAILABILITY STATEMENT: The data that support the findings of this study are available from the corresponding author (B.T.) upon reasonable request.

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