Comparative assessment of pain and paresthesia using articaine and mepivacaine in mandibular third molar surgery: a split-mouth randomized clinical trial

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https://doi.org/10.1590/SciELOPreprints.17533

Submitted on: 2026-09-02
Posted on: 2026-09-02 (version 1)
(YYYY-MM-DD)

e20260032
Original Article

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Avaliação comparativa da dor e parestesia com o uso de articaína e mepivacaína em cirurgia de terceiro molar inferior: um ensaio clínico randomizado com boca dividida

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How to cite:
Oliveira JCS, Delamura IF, Ferreira DSB, Viotto AHA, Prado GAS, Bassi APF. Comparative assessment of pain and paresthesia using articaine and mepivacaine in mandibular third molar surgery: a split-mouth randomized clinical trial. Rev Odontol UNESP. 2026;55:e20260032. https://doi.org/

Resumo

Objetivo: Comparar a intensidade da dor pós-operatória e a ocorrência de parestesia após a cirurgia de terceiros molares inferiores utilizando articaína a 4% ou mepivacaína a 2% como anestésicos locais. **Material e método:** Foi realizado um ensaio clínico randomizado, duplo-cego e de desenho *split-mouth* (boca dividida) com 30 pacientes saudáveis submetidos à extração bilateral de terceiros molares inferiores. Todos os procedimentos foram realizados por um único cirurgião. Seguindo uma sequência aleatória, cada paciente recebeu mepivacaína a 2% em um lado e articaína a 4% no lado contralateral. A intensidade da dor pós-operatória foi avaliada às 6, 12 e 24 horas utilizando uma escala de dor validada. A parestesia foi avaliada por meio de questionários aplicados aos pacientes e testes neurossensoriais aos 7 e 30 dias após a cirurgia. **Resultado:** Não foram observados casos de parestesia persistente em nenhum dos grupos. A intensidade da dor não diferiu significativamente entre as soluções anestésicas às 6 ou 12 horas de pós-operatório. No entanto, às 24 horas, os pacientes que receberam mepivacaína relataram escores de dor significativamente mais altos do que aqueles que receberam articaína ($p < 0,05$). Ambos os anestésicos proporcionaram anestesia

intraoperatória adequada. **Conclusão:** Ambas as soluções anestésicas foram seguras e eficazes para a cirurgia de terceiros molares inferiores. Contudo, a articaína a 4% proporcionou analgesia pós-operatória superior às 24 horas, sem aumentar o risco de parestesia persistente.

Descritores: Terceiro molar; anestesia local; articaína; mepivacaína; parestesia; dor.

Abstract

Objective: To compare postoperative pain intensity and the occurrence of paresthesia following mandibular third molar surgery using 4% articaine or 2% mepivacaine as local anesthetics. **Material and method:** A randomized, double-blind, split-mouth clinical trial was conducted with 30 healthy patients undergoing bilateral mandibular third molar extractions. All procedures were performed by a single surgeon. According to a randomized sequence, each patient received 2% mepivacaine on one side and 4% articaine on the contralateral side. Postoperative pain intensity was assessed at 6, 12, and 24 hours using a validated pain scale. Paresthesia was evaluated through patient questionnaires and neurosensory testing at 7 and 30 days after surgery. **Result:** No cases of persistent paresthesia were observed in either group. Pain intensity did not differ significantly between anesthetic solutions at 6 or 12 hours postoperatively. However, at 24 hours, patients receiving mepivacaine reported significantly higher pain scores than those receiving articaine ($p < 0.05$). Both anesthetics provided adequate intraoperative anesthesia. **Conclusion:** Both anesthetic solutions were safe and effective for mandibular third molar surgery. However, 4% articaine provided superior postoperative analgesia at 24 hours without increasing the risk of persistent paresthesia.

Descriptors: Third molar; local anesthesia; articaine; mepivacaine; paresthesia; pain.

INTRODUCTION

The extraction of impacted mandibular third molars is one of the most frequent surgical procedures in oral surgery[1,2]. As it often requires reflecting soft tissue flaps and removing bone, postoperative trauma may result in significant inflammation, manifested as pain, edema, and restricted mouth opening[3,4]. Thus, this surgical model is well suited to investigate acute postoperative pain and to compare analgesic or anesthetic interventions[5-10].

Local anesthesia with amide agents is central to pain control in oral surgery[11-13]. While local anesthesia is generally safe, one rare but notable complication is paresthesia: a sensory disturbance ranging from numbness, tingling, burning sensations to altered or persistent sensation[14-16]. Several retrospective reports have raised concern that 4% articaine (ART) may be disproportionately associated with paresthesia compared with other amide anesthetics[14,17-21]. However, recent systematic reviews and meta-analyses have not found a statistically significant increase in risk of hypesthesia or nerve injury with articaine, especially when applied in third molar surgery[17,20].

Pharmacokinetic and molecular differences among local anesthetics may influence both clinical efficacy and safety[22]. ART contains a thiophene ring and an ester side chain that allows for rapid plasma hydrolysis, potentially reducing systemic toxicity, and also has high lipid solubility, which enhances tissue diffusion[23-25].

In contrast, mepivacaine (MEP), a classic amide anesthetic widely used in dentistry, is metabolized in the liver and exhibits low intrinsic vasodilatory activity, which allows for effective anesthesia even without a vasoconstrictor[26]. However, comparative studies indicate that, when compared with ART, MEP may show slower onset, lower tissue diffusion, and slightly reduced anesthetic success rates in procedures that require extensive bone or soft-tissue penetration, such as mandibular third molar surgery or supplementary infiltrations[27-28].

Given these pharmacological differences, randomized clinical trials are essential to clarify both analgesic efficacy and sensory safety. The aim of this clinical study was to compare postoperative pain intensity and the occurrence of paresthesia in patients undergoing mandibular third molar surgery using ART versus MEP as local anesthetics.

MATERIAL AND METHOD

Study design

The study was approved by the Research Ethics Committee of the Faculty of Dentistry, Aracatuba Dental School – UNESP, Brazil (CAAE: 12349319.0.0000.5420). The study was designed as a randomized, double-blind, split-mouth, crossover, paired clinical trial. Each participant underwent two separate mandibular third molar surgeries performed at least 15 days apart, receiving 4% articaine in one procedure and 2% mepivacaine in the other according to a randomized allocation sequence.

The study report followed the CONSORT (Consolidated Standards of Reporting Trials) guidelines (http://www.consort-statement.org). Participants who did not strictly adhere to the study protocol were excluded.

Participants

The study included patients from the Araçatuba Dental School, Universidade Estadual Paulista “Júlio de Mesquita Filho” (UNESP), who were referred for elective surgical removal of bilateral mandibular third molars.

Inclusion criteria were: individuals aged 18–35 years, in good general and oral health, presenting orthodontic indication for bilateral extraction of the lower third molars (teeth 38 and 48) positioned similarly and unrelated to the inferior alveolar nerve, and with at least two-thirds of root formation confirmed radiographically.

Exclusion criteria included: asymmetric or non-homologous positions of mandibular third molars, or proximity to the inferior alveolar nerve; presence of local conditions contraindicating surgery (such as pericoronitis, odontogenic cysts or tumors, or infection symptoms); systemic diseases that could interfere with healing or drug safety (e.g., diabetes, hypertension, hyperthyroidism, osteoporosis, or gastrointestinal disorders); use of any medication within 30 days before surgery; hypersensitivity to articaine or mepivacaine; intolerance to materials used in the study (chlorhexidine alcoholic or gluconate solution, or articaine hydrochloride with epinephrine 1:100,000); and female participants who were menstruating, pregnant, or breastfeeding at the time of the procedures.

All participants provided written informed consent prior to enrollment in the trial.

Sample size

The sample size calculation was based on postoperative pain intensity (Box Scale-11) as the primary outcome, since paresthesia is a binary event with very low incidence and would require an unfeasibly large sample to achieve adequate power. Assuming a paired design, an effect size of dz = 0.54 (medium according to Cohen, 1988) was considered clinically relevant to detect a difference of approximately one point in the BS-11 pain scale between anesthetics. A sample of 30 paired surgeries (15 participants) provided 80 % power ($\beta = 0.20$) at a 5 % significance level ($\alpha = 0.05$). Calculations were performed using the G*Power 3.1 software[29-30].

Randomization and interventions

After eligibility screening, all participants underwent bilateral mandibular third molar extractions performed by the same surgeon. For each side, the type of local

anesthetic - either 4% ART with 1:100,000 epinephrine or 2% MEP with 1:100,000 epinephrine - was randomly assigned using a computer-generated randomization list (Microsoft Excel, 2018). The contralateral side automatically received the alternate anesthetic.

Bilateral mandibular third molar extractions were performed in two separate surgical sessions, with an interval of 15 days between procedures. Each participant received 4% articaine during one surgery and 2% mepivacaine during the contralateral surgery, according to the randomized allocation sequence. The interval between surgeries was considered sufficient to ensure complete recovery from the first procedure and to eliminate any residual pharmacological effects of the previously administered local anesthetic, thereby minimizing potential carryover effects.

Surgical procedure

All surgical procedures were performed by the same experienced surgeon under standardized clinical conditions.

Antisepsis protocol: intraoral antisepsis was carried out using a 0.12% chlorhexidine digluconate aqueous solution, applied through vigorous mouth rinsing for 1 minute, followed by extraoral antisepsis with 0.5% chlorhexidine alcoholic solution.

Anesthetic protocol: anesthesia was achieved through inferior alveolar, lingual, and buccal nerve blocks, administered with a carpule-type aspirating syringe (Duflex®, Brazil) and a 27G long gingival needle (Unoject®, DFL, Brazil). According to random allocation, participants received either 4% articaine with 1:100,000 epinephrine (Articaine®, DFL, Brazil) or 2% mepivacaine with 1:100,000 epinephrine (Mepiadre®,

DFL, Brazil). The maximum dose administered was four cartridges (1.8 mL each; total volume 7.2 mL).

Surgical technique: a linear mucoperiosteal incision was made distal to the lower second molar, with or without a relaxing buccal incision, followed by mucoperiosteal flap elevation using a Molt No. 9 periosteal elevator and a Minnesota retractor for exposure. Ostectomy and odontosection were performed using a tapered fissure carbide bur (No. 702) and/or a round carbide bur (No. 6) mounted on a Magno 604 high-speed handpiece, under copious irrigation with sterile 0.9% saline.

Tooth removal was completed with curved and straight Seldin-type elevators, followed by inspection and removal of the pericoronal tissue using a Lucas curette and curved Kelly forceps. The alveolar bone margins were smoothened with a bone file and irrigated with sterile saline. Finally, interrupted sutures were placed using 4-0 nylon thread (Ethicon®, Johnson & Johnson, Brazil).

All surgeries were performed in an air-conditioned clinical environment between 8:00 a.m. and 6:00 p.m. at the **Faculty of Dentistry of Araçatuba.

Analgesic monitoring

All participants received a prescription for paracetamol 500 mg to be taken “if pain”, at intervals no shorter than 6 hours. Each patient was provided with a pain-diary sheet to record the exact time of each tablet intake, whether partial or full dose, and to note any additional discomfort. Participants were reminded to complete the diary and return it at the 7-day follow-up. Adherence was assessed by comparing self-reported consumption with the number of remaining tablets in the medication envelope. No other analgesics or anti-inflammatory drugs were allowed.

Assessment of pain

Postoperative pain intensity was assessed using the Box Scale-11 (BS-11) visual pain scale. The scale consists of 11 numbered boxes (0–10), where 0 represents "no pain" and 10 represents "worst pain imaginable." Participants were instructed to select the box that best reflected the highest level of pain experienced during the first 24 hours after surgery. The terminology used in the scale was adapted to ensure clarity and comprehension for all participants.

Assessment of paresthesia

Any participant reporting numbness, tingling, or altered sensation in the innervation area of the inferior alveolar or mental nerves was examined using a Semmes–Weinstein esthesiometer on the lower lip, chin, and vestibular mucosa of the mandibular incisors (midline) on postoperative day 7. Testing was performed at five standardized points per region, with three repeated stimulations per point. Before data collection, the examiner was calibrated on ten volunteers, achieving intra-examiner reliability ($\kappa \geq 0.80$). Paresthesia was defined as persistent sensory alteration beyond 14 days or objective sensory deficit detected by esthesiometry at day 7 confirmed by follow-up at day 30.

Statistical analysis

Descriptive and exploratory analyses were conducted for all variables. Categorical data were expressed as absolute and relative frequencies, while continuous variables were summarized by median, minimum, maximum, and interquartile range. The paired Wilcoxon test was used to compare differences between anesthetic agents, whereas the Friedman test followed by the Nemenyi post hoc test was applied to evaluate changes

over time. Fisher's exact test and the chi-square test were used for categorical comparisons.

All statistical analyses were performed using the R software (R Foundation for Statistical Computing, Vienna, Austria), adopting a 5% significance level ($\alpha = 0.05$). Considering the split-mouth paired design, paired nonparametric tests were selected to account for the within-subject nature of the observations. The paired Wilcoxon test was used for comparisons between anesthetic agents, whereas the Friedman test followed by the Nemenyi post hoc test was used to assess changes over time.

RESULT

Of the 55 patients initially evaluated, 20 were excluded for not meeting the inclusion criteria or declining to participate. Among the remaining 35 patients, three were excluded because only one mandibular third molar could be surgically removed, and two withdrew consent before completing the study.

The final sample therefore comprised 30 participants (60 bilateral third molars), which were subdivided according to surgical side (right or left) and randomly assigned to receive either articaine (ART) or mepivacaine (MEP).

The sample included 12 male and 18 female participants, with a mean age of 22 ± 2.6 years. All patients were followed for 30 days postoperatively by telephone to identify any potential complications or adverse effects.

There was no significant difference between the right and left sides regarding anesthetic allocation ($p > 0.05$; Table 1).

Similarly, no significant differences were found between ART and MEP in total surgery time, duration of anesthesia, number of cartridges used, or postoperative analgesic consumption ($p > 0.05$; Table 2).

Surgeries lasted from 9 to 45 minutes, with anesthesia duration ranging from 1.3 to 6.3 hours. Each procedure required two to three anesthetic cartridges, and participants reported consuming up to three analgesic tablets during the postoperative period.

Table 1. Distribution of operated sides according to anesthetic group

Side	Anesthetic		p-value
	Articaine	Mepivacaine	
	Frequency (%)	Frequency (%)	
Right	18 (60.0)	12 (40.0)	0.121
Left	12 (40.0)	18 (60.0)	
Total	30 (100.0)	30 (100.0)	

Values are presented as absolute and relative frequencies. Statistical analysis was performed using the Chi-square test.

Table 2. Median (interquartile range, IQR), minimum and maximum values, and total surgery time for both anesthetic groups

Variable	Anesthetic base				p-value
	Articaine		Mepivacaine		
	Median (interquartile range)	Minimum - maximum	Median (interquartile range)	Minimum - maximum	
Total surgery time (minutes)	15.0 (5.8)	10 - 34	16.5 (9.8)	9 - 45	0.078
Anesthesia duration (hours)	4.0 (1.9)	1.3 – 6.3	3.6 (1.6)	1.9 – 5.2	0.658
Number of tubes	2.0 (0.0)	2 – 3	2.0 (0.0)	2 – 2	0.317
Number of analgesics	2.0 (2.0)	0 - 3	2.5 (2.0)	0 – 3	0.113

Statistical analysis was performed using the paired Wilcoxon test.

At 6 and 12 hours after surgery (Figure 1), there were no significant differences in pain intensity between ART and MEP ($p > 0.05$).

After 24 hours, however, the MEP group showed a significant increase in pain scores compared with the ART group ($p < 0.05$). Pain scores ranged from 0 to 5 for ART and 0 to 6 for MEP.

When analyzed over time, overall pain intensity decreased significantly at 24 hours compared with the earlier postoperative assessments ($p < 0.05$), regardless of the anesthetic used.

No cases of true paresthesia were detected in either group during the 30-day follow-up, according to our operational definition (persistent sensory alteration beyond 14 days and/or objective sensory deficit on esthesiometry at day 7 confirmed at day 30). At the postoperative day-7 assessment, transient sensory complaints (discomfort, tingling, or pain on touch) were reported by 63.3% of participants in the ART group and 60.0% in the MEP group, with no significant difference between anesthetics ($p > 0.05$; Figure 2).

No significant differences were found between ART and MEP regarding participants' perceptions of discomfort or overall satisfaction after the anesthesia effect subsided ($p > 0.05$; Figure 3).

A total of 56.7% of participants in the ART group and 66.7% in the MEP group reported experiencing bothersome postoperative pain and used analgesic medication during recovery.

DISCUSSION

The present randomized split-mouth crossover clinical trial demonstrated that both articaine and mepivacaine were effective local anesthetics for mandibular third molar surgery, with no cases of persistent paresthesia observed during the 30-day follow-up. Although pain intensity was similar during the first 12 postoperative hours, articaine

provided significantly better pain control after 24 hours, suggesting a slight clinical advantage in postoperative analgesia.

The absence of persistent paresthesia corroborates the findings of recent systematic reviews and meta-analyses, which have not demonstrated a significant increase in the risk of neurosensory injury associated with 4% articaine when compared with other local anesthetics. Although earlier retrospective studies raised concerns regarding the potential neurotoxicity of articaine, current evidence suggests that factors such as surgical trauma, needle injury, and anatomical proximity to the inferior alveolar nerve are more likely to influence the occurrence of postoperative sensory disturbances than the anesthetic solution itself. Therefore, the present findings reinforce the current evidence supporting the clinical safety of articaine for mandibular third molar surgery[15-19].

The lower pain intensity observed in the articaine group after 24 hours may be related to its pharmacological properties. Articaine presents greater lipid solubility because of its thiophene ring, favoring tissue diffusion and potentially improving the quality of anesthesia during surgical procedures. Although both anesthetics produced adequate intraoperative anesthesia, this greater tissue penetration may have reduced peripheral nociceptive stimulation during surgery, contributing to lower postoperative pain scores. Similar findings have been reported by previous randomized clinical trials, although not all studies have demonstrated statistically significant differences between anesthetic agents[20,21].

The variability among published studies may be explained by methodological differences. Factors such as surgical difficulty, operator experience, anesthetic volume, postoperative analgesic protocols, patient characteristics, and pain assessment methods may influence postoperative outcomes. Furthermore, because pain perception is

subjective and influenced by biological and psychological factors, direct comparisons among clinical trials should be interpreted with caution[23-25].

One of the strengths of the present study was the split-mouth crossover design, in which each participant served as his or her own control, reducing interindividual variability in pain perception and inflammatory response[25-26]. However, some limitations should be considered. The sample size was relatively small, which limits the ability to detect rare adverse events such as paresthesia. Additionally, mandibular third molars were not categorized according to the Winter or Pell and Gregory classifications. Although only patients with bilaterally similar impacted teeth were included to reduce variability in surgical difficulty, the absence of these standardized classifications limits comparison with other clinical studies[27,28].

From a clinical perspective, the present findings suggest that both anesthetic solutions can be safely used for mandibular third molar surgery. The lower pain scores observed with articaine after 24 hours may contribute to greater postoperative comfort without increasing the risk of persistent sensory disturbances, supporting its use as a predictable anesthetic option for routine oral surgery[29,30].

Future studies should include larger patient samples, longer follow-up periods, standardized classification of impacted mandibular third molars, and objective neurosensory assessment methods. In addition, evaluating patient-reported outcomes, quality of life, and postoperative functional recovery may provide a broader understanding of the clinical performance of local anesthetics in oral surgery.

CONCLUSION

Within the limitations of this randomized clinical trial, articaine demonstrated superior analgesic performance and comparable safety to mepivacaine, without evidence of neurotoxicity or increased risk of paresthesia.

ACKNOWLEDGEMENT

We would like to thank the State of Sao Paulo Research Foundation (FAPESP) (grant 2019/20812-6) for financial support. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHORS' CONTRIBUTIONS

Conceptualization, JCSO, IFD and AHAV; methodology IFD, DSBF, GASP and APFB ; software, IFD and AHAV; validation, JCSO; formal analysis IFD and AHAV; investigation, IFD, DSBF, GASP and APFB; resources, JCSO; data curation, GASP and JCSO; writing - original draft preparation, IFD, DSBF and AHAV; writing - review and editing, IFD, DSBF, GASP and APFB; visualization, JCSO; supervision, APFB; project administration, APFB; funding acquisition. APFB and GASP

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CONFLICTS OF INTERESTS

The authors declare no conflict of interest related to this study.

DATA AVAILABILITY

The contents underlying the research text are included in the manuscript.

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Received: June 10, 2026

Accepted: August 10, 2026

Figure 1. Box plot illustrating postoperative pain intensity (Box Scale-11, range 0–10) at 6, 12, and 24 hours after mandibular third molar surgery, comparing

ART and MEP groups.

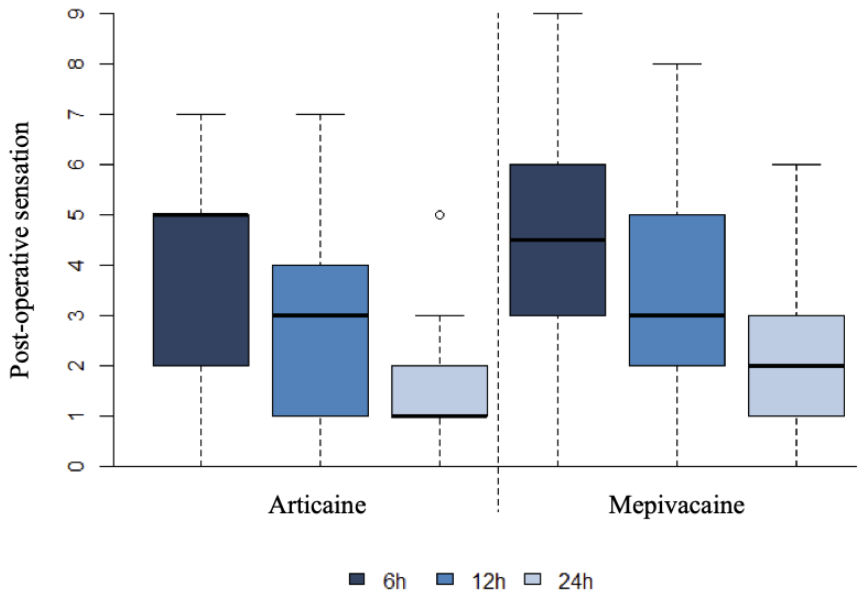


Figure 2. Distribution of participants reporting transient sensory complaints (discomfort, tingling, or pain on touch) at postoperative day 7 according to the anesthetic used.

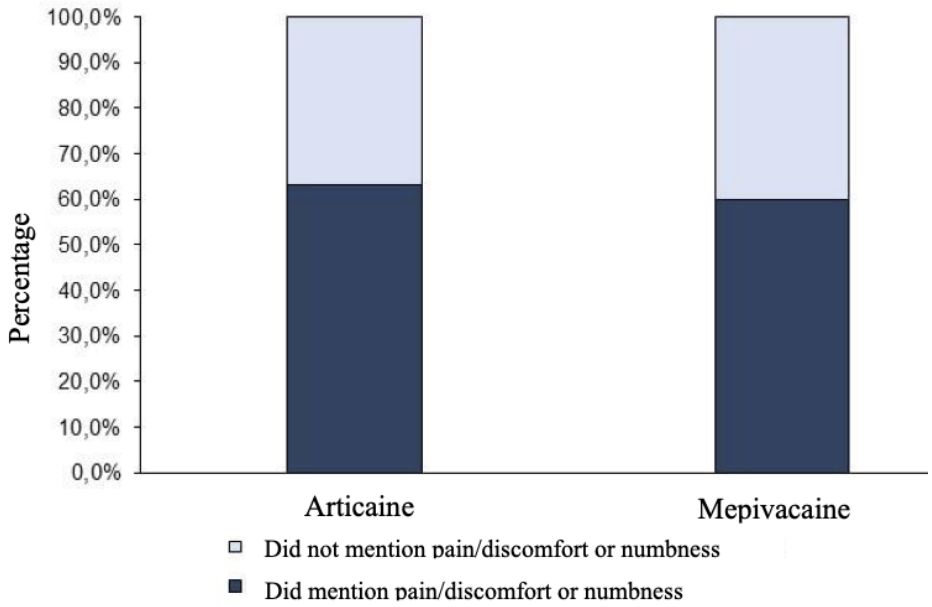
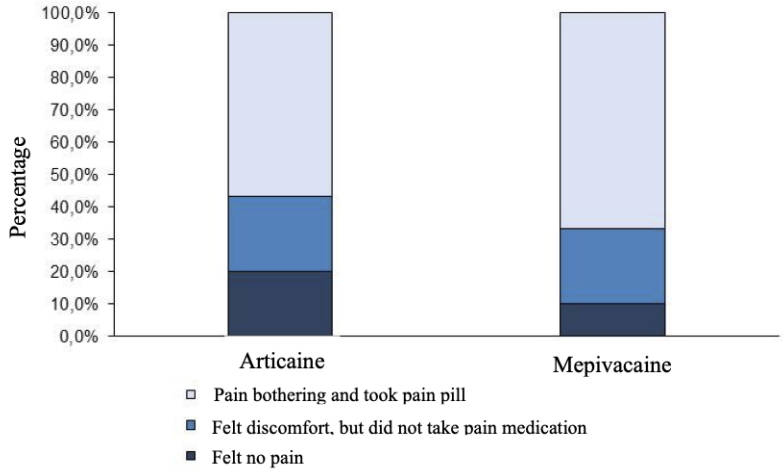


Figure 3. Distribution of participants according to self-reported pain or discomfort immediately after the anesthetic effect subsided, comparing ART and MEP groups.



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