Safety and efficacy of articaine 4% in lower third molar extraction: a systematic review and meta-analysis of randomised clinical trials.

Short title: *Articaine 4% for lower third molar removal.*

Authors: Laura Santos-Sanz [1], Jorge Toledano-Serrabona [2], Cosme Gay-Escoda [3]

[1]DDS. Fellow of the master's degree programme in Oral Surgery (EFHRE International University/ FUCSO, Belize City, Belize).

[2] DDS. Fellow of the master's degree programme in Oral Surgery and Buccofacial Implantology, Faculty of Medicine and Health Sciences, University of Barcelona. Coordinator of master's degree programme in Oral Surgery and Implantology (EFHRE International University/FUCSO, Belize City, Belize). Researcher at IDIBELL (Bellvitge Biomedical Research Institute), Barcelona, Spain.

[3] MD, DDS, MS, PhD, EBOS, OMFS. Chairman and Professor of Oral and Maxillofacial Surgery, University of Barcelona. Director of the master's degree programme in Oral Surgery and Implantology (EFHRE International University/FUCSO). Coordinator/Researcher at IDIBELL (Bellvitge Biomedical Research Institute). Head of the Oral Surgery, Implantology and Maxillofacial Surgery Department of the Teknon Medical Centre, Barcelona (Spain).

Corresponding author: Jorge Toledano-Serrabona

School of Medicine and Health Sciences. Campus de Bellvitge. University of Barcelona.

C/ Feixa Llarga, s/n; Pavelló Govern, 2ª planta, Despatx 2.9

08907 L'Hospitalet de Llobregat; Barcelona (Spain)

Tel: +34 93 402 42 74; E-mail: jorgetoledano25@gmail.com

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

ABSTRACT

Background: To assess whether articaine 4% is a safe and effective local anaesthetic for lower third molar extractions.

Types of studies reviewed: MEDLINE (Pubmed), Cochrane Library, Scopus and Web of Science databases were searched to identify randomised clinical trials that fulfilled the eligibility criteria. Risk of bias was evaluated using the Cochrane risk-of-bias assessment tool. A meta-analysis of safety and efficacy variables was performed by comparing articaine 4% against different local anaesthetics.

Results: We assessed 482 papers, but only 14 randomised clinical trials met the inclusion criteria for review. No statistically significant differences were found between selected local anaesthetics regarding safety. Articaine 4% needed fewer re-injections than lidocaine 2% and exhibited a shorter onset time than lidocaine 2%, bupivacaine 0.5% and lidocaine 4%. Articaine 4% showed a longer anaesthetic effect than lidocaine 2% and mepivacaine 2%, but shorter than bupivacaine 0.5%.

Practical implications: The use of articaine 4% for the lower third molar extraction is a safe choice that needs fewer re-injections and presents shorter onset time than other aminoamide local anesthetics.

Key words*: Articaine, local anaesthesia, adverse events, neurotoxicity, efficacy, safety, lower third molar.*

INTRODUCTION

The inferior alveolar nerve block (IANB) is the most common technique used in the removal of lower third molar (L3M) teeth (1). It involves injecting a local anaesthetic (LA) close to the mandibular foramen, achieving intraoperative and postoperative pain control (2). LAs have typically been classified as either aminoester or aminoamide-type according to their intermediate chain structure. Aminoamide-type anaesthetics have replaced aminoester-type LAs because they provoke fewer allergic reactions (3).

Articaine is an aminoamide LA widely used in dentistry (4). Its chemical structure differs from other aminoamide LAs because it features a thiophene ring which improves its liposolubility and therefore increases its capacity to penetrate cell membranes (4,5).

While the safety of aminoamide anaesthetics is well documented in the literature, some local and systemic complications have been described, such as nerve injury, diplopia, trismus, pain, infection and allergic reactions, among others (2,3,6). As for local adverse events, some studies have indicated that articaine should be avoided in inferior alveolar nerve blocks (IANB) to prevent nerve damage (7–9). However, there is a lack of solid evidence to support the causality relationship between LA drug and nerve injuries.

Although articaine and lidocaine have been compared in two previous meta-analyses (10,11), the anaesthetic of choice for the removal of the L3M is still open for debate. Therefore, the present systematic review intends to analyse relevant data gathered from randomised clinical trials to compare the safety and efficacy of articaine against other aminoamide anaesthetics when used in L3M extractions.

MATERIALS AND METHODS

This paper adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) declaration (12).

- **Eligibility criteria**

Table 1 summarises the predefined study framework parameters: population (P), intervention (I), comparison (C), outcomes (O) and study design (S).

The study population were healthy patients aged over 18 years with no nerve disorders who underwent an L3M extraction (*participants*). Patients included in the study group had to have received an IANB with articaine 4% (*intervention*). These were compared against patients in the control group who were treated with other aminoamide LAs (*comparison*).

The primary outcome measure of anaesthetic safety was assessed according to the number of LA-related postoperative adverse events. Similarly, anaesthetic efficacy was based on the number of interventions that did not require a re-injection, the onset time and duration of the anaesthetic effect *(outcomes).* Finally, all randomised clinical trials (RCTs) published in English were selected without any restrictions on the year of publication *(study design)*.

- **Search strategy**

To identify relevant studies, we searched MEDLINE (PubMed), Cochrane Library, Scopus and Web of Science databases between December 2019 and January 2020 by applying the search strategy shown in Table 2. This electronic search was complemented by a manual search of the Journal of Dental Research, the Journal of Dentistry, the Journal of the American Dental Association, Clinical Oral Investigations, the International Journal of Oral and Maxillofacial Surgery, the Journal of Oral and Maxillofacial Surgery and Medicina Oral Patología Oral y Cirugía Bucal.

- **Study selection**

Two independent investigators (L.S-S. and J.T-S.) selected the studies in line with the preestablished inclusion criteria. The abstracts were examined after excluding duplicates and irrelevant publications (based on the title). We assessed the full text of the remaining papers according to the inclusion criteria. Any disagreements during the screening process were resolved by a third independent investigator (C.G-E.). We calculated Cohen's kappa coefficient to measure the level of agreement between the two investigators.

- **Data extraction**

Whenever possible, two reviewers (L.S-S. and J.T-S.) independently collected the following data: author(s), year of publication, country of origin, study design, study type, participant data, interventions and outcomes using data-extraction tables. Authors were contacted to ascertain any missing information, where necessary.

- **Quality and risk-of-bias assessment**

Two independent investigators (L.S-S. and J.T-S.) assessed the risk of bias for the RCTs included in the meta-analysis using the Cochrane Collaboration's tool. We evaluated sources of bias based on the quality components derived from the Cochrane Handbook for Systematic Reviews of Interventions (13). We classified each study as low risk (well-described articles that define patient allocation; have few drop-outs; and measure outcomes, and analyse and report results), unclear risk (papers that missed some information that meant it was hard to assess their limitations) or high risk of bias (studies with flaws that might limit the results). Any disagreements were resolved by a third independent investigator (C.G-E.).

- **Statistical analysis**

Quantitative synthesis was carried out using RevMan software (Review Manager version 5.3; The Cochrane Collaboration, Copenhagen, Denmark). We used the odds ratio (OR) with 95% confidence intervals (CI) to estimate the intervention safety and re-injection outcomes. Mean differences (MDs) and the standard deviation (SD) were used to summarise the anaesthesia onset time and duration data for each group.

Pairwise meta-analyses (PMA) were performed on studies that compared the same outcome measures. We used random effect models as we expected to observe variability between the studies (14). We selected the generic inverse variance method to combine data from split-mouth studies with data from parallel group trials (15). We used forest plots to depict an estimation of the overall effect. The effect estimates from each study are represented by boxes, while the diamond at the bottom of the figure shows the pooled results. The CI is shown by a horizontal line through the boxes and also corresponds to the width of the diamond. The position of no effect is represented by the vertical line. When the outcome favoured the study group, the

results appear on the right of the vertical line, and if the diamond touches this line, the overall effect is not statically significant. Finally, the heterogeneity of effect across studies was estimated through I^2 analyses. When a significant heterogeneity ($I^2 > 50\%$) was observed, we carried out a sensitivity analysis. Statistical significance was defined as $P < 0.05$ for all analyses.

RESULTS

- **Study selection and description**

The initial electronic and manual search yielded a total 482 references. After discarding duplicates and articles based on their titles, 32 papers were selected for full-text assessment. Inter-rater concordance was 92%, with a Cohen's kappa coefficient of 0.75 (substantial agreement).

Eighteen publications were excluded after applying the eligibility criteria: five papers with an inappropriate study design (16–20); four studies that did not involve exclusively L3M extractions (21–24); while nine articles lacked some data (25–33).

Finally, 14 RCTs met the inclusion criteria and were selected for qualitative and quantitative synthesis (34–47).

All studies were two-arm trials, wherein one treatment arm included patients administered articaine 4% and the other involved the use of one of the following anaesthetics: lidocaine 2% (35–38,42–45), lidocaine 4% (34), mepivacaine 2% (40) or bupivacaine 0.5% (39,41,46,47).

We contacted four authors to obtain missing data (35,39,44,46) (Table 3).

Figure 1 represents the article selection process.

- **Risk-of-bias assessment**

As shown in Figure 2 and Supplementary File 1, three of the selected studies were determined to have a high risk of bias due to performance (39,44), attrition (42) and/or reporting bias (39,42,44). The risk of bias for most of the papers included in the meta-analysis (34–38,40,41,43,45,47) was unclear; this was mainly due to the lack of data reporting the random

sequence generation and allocation concealment or a description of the blinding methods. Finally, only one study was considered to have a low risk of bias (46).

- **Extraction data:**

Qualitative synthesis

Based on pooled patient samples from the 14 selected articles, 619 patients were included with a total of 966 L3M extractions. Articaine 4% was used in 486 cases and was compared to lidocaine 4%, lidocaine 2%, bupivacaine 0.5 % and mepivacaine 2% in combination with different amounts of vasoconstrictor. Table 4 shows the data extracted from the selected papers, organised according to the meta-analysis parameters.

There were no significant differences between studies in terms of safety ($P > 0.05$). Only six cases of paraesthesia were reported in all the studies included in the review. Four (0.9%) occurred in the articaine 4% group; half of them were affected in the IAN and the other half in the lingual nerve (38,43). The lidocaine 2% group exhibited two cases of paraesthesia (0.7%) in the IAN (35). In all cases, the nerve damage was temporary, but none of the articles reported the recovery time.

Other adverse events such as vomiting (41), vasovagal syncope (44), prolonged postoperative swelling and pain (35,44), trismus (36,37) and general malaise or dizziness (41) were also recorded.

In two trials, the articaine group presented significantly fewer re-injections than bupivacaine 0.5% (46) and lidocaine 2% (38).

Regarding the anaesthesia onset time, articaine 4% had a shorter onset time compared with lidocaine 4% (34), lidocaine 2% (35,38,42) and bupivacaine 0.5% (41,46).

Finally, the articaine group also recorded a longer anaesthetic duration compared to the mepivacaine 2% (40) and lidocaine 2% (35–38,42,45) groups, but shorter than the bupivacaine 0.5% group (39,41,46,47).

Quantitative synthesis

We estimated the effect size by combining the data from 14 articles, ten of which had a split-mouth design (34,35,38–41,43,45–47) (Table 3).

Safety

Twelve studies with a total of 858 L3M extractions in 530 patients (34–38,40,41,43–47) were included for the safety analysis (Table 4). We were unable to estimate the effect size for the comparisons between articaine 4% and lidocaine 4% and mepivacaine 2%.

We did not observe any statistically significant differences in terms of safety for lidocaine 2% (OR:1.28; 95% CI: 0.55 to 2.97; P = 0.57; I^2 = 0%) and bupivacaine 0.5% (OR: 0.49; 95% CI: 0.04 to 5.58: P = 0.57).

Re-injections

Thirteen studies involving a total of 916 L3M extractions in 569 patients (34–36,38–47) were considered for the re-injection analysis (Table 4).

Quantitative results showed that patients who received articaine 4% needed significantly fewer re-injections than lidocaine 2% (OR: 2.00; 95% CI: 1.29 to 3.09; P = 0.002; I^2 = 0%). No other statically significant differences were found for the rest of the comparisons (bupivacaine 0.5%, mepivacaine 2% and lidocaine 4%) (Figure 3B).

After a sensitivity analysis of the comparison between articaine 4% and bupivacaine 0.5%, excluding the work by Trullenque-Eriksson et al. (39), the heterogeneity diminished which affected the overall results and highlighted that articaine 4% needed significantly fewer re-injections than bupivacaine 0.5% (OR: 3.14; 95% CI: 1.14 to 8.67; P = 0.03; I^2 = 22%).

Onset of anaesthesia

Fourteen studies involving 966 L3M extractions in 619 patients (34–47) were used to analyse the onset of anaesthesia (Table 4).

Quantitative synthesis revealed a shorter anaesthesia onset time in patients treated with articaine 4% than those administered lidocaine 2% (MD: 0.28 minutes; 95% CI: 0.16 to 0.39; P <

0.00001; I^2 = 83%), bupivacaine 0.5% (MD: 0.72 minutes; 95% CI: 0.28 to 1.17; P = 0.001; I^2 = 51%) and lidocaine 4% (MD: 1.98 minutes; 95% CI: 0.81 to 3.15; P = 0.0009). No statistically significant differences were found when articaine 4% was compared with mepivacaine 2%, which was based upon one trial (40) (MD: 0.00 minutes; 95% CI: -0.11 to 0.11; P = 1.00) (Figure 3C).

For the lidocaine 2% comparison, heterogeneity was explained by differences in the reporting of the onset time. A sensitivity analysis conducted after excluding three articles (36,37,42), led to reduced heterogeneity without affecting the overall results (MD: 0.31 minutes; 95% CI: 0.22 to 0.39; P = 0.03; I^2 = 38%). On the other hand, in the articaine 4% and bupivacaine 0.5% comparison, we excluded the study by Sancho-Puchades et al. (47) resulting in diminished heterogeneity without affecting the overall results (MD: 0.85 minutes; 95% CI: 0.78 to 0.92; P < 0.00001; I^2 = 0%).

Duration of anaesthesia

Fourteen studies comprising 966 L3M extractions in 619 patients (34–47) were deemed eligible for the duration of anaesthesia analysis (Table 4).

Quantitative synthesis showed a longer duration of anaesthesia for articaine 4% when compared with lidocaine 2% (MD: 63.37 minutes; 95% CI: 36.48 to 90.26; P < 0.00001; I^2 = 95%) and mepivacaine 2% (MD: 56.95 minutes; 95% CI: 45.69 to 68.21; P < 0.00001). The heterogeneity observed in the lidocaine 2% comparison can be explained by the differences in vasoconstrictor concentration and the populations. After a sensitivity analysis that excluded Chawla et al. (35) and Saralaya et al. (36), the heterogeneity decreased without affecting the overall results (MD: 52.66 minutes; 95% CI: 46.39 to 58.93; P < 0.00001; I^2 = 31%). The effect of bupivacaine 0.5% lasted significantly longer than articaine 4% (MD: -136.70 minutes; 95% CI: -197.21 to -76.18; P < 0.00001; I^2 = 93%). The heterogeneity diminished after a sensitivity analysis that excluded Sancho-Puchades et al. (47) and without affecting the overall results (MD: -67.03 minutes; 95% CI -80.51 to -53.54; P < 0.00001; I^2 = 16%). Only the comparison between articaine 4% and

lidocaine 4%, which was based on one trial (34), did not reveal any statistically significant differences (Figure 3D).

DISCUSSION

Several different LAs are commercially available to ensure patient comfort and manage their anxiety during the procedure (10). The choice of which LA should be used for L3M extractions must be based on safety and efficacy parameters.

Our results suggest that articaine seems to be as safe as other aminoamide anaesthetics and requires fewer re-injections than lidocaine 2% during the removal of the L3M. Regarding onset time, articaine 4% showed shorter latency periods than lidocaine 2%, bupivacaine 0.5% and lidocaine 4%. In addition, meta-analyses revealed that articaine 4% had a longer anaesthetic duration than lidocaine 2% and mepivacaine 2%, but shorter than bupivacaine 0.5%. To the best of our knowledge, the present review is the first to compare articaine 4% with other aminoamide LAs such as lidocaine 2%, lidocaine 4%, bupivacaine 0.5% and mepivacaine 2% in L3M extractions.

Different studies have reported paraesthesia after using the IANB technique. They described incidences of between 1:27,000 and 1:785,000 (6,48) and it seems to affect the lingual nerve more frequently than the IAN (7). Some authors have suggested that articaine 4% can produce a higher number of nerve injuries due to its high concentration and neurotoxicity (7–9). Consequently, after a retrospective analysis of 56 consecutive patients, Hillerup et al. (9) suggested that articaine 4% should not be used in IANB. However, several papers highlighted a lack of scientific evidence to support this recommendation, as they did not find any relationship between articaine and nerve damage (19,23,49). There are many factors that can provoke nerve damage during L3M removal; therefore, it is hard to determine which is the most significant causal factor (or factors) with respect to nerve injuries. Additionally, although regional and systemic complications can also occur while administering LAs, the prevalence of these adverse events is low (6).The present review included six cases of transient paraesthesia, four of which affected the IAN, while the other two were reported on the lingual nerve. The incidence of

paraesthesia in our study was 0.9% in association with the use of articaine 4% and 0.7% after the administration of lidocaine 2%. We did not find any differences regarding safety between the different anaesthetic solutions. It is difficult to determine whether the paraesthesia was caused by the administration of the anaesthetic solution or the surgery itself. Indeed, due to the relatively low incidence of nerve injuries associated with local anaesthetics, a very large study sample is required to statistically determine if articaine or any other LA has a greater incidence of paraesthesia.

Compared to lidocaine 2%, a recent meta-analysis (11) found that articaine 4% required fewer re-injections during L3M extraction, which agrees with the present review. Curiously, these authors recommended the use of lidocaine 2% for this intervention based on the cost of anaesthetics and on the findings of the aforementioned study (9). However, our results did not reveal any significant differences between articaine 4% and lidocaine 2% in terms of safety, furthermore, articaine 4% provided more effective anaesthesia in the removal of the L3M. In terms of re-injections, we observed a statistically significant difference between articaine 4% and lidocaine 2%, and between articaine 4% and bupivacaine 0.5% after the sensitivity analysis. However**,** it should be noted that the studies used for the meta-analysis did not use a uniform volume of local anaesthetic, which could affect the onset time, the duration and the need of re-injection. To his end, we performed a sensitivity analysis to reduce the consequent heterogeneity. In addition, with respect to onset time, the mean difference in onset between articaine 4% and the onset for three LAs included in the study (lidocaine 2%, bupivacaine 0.5% and lidocaine 4%) ranged from approximately 30 seconds to 2 minutes. Although this difference was statistically significant for three of the LAs, it is important to point out that the slightly longer onset times for the LAs may have minimal clinical significance.

The clinical behaviour of LAs can be explained by differences in their chemical properties (5). For instance, the efficacy (reduced need for re-anaesthesia), the onset time and duration of the anaesthetic effect depend on both LA- (e.g., liposolubility, LA concentration, amount of vasoconstrictor) and patient-related factors (e.g., tissue pH, blood supply and anatomical

variations). Furthermore, these parameters can also be influenced by injection precision, which is related to operator experience, and the type of technique used to perform the IANB (50,51).

In the present meta-analysis, bupivacaine 0.5% had a significantly longer anaesthetic duration than articaine 4%, which, in turn, provided anaesthesia for a significantly longer period than lidocaine 2% and mepivacaine 2%. These differences can be explained by the fact that bupivacaine was the only long-acting LA in the review, as it has a much greater liposolubility than the rest (51).

The present review has several drawbacks that should be mentioned. The results were mostly based on papers deemed to have an undetermined or high risk of bias (34,35,44,45,47,36–43) and, we also observed a high heterogeneity in some of the comparisons. Consequently, although a sensitivity analysis was performed to assess the impact of confounding factors, our results should still be interpreted with caution.

CONCLUSIONS

Within these limitations, we can draw the following conclusions:

- All LAs assessed were safe regardless of their formulation and concentration. Articaine 4% requires fewer re-injections and has a shorter onset time during L3M extractions. Articaine 4% also exhibits a longer anaesthetic duration than other aminoamide anaesthetics, except for bupivacaine 0.5%.
- Further investigations are needed to determine with confidence which is the safest and most effective LA in L3M procedures.

Conflicts of interest: The authors do not have any conflicts of interest related to this study.

REFERENCES:

1. Yu F, Xiao Y, Liu H, Wu F, Lou F, Chen D, et al. Evaluation of three block anesthesia methods for pain management during mandibular third molar extraction: A meta-analysis. Sci Rep. 2017;7:1-9.

2. Senes AM, Calvo AM, Colombini-Ishikiriama BL, Gonçalves PZ, Dionísio TJ, Sant'ana E, et al. Efficacy and safety of 2% and 4% articaine for lower third molar surgery. J Dent Res. 2015;94:166-73.

3. Lagan G, McLure HA. Review of local anaesthetic agents. Curr Anaesth Crit Care. 2004;15:247-54.

4. Kaemmerer PW, Schneider D, Palarie V, Schiegnitz E, Daublander M. Comparison of anesthetic efficacy of 2 and 4 % articaine in inferior alveolar nerve block for tooth extraction - A double-blinded randomized clinical trial. Clin Oral Investig. 2017;21:397-403.

5. Becker DE, Reed KL. Local anesthetics: Review of pharmacological considerations. Anesth Prog. 2012;59:90-101.

6. Cummings DR, Yamashita DDR, McAndrews JP. Complications of local anesthesia used in oral and maxillofacial surgery. Oral Maxillofac Surg Clin North Am. 2011;23:369-77.

7. Gaffen AS, Haas DA. Retrospective review of voluntary reports of nonsurgical paresthesia in dentistry. J Can Dent Assoc. 2009;75:579-85.

8. Renton T, Janjua H, Gallagher JE, Dalgleish M, Yilmaz Z. UK dentist's experience of iatrogenic trigeminal nerve injuries in relation to routine dental procedures: Why, when and how often? Br Dent J. 2013;214:633-42.

9. Hillerup S, Jensen RH. Nerve injury caused by mandibular block analgesia. Int J Oral Maxillofac Surg. 2006;35:437-43.

10. Katyal V. The efficacy and safety of articaine versus lignocaine in dental treatments: A meta-analysis. J Dent. 2010;38:307-17.

11. Zhang A, Tang H, Liu S, Ma C, Ma S, Zhao H. Anesthetic efficiency of articaine versus lidocaine in the extraction of lower third molars: A meta-analysis and systematic review. J Oral Maxillofac Surg. 2019;77:18-28.

12. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Int J Surg. 2010;8:336-41.

13. Higgins JPT, Green S (2011) Cochrane handbook for systematic reviews of interventions version 5.1.0. [update March 2011]. The Cochrane Collaboration. Available from www.cochrane-handbook.org.

14. Simonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177-88.

15. Elbourne DR, Altman DG, Higgins JPT, Curtin F, Worthington H V, Vail A. Meta-analyses involving cross-over trials: Methodological issues. Int J Epidemiol. 2002;31:140-9.

16. Aksu K, Kurt E. Immediate reaction to articaine. Allergol Immunopath. 2013;41:127-8.

17. Dower JS Jr. Articaine vs. lidocaine. J Calif Dent Assoc. 2007;35:24-4.

18. Albalawi F, Lim JC, DiRenzo KV, Hersh EV, Mitchell CH. Effects of lidocaine and articaine on neuronal survival and recovery. Anesth Prog. 2018;65:82-8.

19. Malamed SF. Nerve injury caused by mandibular block analgesia. Int J Oral Maxillofac Surg. 2006;35:876-7.

20. Malamed SF, Gagnon S, Leblanc D. Articaine hydrochloride is a safe and effective local anesthetic. J Evid Based Dent Pract. 2001;1:119-20.

21. Elad S, Admon D, Kedmi M, Naveh E, Benzki E, Ayalon S, et al. The cardiovascular effect of local anesthesia with articaine plus 1: 200,000 adrenalin versus lidocaine plus 1:

100,000 adrenalin in medically compromised cardiac patients: A prospective, randomized, double blinded study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;105:725-30.

22. Mikesell P, Nusstein J, Reader A, Beck M, Weaver J. A comparison of articaine and lidocaine for inferior alveolar nerve blocks. J Endod. 2005;31:265-70.

23. Malamed SF, Gagnon S, Leblanc D. Articaine hydrochloride: A study of the safety of a new amide local anesthetic. J Am Dent Assoc. 2001;132:177-85.

24. Mollaoglu N, Yucel E, Cevik C. The evaluation of changes in blood glucose level by the effect of dental local anaesthetics during oral surgery. Gazi Med J. 2000;11:165-9.

25. Carrera I, Mestre R, Berini L, Gay-Escoda C. Alterations in monitored vital constants induced by various local anesthetics in combination with different vasoconstrictors in the surgical removal of lower third molars. Bull Group Int Rech Sci Stomatol Odontol. 2000;42:1-10.

26. Mestre-Aspa R, Carrera-Grañó I, Berini-Aytés L, Gay-Escoda C. Pulsioxymetry monitorization during lower third molar extraction. A comparative study of three local anesthetics with epinephrine 1:100,000. Med Oral. 2001;6:195-204.

27. Olmedo-Gaya M V, Manzano-Moreno FJ, Munoz-Lopez JL, Vallecillo-Capilla MF, Reyes-Botella C. Double-blind, randomized controlled clinical trial on analgesic efficacy of local anesthetics articaine and bupivacaine after impacted third molar extraction. Clin Oral Investig. 2018;22:2981-8.

28. Silva LC, Santos TD, Santos JA, Maia MC, Mendonça CG. Articaine versus lidocaine for third molar surgery: A randomized clinical study. Med Oral Patol Oral Cir Bucal. 2012;17:1-6.

29. Vigneswaran T, Vijay Aravind R. A randomized study of 4% articaine versus 2% lignocaine for surgical removal of the third molar. Drug Invent Today. 2019;12:632-5.

30. Arteagoitia I, Zumarraga M, Dávila R, Barbier L, Santamaría G, Santamaria J. Plasma variations in stress markers: Clinical trial of two anesthetics used in regional block in the extraction of impacted inferior third molars. Med Oral Patol Oral Cir Bucal. 2014;19:274-9.

31. Vasconcellos RJ, Vasconcelos BC, Genú PR. Influence of local anesthethics with adrenalina 1: 100.000 in basic vital constants during third molar surgery. Med Oral Patol Oral Cir Bucal. 2008;13:431-7.

32. De Morais HH, de Santana-Santos T, Araújo FA, Vajgel A, de Holanda-Vasconcellos RJ. Hemodynamic changes comparing lidocaine HCl with epinephrine and articaine HCl with epinephrine. J Craniofac Surg. 2012;23:1703-8.

33. De Morais HH, de Santana-Santos T, Araújo FA, de Freitas-Xavier RL, Vajgel A, de Holanda-Vasconcellos RJ. Hemodynamic changes comparing 2% lidocaine and 4% articaine with epinephrine 1:100,000 in lower third molar surgery. J Craniofac Surg. 2012;23:1204-11

34. Boonsiriseth K, Chaimanakarn S, Chewpreecha P, Nonpassopon N, Khanijou M, Ping B, et al. 4% lidocaine versus 4% articaine for inferior alveolar nerve block in impacted lower third molar surgery. J Dent Anesth Pain Med. 2017;17:29-35.

35. Chawla J, Pandilwar PK, Kumar P, Sonowal ST. Comparison of anesthetic efficacy of 4% articaine with 2% lignocaine in surgical extraction of mandibular third molars: A double blinded randomised controlled trial. Int J Curr Res. 2016;8:39066-70.

36. Saralaya S, Adirajaiah SB, Anehosur V. 4% articaine and 2% lignocaine for surgical removal of third molar by mandibular nerve block: A randomized clinical trial for efficacy and safety. J Maxillofac Oral Surg. 2019;18:405-11.

37. Shruthi R, Kedarnath N, Mamatha N, Rajaram P, Bhadrashetty D. Articaine for surgical removal of impacted third molar: A comparison with lignocaine. J Int Oral Health.

2013;5:48-53.

38. Sierra-Rebolledo A, Delgado-Molina E, Berini-Aytés L, Gay-Escoda C. Comparative study of the anesthetic efficacy of 4% articaine versus 2% lidocaine in inferior alveolar nerve block during surgical extraction of impacted lower third molars. Med Oral Patol Oral Cir Bucal. 2007;12:139-44.

39. Trullenque-Eriksson A, Guisado-Moya B. Comparative study of two local anesthetics in the surgical extraction of mandibular third molars: Bupivacaine and articaine. Med Oral Patol Oral Cir Bucal. 2011;16:390-6.

40. Colombini BL, Modena KC, Calvo AM, Sakai VT, Giglio FP, Dionísio 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;102:169-74.

41. Gregorio LV, Giglio FP, Sakai VT, Modena KC, Colombini BL, Calvo AM, et al. 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. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;106:19-28.

42. Jain NK, John RR. Anesthetic efficacy of 4% articaine versus 2% lignocaine during the surgical removal of the third molar: A comparative prospective study. Anesth Essays Res. 2016;10:356-61.

43. Kambalimath DH, Dolas RS, Kambalimath H V., Agrawal SM. Efficacy of 4 % Articaine and 2 % Lidocaine: A clinical study. J Maxillofac Oral Surg. 2013;12:3-10.

44. Martínez-Rodríguez N, Barona-Dorado C, Martín-Arés M, Cortés-Bretón-Brinkman J, Martínez-González JM. Evaluation of the anaesthetic properties and tolerance of 1:100,000 articaine versus 1:100,000 lidocaine. A comparative study in surgery of the lower third molar. Med Oral Patol Oral Cir Bucal. 2012;17:345-51.

45. Mittal J, Kaur G, Mann HS, Narang S, Kamra M, Kapoor S, et al. Comparative study of the efficacy of 4% articaine vs 2% lidocaine in surgical removal of bilaterally impacted mandibular third molars. J Contemp Dent Pract. 2018;19:743-8.

46. Pellicer-Chover H, Cervera-Ballester J, Sanchis-Bielsa JM, Peñarrocha-Diago MA, Peñarrocha-Diago M, Garcia-Mira B. Comparative split-mouth study of the anesthetic efficacy of 4% articaine versus 0.5% bupivacaine in impacted mandibular third molar extraction. J Clin Exp Dent. 2013;5:66-71.

47. Sancho-Puchades M, Vílchez-Pérez MÁ, Valmaseda-Castellón E, Paredes-García J, Berini-Aytés L, Gay-Escoda C. Bupivacaine 0.5% versus articaine 4% for the removal of lower third molars. A crossover randomized controlled trial. Med Oral Patol Oral Cir Bucal. 2012;17:462-8.

48. Stirrup P, Crean S. Does articaine, rather than lidocaine, increase the risk of nerve damage when administered for inferior alveolar nerve blocks in patients undergoing local anaesthesia for dental treatment? A mini systematic review of the literature. Br Dent J. 2019;226:213-23.

49. Pogrel MA. Permanent nerve damage from inferior alveolar nerve blocks: A current update. J Calif Dent Assoc. 2012;40:795-7.

50. St George G, Morgan A, Meechan J, Moles DR, Needleman I, Ng YL, et al. Injectable local anaesthetic agents for dental anaesthesia. Cochrane Database Syst Rev. 2018;7:CD006487.

51. Haas DA. An update on local anesthetics in dentistry. J Can Dent Assoc. 2002;68:546-51.

FIGURE LEGENDS:

Figure 1. PRISMA flowchart summarising the selection process.

Figure 2. Risk-of-bias assessment according to the Cochrane Collaboration's tool.

Figure 3. Forest plot for safety (A), re-injections (B), anaesthesia onset time (C) and duration of the anaesthetic effect (D).

TABLE LEGENDS:

Table 1. Issues of interest according to study Population (P), Intervention (I), Comparison (C), Outcomes (O) and Study design (S) (PICOS factors).

Table 2. Search strategy.

Table 3. Description of the selected studies.

Table 4. Comparison of the selected studies.

Supplementary File 1. Risk-of-bias assessment according to the Cochrane Collaboration's tool.