Submitted: 13 January, 2023 Accepted: 28 February, 2023 Published: 03 November, 2023 DOI:10.22514/jocpd.2023.078

SYSTEMATIC REVIEW

Journal of Clinical Pediatric Dentistry

Adverse effects of articaine versus lidocaine in pediatric dentistry: a meta-analysis

Ling Li[1], Da-lei Sun[1,*]

[1]Department of Stomatology, Hangzhou Normal University Affiliated Hospital, 310000 Hangzhou, Zhejiang, China

***Correspondence**
yb2118050@zju.edu.cn
(Da-lei Sun)

Abstract

Over the last few years, numerous reports have lauded the efficacy of articaine hydrochloride as a local anesthetic (LA) in dental procedures. Numerous studies have shown that articaine outperforms lidocaine in various aspects of dental treatment, leading to its widespread adoption in both adults and children. Despite the publications of comparative studies, there remains a dearth of systematic reviews examining the adverse effects of articaine versus lidocaine in randomized controlled trials. The aim was to assess the available research on the adverse effects of articaine and lidocaine in pediatric dentistry. A comprehensive search was conducted on Cochrane Library, Pubmed, Chinese Biomedical Literature Database (CBM), Embase, Web of Science and China National Knowledge Infrastructure (CNKI). Randomized controlled trials (RCT) that compared articaine with lidocaine in pediatric dentistry were included. Methodological quality assessment and risk of bias were determined for each of the included studies. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach was used to assess the strength of evidence for every research. A total of 333 studies were identified through electronic searches. After conducting primary and secondary assessments, eight studies were included for the final qualitative analysis. We found no difference in the probability of adverse reactions between articaine and lidocaine after treatment in pediatric patients (risk ratio (RR) = 1.08, 95% confidence interval (CI) (0.54–2.15), p = 0.83). However, a high heterogeneity was reported among the outcomes in the investigated studies (I^2 = 57%), and the strength of the evidence was classified as "moderate" based on the GRADE approach. Besides, we found no significant difference in the probability of postoperative pain, postoperative soft tissue injury and edema between articaine and lidocaine in pediatric patients following treatment. There was moderate quality evidence suggesting no difference in the occurrence of adverse events between articaine and lidocaine when used for pediatric dental procedures.

Keywords

Articaine; Children; Inferior alveolar nerve block; Infiltration; Lidocaine

1. Introduction

Pain management is an essential component of pediatric dentistry, and lidocaine hydrochloride has been a widely used and marketed amide local anesthetic (LA) since its clinical introduction in 1948 [1]. Over the years, clinical practice and research have consistently demonstrated its efficacy and safety, with minimal toxicity and few reports of allergic reactions, making lidocaine the "gold standard" for all new LA.

Articaine was first introduced in clinics in 1976 [2] and has since been widely used in pediatric dentistry. Notably, it is administered *via* a special syringe and a disposable small-diameter injection needle. The recommended dosage for adults is 7 mg/kg and 5 mg/kg for children aged 4–12. Despite their widespread use, local anesthetics, including articaine, have the potential to be unsafe and can cause adverse reactions such as dizziness, disorientation, tremors, convulsions, seizures, hypotension and respiratory depression [3–5]. However, articaine is considered a relatively safe local anesthetic due to its rapid metabolism into an inactive metabolite, thereby reducing the risk of systemic toxicity and overdose, even after repeated injection [3]. Additionally, studies have shown that in children aged 3–12, the serum concentration of articaine was comparable to that of adults, and the maximum concentration of a 2% solution was significantly lower than that of a 4% one [6]. Present literature on articaine use in children indicates that it is safe and effective for clinical surgery in children of all ages [7–10].

Due to its favorable performance in reviewed randomized controlled trials, articaine hydrochloride has garnered recogni-

tion and support from numerous researches [11–17]. According to Nizharadze *et al.* [12], articaine appears to be the best choice of local anesthetic for suppurative inflammation tissues, making it suitable for children (over 4 years old), adults, elderly individuals, pregnant and breastfeeding women, as well as patients with hepatic and renal function impairment [12]. Powell reported that articaine was superior to lidocaine in providing pulpal anesthesia [13, 14]. Similarly, Leith supported articaine as a safer and more effective alternative to lidocaine in children [15]. Meechan also suggested that articaine was more effective than lidocaine and was associated with successful anesthesia in the first molar area of routine dental surgery [18].

Despite the extensive use of local anesthetics in pediatric dentistry, there remains a lack of consensus on the safety of various solutions. Therefore, this meta-analysis was aimed to compare the effects and adverse reactions between articaine and lidocaine in pediatric dental procedures and provide evidence for the safety of articaine in children.

2. Material and methods

This systematic review was designed, implemented and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol was registered on International prospective register of systematic reviews (PROSPERO) (ID: CRD42022293058). The population, intervention, comparison and outcome (PICO) method was used to formulate the research question, which was as follows: "In children undergoing dental treatments, is the use of articaine LA associated with a safer anesthetic effect compared to lidocaine LA?".

2.1 Inclusion and exclusion criteria

Research scientific publications on randomized controlled trials (RCTs) that compared the use of articaine and lidocaine for anesthesia during dental procedures were queried and assessed. Repetitive articles, non-randomized trials, observational studies, case reports, narrative and systematic reviews, letters to the editor, review articles, *in vitro* studies, case-control studies and cohort studies, as well as those using computerized delivery routes and trials evaluating the less commonly used supplementary anesthesia techniques, were excluded. After this initial screening, potentially suitable studies were included for full-text evaluation. The following inclusion criteria were applied in this study:

- Randomized clinical trials involving pediatric subjects (age <14 years) who were in good health and required dental treatments under anesthesia;
- Studies with raw data generated by comparing randomized controlled clinical trial designs;
- Studies evaluating the adverse effects of local anesthetics of articaine compared to lidocaine;
- Studies evaluated adverse effects comparing local anesthetic solutions between articaine and lidocaine for both local infiltration anesthesia and inferior alveolar nerve block anesthesia (IANB);
- Studies with detailed descriptions of the type of LA used.

2.2 Search strategy

A systematic electronic search and reference list screening were conducted, and the following electronic databases were searched: Cochrane Library, Pubmed, CBM, Embase, Web of Science and CNKI. Each database was last searched on Nov. 2021.

The mesh terms and subject index terms used for the search were as follows:

- Carticaine, Carticain, Articain, Articaine, Carticaine Hydrochloride, Hydrochloride, Carticaine, Hoe-40045, Hoe 40045, Hoe-045, Hoe 045, Ultracaine, Septocaine.
- Child, children, pediatric dentistry.

2.3 Data extraction and qualitative assessment

Two reviewers independently analyzed the data extracted from each study according to the following criteria: (1) author; (2) year of publication; (3) origin study country; (4) type of study; (5) number of patients; (6) gender; (7) age group; (8) intervention; (9) follow-up time for each study; and (10) adverse effects. In case of disagreement, the overall risk of bias was unanimously resolved after mutual discussion.

Risk of bias assessment was performed to evaluate the research methodology and outcome measures of all included studies. Quality assessment was based on the guidelines recommended in the Cochrane Handbook of Systematic Reviews of Interventions 5.0.2. to assess the risk bias in randomized controlled trials (RCTs). The risk bias assessment was conducted based on the following aspects: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting, (7) other bias or potential threats to validity. The quality of the included studies was assessed independently by two reviewers. In the case of inconsistencies, a third author was consulted. The overall risk bias of the individual studies was evaluated, with a low risk of bias considered when all fields were determined to be at low risk. An unclear risk of bias was considered when one or more fields were determined as unclear risk. A high risk of bias was considered when one or more fields were evaluated as high risk. Lastly, we used the GRADE approach (classification of recommendations, evaluation, development, and evaluations) to evaluate the strength of evidence for each study, and publication bias was assessed using a funnel plot.

2.4 Outcome measures and final results

The primary outcome measure was adverse events rate. The safety of LA solutions was assessed by measuring vital signs (before and after administering the anesthetic) and adverse reactions throughout the study. Adverse reactions were elicited during telephone follow-up. Meta-analysis and graphics were generated using the Revman Manager 5.3 (Review Manager 5.3.5, The Nordic Cochrane Centre, The Cochrane Collaboration, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark).

For all meta-analyses, the mean and standard deviation data for each selected study were considered to calculate the

standardized mean difference with a confidence interval of 95%. A random effects model was also used.

I^2 statistics and the chi-square test were used to evaluate statistical heterogeneity in all studies. I^2 statistics $\geq$50% and a threshold p-value < 0.1 for the chi-square test were used to determine substantial heterogeneity. Irrespective of their risk of bias, all included studies are used for preliminary analysis.

Sensitivity analyses were performed to assess the robustness of the selected studies, and the strength of evidence from these studies for the meta-analyses was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The domain's risk of bias, inconsistency, indirectness, imprecision and other considerations were evaluated. For each area, the strength of the evidence could be reduced by one or two levels. Evidence based on the GRADE system was classified as very low, low, moderate or high.

3. Result

3.1 Search results

A total of 333 articles were included in the initial search. After assessing the titles and abstracts, 132 articles were selected for full-text assessment. Of those, 122 trials lacked data on adverse events, and 2 reported no adverse effects in the articaine and lidocaine groups. Based on the inclusion and exclusion criteria, a total of eight trials were eligible for systematic review, of which seven were in English and one in Chinese [9, 10, 19–24]. The search process is detailed in the PRISMA flowchart (Fig. 1).

3.2 Design of included studies

A cross-over design was utilized for three of the eight eligible studies [20], all of which were randomized controlled trials comprising subjects younger than 13 years old and comparing the effects and outcomes of articaine and lidocaine in dental treatments using buccal infiltration (BI) or IANB technique. Four studies mentioned the use of standardized needles [20–22, 24]. A total of 470 subjects using articaine and 441 subjects using lidocaine were compared (Tables 1 and 2).

3.3 Age range

The age of the subjects differed across the investigated trials, ranging from 3 to 13 years old. One study selected subjects under 4 years old [22]. One study contained subjects under 4 years old [24].

3.4 Analysis of outcome measures

Reports of postoperative complications included postoperative soft tissue injury (accidental lip/cheek injury), postoperative analgesic/medication use, nausea, dizziness, abnormal heart rate, edema, headache, post-procedural pain (including injection site pain), tooth tenderness and aching jaw. Among them, Elheeny *et al.* [22]'s study noted that "parents' postoperative pain measure" was repetitive to postoperative analgesia. Khanna and Alzahrani's study mentioned "need for reanesthesia" was excluded from adverse effects but regarded it as a miss in clinical practice [19, 23]. Alzahrani *et al.* [19]'s study considered "pain" to be repetitive to medication. All research acquired these reported adverse effects mainly through postoperative phone calls, and the parents provided responses or elicited directly from the patients. For all included studies summarising the aforementioned adverse reactions, no significant differences were identified in terms of risk of adverse between lidocaine and articaine (RR = 1.08; 95% CI (0.54, 2.15); $p = 0.83$; Fig. 2). However, high heterogeneity was observed ($I^2 = 57\%$; p-value for chi-square test = 0.02).

3.5 Risk bias and quality assessment

Visual inspection of the funnel plot (Fig. 3) indicated no publication bias for adverse events.

The results of the RCT quality assessment are shown in Fig. 4. In many of the evaluated studies (D. Ram, Khanna and Malamed's studies), the methodological description of random sequence generation was flawed or informative. The allocation concealment was missed in two studies (D. Ram and Khanna's study) and not explained properly in two studies (Ma and Malamed's studies). The blinding intervention of participants in clinical procedures was missed in Khanna's study and presented insufficient information in five studies (Alzahrani, D. Ram, Elheeny, Ma and Malamed's studies). Two studies (D. Ram, and Ma's study) were considered to have other biases because their telephone recall was not 24 hours after treatment. Detection bias, attrition bias and reporting bias were at minimal risk in all included studies.

Among the included studies, only two had a low risk of bias [20, 21], three had a high risk of bias [9, 23, 24], and three had a moderate/uncertain risk of bias [10, 19, 22]. Fig. 4 shows a summary of the risk of bias for each of the assessment categories included in this present study.

3.6 Strength of the evidence assessment

Based on the GRADE evaluation, the strength of the evidence was defined as "moderate" (Fig. 5).

3.7 Sensitivity analysis

In general, the included trials showed high heterogeneity concerning the risk of bias ($I^2 = 57\%$). However, after the removal of Ma's study (Ma *et al.* [24], 2019), low heterogeneity was observed ($I^2 = 30\%$; RR = 1.39; 95% CI (0.78, 2.50); p-value for chi-square test = 0.20). The result of no difference between groups also remained (Fig. 6A).

3.8 Subgroups analysis

To compare the postoperative pain between the two LA, 5 trials comprising 309 patients using articaine and 280 patients using lidocaine were evaluated [9, 10, 19, 20, 22]. The results showed no significant heterogeneity in the results ($p = 0.26$, $I^2 = 24\%$). The RR was 1.62 (95% CI (0.84, 3.12)), with no statistically significant differences between the treatment and control groups ($p = 0.15$) (Fig. 6B).

To compare the postoperative soft tissue injury of the two LA, 6 trials comprising 409 patients using articaine and 380 patients using lidocaine were evaluated [9, 10, 19, 20, 22, 23].

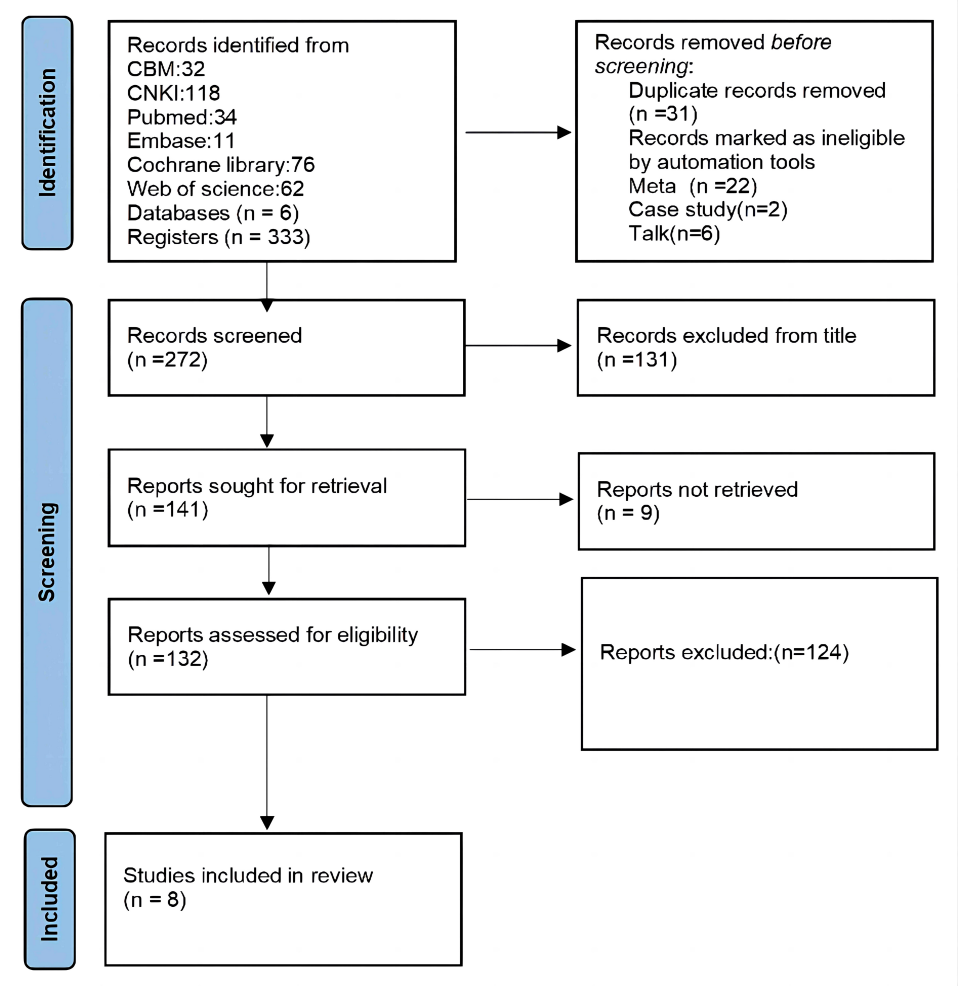

FIGURE 1. Flow diagram of the study selection. CBM: Chinese Biomedical Literature Database; CNKI: China National Knowledge Infrastructure.

TABLE 1. Study characteristics of the investigated RCT.

Number	Author	Year of Publication	Study type	Number of patients	Age group	Follow-up time
1	Elheeny *et al.* [22]	2020	RCT	184 (Articaine: Lidocaine = 92:92)	36 to 47 months	24 h
2	Ying Ma *et al.* [24]	2019	RCT	78 (Articaine: Lidocaine = 39:39)	Articaine group: 3∼8 y; Lidocaine group: 3∼7 y (5.65 ± 0.92)	NR
3	Khanna *et al.* [23]	2021	RCT	100	6–8 y	24 h
4	Alzahrani *et al.* [19]	2018	RCT	98 (Articaine: Lidocaine = 49:49)	5–9 y	24 h
5	D. RAM *et al.* [9]	2006	RCT	62	5–13 y	1, 2 or more hours
6	Malamed *et al.* [2]	2000	RCT	70 (Articaine: Lidocaine = 50:20)	4–13 y	24 h; 7 days
7	Massignan *et al.* [21]	2020	RCT	43 (Articaine: Lidocaine = 21:22)	6–10 y	2 h; 6 h; 24 h
8	Arrow *et al.* [20]	2012	RCT	57	mean age = 12.4 y	2 h; 4 h; 24 h; 1 week

NR, not reported; RCT: randomized control trial.

TABLE 2. Interventions and outcomes of the investigated RCT.

Intervention			Adverse events	
Articaine group	Lidocaine group	Site/Speed	Articaine group	Lidocaine group
articaine 4% and epinephrine 1:100,000; 5 mg/kg	lidocaine 2% and epinephrine 1:100,000; 4.4 mg/kg	Both BI/1 mL/min	Parents' postoperative pain measure = 4; soft tissue injury = 7; analgesic = 7	Parents' pain measure = 7; soft tissue injury = 2; analgesic = 5
0.3–0.6 mL/tooth	2.4 mL	BI for both LA/NR	nausea = 1; Dizziness = 1; abnormal heart rate = 0; oedema = 1	Nausea = 4; Dizziness = 4; abnormal heart rate = 2; oedema = 3
4% articaine with 1:100,000 epinephrine	2% lidocaine with 1:80,000 epinephrine	BI; IANB/NR	Need for re-anesthesia = 3; Pain = 2; Soft tissue injuries = 0	Need for re-anesthesia = 6; Pain = 2; Soft tissue injuries = 3
articaine 4% with 1:100,000 epinephrin	lidocaine 2% and 1:80,000 epinephrine	BI; IANB/<1 mL/min	Need for re-anaesthesia = 3; Pain = 4; Soft tissue injuries = 1; Medication = 9; Others = 1	Need for re-anaesthesia = 1; Pain = 0; Soft tissue injuries = 1; Medication = 2; Others = 0
articaine 4% with 1:200,000 epinephrine	lidocaine 2% with 1:100,000 epinephrine	BI; IANB/1 mL/min	Soft tissue injuries = 1; Post-procedural pain = 3; oedema = 0	Soft tissue injuries = 2; Post-procedural pain = 1; oedema = 1
articaine 4% with epinephrine 1:100,000	lidocaine 2% with epinephrine 1:100,000	BI; IANB/NR	Accidental injury = 1; Headache = 1; Injection site pain = 1; Pain = 1	Accidental injury = 0; Headache = 0; Injection site pain = 0; Pain = 2
articaine 4% 1:100,000 epinephrine	lidocaine 2% 1:100,000 epinephrine	BI for both LA, NR	nausea = 1; oedema = 8	nausea = 0; oedema = 2
articaine 4% with 1:100,000 adrenaline	lignocaine 2% with 1:80,000 adrenaline	BI; IANB/NR	pain at injection site = 1; tender tooth = 1; aching jaw = 2	lip-bite = 1; cheek-bite = 1; aching jaw = 2

Abbreviations: NR: not reported; LA: local anesthetic; BI: buccal infiltration; IANB: inferior alveolar nerve block anesthesia.

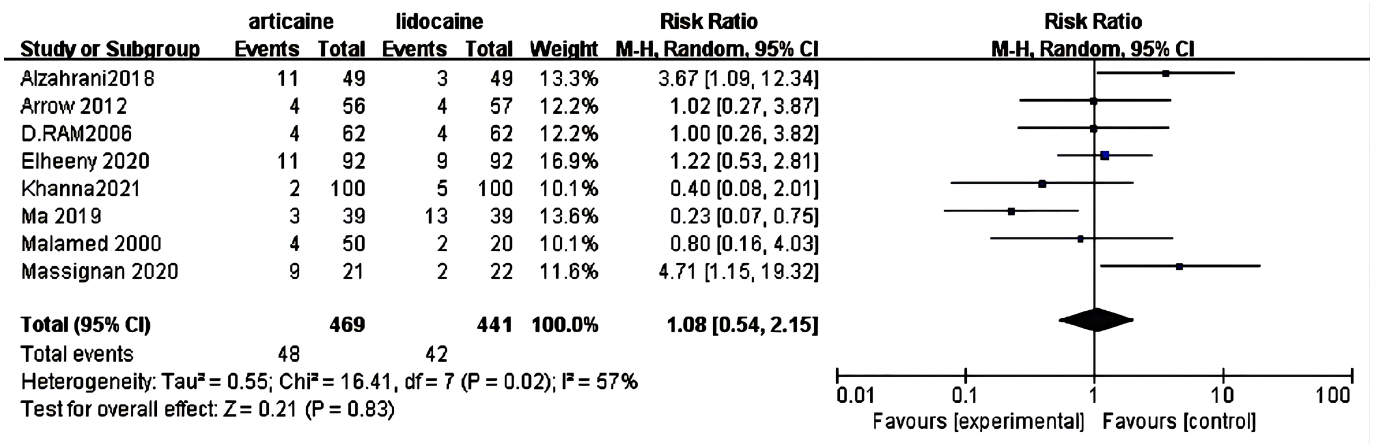

FIGURE 2. Forest plot of adverse effect compared with articaine and lidocaine of the 8 investigated RCT. RR: risk ratio; 95% CI: 95% confidence interval.

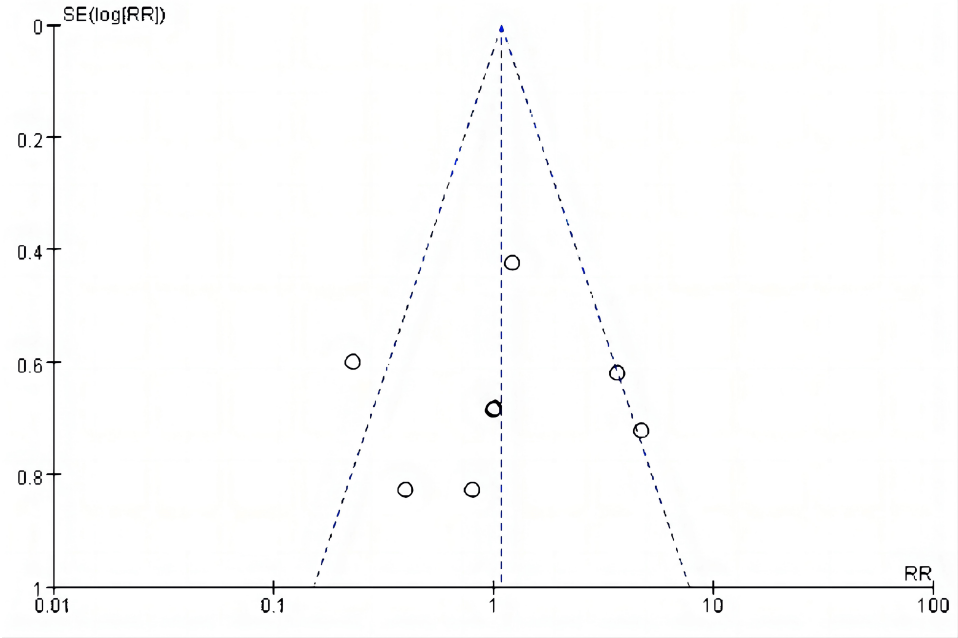

FIGURE 3. Funnel plot of the 8 investigated RCT. RR: risk ratio; SE: standard error.

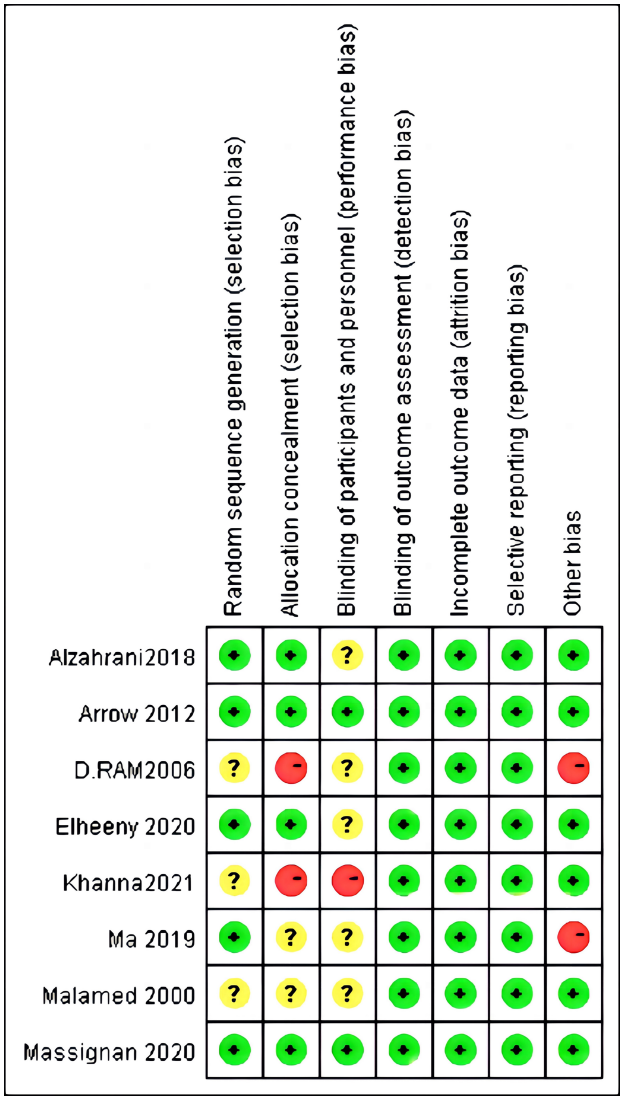

FIGURE 4. Risk of bias summary of the 8 investigated RCT.

articaine compared to lidocaine for dental treatment among children

Patient or population: patients with adverse reaction
Settings:
Intervention: articaine
Comparison: lidocaine

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Lidocaine	Corresponding risk Articaine	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
adverse effect rate adverse effect rate	**Study population**		**RR 1.02** (0.68 to 1.53)	910 (8 studies)	⊕⊕⊕⊖ moderate[1]	
	91 per 1000	**93 per 1000** **(62 to 139)**				
	Moderate					
	81 per 1000	**83 per 1000** (55 to 124)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] In many of the evaluated studies(D.Ram,Khanna and Malamed's studies) there were failures in the methodological description of random sequence generation or insufficient information was presented. The allocation concealment was missed in two studies(D.Ram and Khanna's study) and not explained properly in two studies(Ma and Malamed's studies). Blinding intervention of participants and personnel in clinical procedures was missed in Khanna's study and was presented insufficient information in five studies(Alzahrani, D.Ram,Elheeny,Ma and Malamed's studies). Two studies(D.Ram,Ma's study) were considered to have other bias cause their telephone recall was not 24 hours after treatment.

FIGURE 5. GRADE evaluation result.

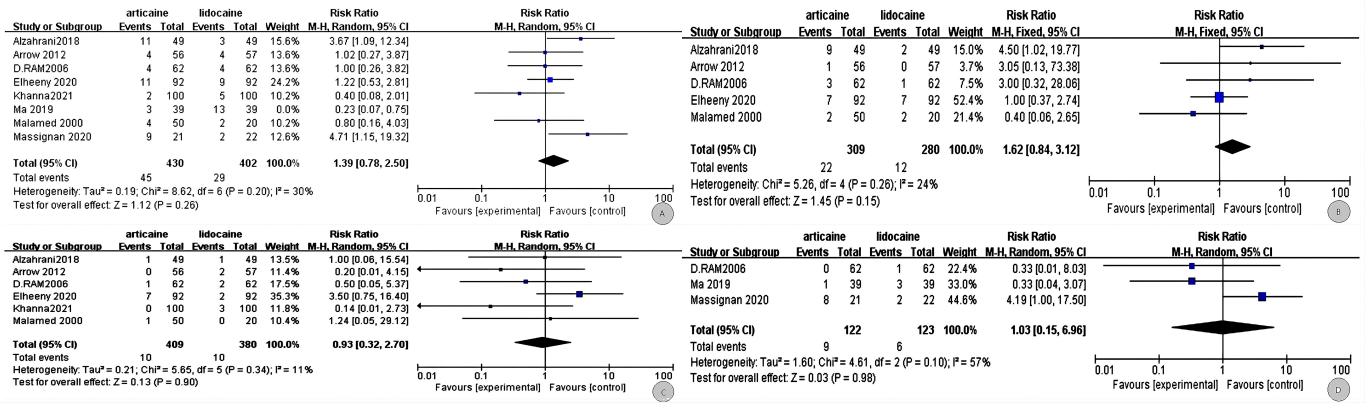

FIGURE 6. Forest plot of subgroup analysis. A: Forest plot of adverse effects for articaine versus lidocaine after excluding high heterogeneity study; RR: risk ratio; 95% CI: 95% confidence interval. B: Forest plot of postoperative pain for articaine versus lidocaine; RR: risk ratio; 95% CI: 95% confidence interval. C: Forest plot of soft tissue injury between articaine and lidocaine; RR: risk ratio; 95% CI: 95% confidence interval. D: Forest plot of edema between articaine and lidocaine; RR: risk ratio; 95% CI: 95% confidence interval.

We found no significant heterogeneity in the results ($p = 0.34$, $I^2 = 11\%$). The RR was 0.93 (95% CI (0.32–2.70)), with no statistically significant differences between treatment and control groups ($p = 0.90$) (Fig. 6C).

To compare the postoperative edema of the two LA, 3 trials comprising 122 patients using articaine and 123 patients using lidocaine were evaluated [9, 21, 24]. No significant heterogeneity was observed in the results ($p = 0.10$, $I^2 = 57\%$). The RR was 1.03 (95% CI (0.15–6.96)), with no statistically significant differences observed between the treatment and control groups ($p = 0.98$) (Fig. 6D).

4. Discussion

This review was based on 8 RCTs that reported on the incidence rate of adverse reactions using articaine and lidocaine in pediatric dentistry and showed that articaine had similar safety performance in children. The occurrence rate of postoperative pain, soft tissue injury and edema was not significantly different between the treatment groups, showing that articaine possesses similar safety features as lidocaine among children for dental treatments.

At present, there is no review specifically studying adverse reactions between the two drugs in dental practice, but some literature included in the meta-analysis had conducted subgroups analysis to compare the adverse reactions, which showed consistent results as our present study due to no observed difference in the incidence rate of adverse reactions between the two local anesthetics [10, 11, 25, 26].

However, it should be noted that a narrative review describing other adverse events about LA: neurological and ocular adverse reactions, hematomas, allergies, jaw ankylosis, tissue necrosis, needle breakage, osteomyelitis, blanching, and iso-

lated atrial fibrillation, suggest the need for more clinical trials to improve this review's results [27].

Furthermore, it is worth noting that two of the included studies contained age groups younger than 4 years, regardless of the manufacturers' recommendation that articaine should not be used in children younger than 4 years [22, 24]. In fact, articaine is already being used clinically in children under 4 years old by many dentists [28]. Articaine's good safety and efficacy in children were confirmed by other researchers. A retrospective study focused on the use of articaine in 211 children younger than 4 years, conducted by Wright *et al.* [29], reported no adverse effects. Brignardello *et al.* [30] claimed that articaine and lidocaine might have similar effects in 3–4 years old children undergoing primary molar pulpotomy. The use of articaine in pediatric dental patients, including children younger than 4 years old, was investigated, with promising results reported. However, there still need more clinical trials to improve the conclusions.

The effectiveness of anesthesia is also related to different anesthesia methods. The bone cortex of the mandible bone is thick, and the anesthesia is not easy to spread using infiltration anesthesia, so IANB is widely used in the operation of mandibular molars. However, the IANB technique is associated with many serious complications like transient facial paralysis, hematoma, nerve damage, prolonged duration of anesthesia and can damage the lips and tongue. In addition to IANB, local infiltration anesthesia is also a commonly used local anesthesia technique. In the maxilla and anterior part of the mandible, local infiltration anesthesia can provide successful anesthesia due to the presence of trabecular bone, however, the bone cortex at the back of the mandible is thick, so the success rate of local infiltration anesthesia is only about 54%–94% [31, 32]. The results of this present study suggested that articaine and lidocaine had similar safety performance. However, in the RCT we selected, articaine was mainly used for oral infiltration anesthesia, and lidocaine was mainly used for IANB. Although it is reported that articaine is safe and effective as a LA for all dental operations, many dentists are unwilling to use it, especially for IANB [33]. There are few studies using articaine by IANB in children. The reason for the higher use of articaine in infiltration anesthesia than lidocaine for IANB may be due to its superior infiltration performance. Martin *et al.* [34] showed that the success rate of articaine in infiltration anesthesia was 2.78 times that of lidocaine. Articaine can be used for local infiltration to obtain good anesthetic effects. However, it remains undetermined whether the good permeability of articaine for IANB would lead to potential safety hazards in children. More research is needed to confirm whether it can be applied to children for IANB.

As for anesthetic concentrations, commonly used concentrations of articaine are 2% and 4%, there are few studies comparing 2% or 4% of articaine, and one study showed that the effect of concentration on anaesthesia was mainly reflected on the length of anaesthesia time and there is no significant difference in other respects [35].

This study had several limitations. First, the sample size of the included trials was relatively limited, which might have led to insufficient statistical efficiency. More RCTs are needed to confirm the conclusions of our study, particularly using multifactor or multilevel analyses for determining potential confounding factors associated with anesthetic safety. Second, there were not enough data to perform subgroup analysis of different treatments in dental practice. Third, it should be noted that the two anesthetic drugs were not injected using the same approach. Most of the studies included in this study were based on the application of articaine to local infiltration anesthesia. Thus, the conclusion of the similar safety performance of articaine and lidocaine is based on the premise that articaine is only used for local infiltration anesthesia. Lastly, it should be emphasized that adverse reactions were not clinically verified and were reported by the patients or parents through postoperative phone calls, making them susceptible to a certain degree of bias. These factors could become the limitations of this review.

5. Conclusions

In summary, both articaine and lidocaine seem safe for pediatric treatments. Articaine can be a good choice for routine dental treatment in pediatric dentistry. The use of articaine by IANB is inconclusive due to the lack of evidence-based medical evidence, so its main advantage is in local infiltration anesthesia.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

LL—designed, performed and analyzed the research. DLS—co-performed the research. LL and DLS—wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This article does not contain any studies with human participants or animals performed by any of the authors. For this type of study, formal consent is not required.

ACKNOWLEDGMENT

The authors would like to thank my colleagues for co-authoring this article.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Vreeland DL, Reader A, Beck M, Meyers W, Weaver J. An evaluation of volumes and concentrations of lidocaine in human inferior alveolar nerve block. Journal of Endodontics. 1989; 15: 6–12.

[2] Malamed SF, Gagnon S, Leblanc D. Efficacy of articaine: a new amide local anesthetic. The Journal of the American Dental Association. 2000; 131: 635–642.

[3] Oertel R, Rahn R, Kirch W. Clinical pharmacokinetics of articaine. Clinical Pharmacokinetics. 1997; 33: 417–425.

[4] Subramaniam S, Tennant M. A concise review of the basic biology and pharmacology of local analgesia. Australian Dental Journal. 2005; 50: S23–S30.

[5] Finder RL, Moore PA. Adverse drug reactions to local anesthesia. Dental Clinics of North America. 2002; 46: 747–757.

[6] Jakobs W, Ladwig B, Cichon P, Ortel R, Kirch W. Serum levels of articaine 2% and 4% in children. Anesthesia Progress. 1995; 42: 113–115.

[7] Sixou JL, Marie-Cousin A. Intraosseous anaesthesia in children with 4% articaine and epinephrine 1:400,000 using computer-assisted systems. European Archives of Paediatric Dentistry. 2015; 16: 477–481.

[8] Wright GZ, Weinberger SJ, Marti R, Plotzke O. The effectiveness of infiltration anesthesia in the mandibular primary molar region. Pediatric Dentistry. 1991; 13: 278–283.

[9] Ram D, Amir E. Comparison of articaine 4% and lidocaine 2% in paediatric dental patients. International Journal of Paediatric Dentistry. 2006; 16: 252–256.

[10] Malamed SF, Gagnon S, Leblanc D. A comparison between articaine HCl and lidocaine HCl in pediatric dental patients. Pediatric Dentistry. 2000; 22: 307–311.

[11] Katyal V. The efficacy and safety of articaine versus lignocaine in dental treatments: a meta-analysis. Journal of Dentistry. 2010; 38: 307–317.

[12] Nizharadze N, Mamaladze M, Chipashvili N, Vadachkoria D. Articaine—the best choice of local anesthetic in contemporary dentistry. Georgian Medical News. 2011; 15–23.

[13] Smith T, Urquiola R, Oueis H, Stenger J. Comparison of articaine and lidocaine in the pediatric population. The Journal of the Michigan Dental Association. 2014; 96: 34–37.

[14] Powell V. Articaine is superior to lidocaine in providing pulpal anesthesia. The Journal of the American Dental Association. 2012; 143: 897–898.

[15] Leith R, Lynch K, O'Connell AC. Articaine use in children: a review. European Archives of Paediatric Dentistry. 2012; 13: 293–296.

[16] Taneja S, Singh A, Jain A. Anesthetic effectiveness of articaine and lidocaine in pediatric patients during dental procedures: a systematic review and meta-analysis. Pediatric Dentistry. 2020; 42: 273–281.

[17] Gholami M, Banihashemrad A, Mohammadzadeh A, Ahrari F. The efficacy of 4% articaine versus 2% lidocaine in inducing palatal anesthesia for tooth extraction in different maxillary regions. Journal of Oral and Maxillofacial Surgery. 2021; 79: 1643–1649.

[18] John M. Articaine and lignocaine. Evidence-Based Dentistry. 2011; 12: 21–22.

[19] Alzahrani F, Duggal MS, Munyombwe T, Tahmassebi JF. Anaesthetic efficacy of 4% articaine and 2% lidocaine for extraction and pulpotomy of mandibular primary molars: an equivalence parallel prospective randomized controlled trial. International Journal of Paediatric Dentistry. 2018; 28: 335–344.

[20] Arrow P. A comparison of articaine 4% and lignocaine 2% in block and infiltration analgesia in children. Australian Dental Journal. 2012; 57: 325–333.

[21] Carla M, Pablo SS, Mariane C, Michele B. Efficacy and adverse events of 4% articaine compared with 2% lidocaine on primary molar extraction: a randomised controlled trial. Journal of Oral Rehabilitation. 2020; 47: 1031–1040.

[22] Elheeny AAH. Articaine efficacy and safety in young children below the age of four years: an equivalent parallel randomized control trial. International Journal of Paediatric Dentistry. 2020; 30: 547–555.

[23] Khanna SR, Rao D, Panwar S, Ameen S. An *in vivo*, randomized, controlled comparative evaluation of efficacy, hemodynamic changes, and postoperative complications of 4% articaine using buccal infiltration and 2% lidocaine using inferior alveolar nerve block in mandibular primary molars of children aged 6 to 8 years. Quintessence International. 2021; 52: 780–786.

[24] Ma Y. Effectiveness and satisfaction evaluation of articaine in the treatment of children's dental and endodontic diseases. Electronic Journal of General Stomatology. 2019; 6: 25–26.

[25] Tong HJ, Alzahrani FS, Sim YF, Tahmassebi JF, Duggal M. Anaesthetic efficacy of articaine versus lidocaine in children's dentistry: a systematic review and meta-analysis. International Journal of Paediatric Dentistry. 2018; 28: 347–360.

[26] Kämmerer PW, Palarie V, Daubländer M, Bicer C, Shabazfar N, Brüllmann D, *et al*. Comparison of 4% articaine with epinephrine (1:100,000) and without epinephrine in inferior alveolar block for tooth extraction: double-blind randomized clinical trial of anesthetic efficacy. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. 2012; 113: 495–499.

[27] Ho JTF, van Riet TCT, Afrian Y, Sem KTHCJ, Spijker R, de Lange J, *et al*. Adverse effects following dental local anesthesia: a literature review. Journal of Dental Anesthesia and Pain Medicine. 2021; 21: 507.

[28] Brickhouse TH, Unkel JH, Webb MD, Best AM, Hollowell RL. Articaine use in children among dental practitioners. Pediatric Dentistry. 2008; 30: 516–521.

[29] Wright GZ, Weinberger SJ, Friedman CS, Plotzke OB. Use of articaine local anesthesia in children under 4 years of age—a retrospective report. Anesthesia Progress. 1989; 36: 268–271.

[30] Brignardello-Petersen R. Articaine and lidocaine probably have similar effects in 3- to 4-year-old children undergoing pulpotomy of a primary molar. The Journal of the American Dental Association. 2020; 151: e93.

[31] Thiem DGE, Schnaith F, Van Aken CME, Köntges A, Kumar VV, Al-Nawas B, *et al*. Extraction of mandibular premolars and molars: comparison between local infiltration *via* pressure syringe and inferior alveolar nerve block anesthesia. Clinical Oral Investigations. 2018; 22: 1523–1530.

[32] Flanagan DF. The effectiveness of articaine in mandibular facial infiltrations. Local and Regional Anesthesia. 2016; 9: 1–6.

[33] Shree R, Kedia MR, Toshi T, Raj N, Anand K, Shahi N. A cross-sectional study on the evidence-based dentistry, perception basis, and use of articaine among dental practitioners. Cureus. 2022; 14: e32510.

[34] Martin E, Nimmo A, Lee A, Jennings E. Articaine in dentistry: an overview of the evidence and meta-analysis of the latest randomised controlled trials on articaine safety and efficacy compared to lidocaine for routine dental treatment. BDJ Open. 2021; 7: 27.

[35] Kämmerer PW, Schneider D, Palarie V, Schiegnitz E, Daubländer M. Comparison of anesthetic efficacy of 2 and 4% articaine in inferior alveolar nerve block for tooth extraction—a double-blinded randomized clinical trial. Clinical Oral Investigations. 2017; 21: 397–403.

How to cite this article: Ling Li, Da-lei Sun. Adverse effects of articaine versus lidocaine in pediatric dentistry: a meta-analysis. Journal of Clinical Pediatric Dentistry. 2023; 47(6): 21-29. doi: 10.22514/jocpd.2023.078.