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Research Article

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Anesthetic efficacy in vital asymptomatic teeth using different local anesthetics: a systematic review with network meta-analysis

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

Objectives: This study aimed to evaluate the efficacy of various local anesthesia (LA) in vital asymptomatic teeth.
Materials and Methods: Randomized controlled trials comparing pulpal anesthesia of various LA on vital asymptomatic teeth were included in this review. Searches were conducted in the Cochrane CENTRAL, MEDLINE (via PubMed), EMBASE, ClinicalTrials.gov, Google Scholar and 3 field-specific journals from inception to May 3, 2019. Study selection, data extraction, and risk of bias assessment using Cochrane Risk of Bias Tool were done by 2 independent reviewers in duplicate. Network meta-analysis (NMA) was performed within the frequentist setting using STATA 15.0. The LA was ranked, and the surface under the cumulative ranking (SUCRA) line was plotted. The confidence of the NMA estimates was assessed using the CINeMA web application.
Results: The literature search yielded 1,678 potentially eligible reports, but only 42 were included in this review. For maxillary buccal infiltration, articaine 4% with epinephrine 1:100,000 was more efficacious than lidocaine 2% with epinephrine 1:100,000 (odds ratio, 2.11; 95% confidence interval, 1.14–3.89). For mandibular buccal infiltration, articaine 4% with epinephrine 1:100,000 was more efficacious than various lidocaine solutions. The SUCRA ranking was highest for articaine 4% with epinephrine when used as maxillary and mandibular buccal infiltrations, and lidocaine 2% with epinephrine 1:80,000 when used as inferior alveolar nerve block. Inconsistency and imprecision were detected in some of the NMA estimates.
Conclusions: Articaine 4% with epinephrine is superior when maxillary or mandibular infiltration is required in vital asymptomatic teeth.

Keywords: Inferior alveolar nerve block; Local anesthetic; Maxillary infiltration; Meta-analysis; Systematic review

Author Contributions

Conceptualization: Liew AKC, Abdullah D, Tu YK; Data curation: Liew AKC, Yeh YC, Abdullah D; Formal analysis: Liew AKC, Yeh YC; Funding acquisition: Yeh YC, Tu YK; Investigation: Liew AKC, Yeh YC, Abdullah D; Methodology: Liew AKC, Yeh YC, Tu YK; Project administration: Yeh YC, Tu YK; Resources: Abdullah D, Yeh YC, Tu YK; Software: Yeh YC, Tu YK; Supervision: Tu YK; Validation: Yeh YC, Tu YK; Visualization: Liew AKC, Yeh YC; Writing - original draft: Liew AKC, Yeh YC; Writing - review & editing: Liew AKC, Abdullah D, Tu YK.

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INTRODUCTION

Local anesthesia (LA) is indispensable for pain control in dentistry. It is defined as the loss of sensation in a confined area of the body caused by the inhibition of excitatory process in nerve endings or inhibition of the conduction process in peripheral nerves without inducing a loss of consciousness [1]. In scientific publications, clinical researchers often categorize anesthetic efficacy in dentistry as either soft-tissue anesthesia or pulpal anesthesia [2,3]. While the former is essential for procedures such as wound management and biopsy, the latter is essential for most restorative work and is harder to achieve clinically.

The different solutions of LA offer a dentist several choices as appropriate for the patient for any given dental procedure. It is unclear which LA is the most efficacious in eliciting pulpal anesthesia because previous reviews synthesized the evidence using pairwise meta-analysis, comparing 2 interventions at a time [4,5]. The contemporary approach of network meta-analysis (NMA) offers a unique advantage over pairwise meta-analysis as it allows multiple treatments to be compared concurrently, thereby synthesizing a more comprehensive body of evidence [6]. Furthermore, evidence for treatment differences can be strengthened and extended by combining indirect and direct evidence [7]. Recently, NMA was used to identify efficacious strategies to anesthetize mandibular molars with irreversible pulpitis. Lidocaine 2% with epinephrine 1:100,000 delivered using intraosseous injection, or articaine 4% with 1:100,000 epinephrine delivered using intraosseous injection or buccal and lingual infiltrations were recommended [8].

For decades, randomized controlled trials (RCTs) have been carried out in the vital asymptomatic teeth of healthy adults to compare the anesthetic efficacy of various LA. Such an experimental model has eligibility criteria that facilitate the recruitment of research participants and are more controlled than studies that tested LA in symptomatic patients. Although the findings may not be applicable to symptomatic patients, they are still invaluable to inform clinicians on the pharmacological characteristics of a particular LA when restoring vital asymptomatic teeth. There is a limit, however, on the number of LA that could be tested in each trial. The plethora of LA types, volumes, concentrations, and combinations with vasoconstrictors poses a challenge in synthesizing the evidence. In this instance, NMA could further elucidate on the matter by pooling information from various trials.

The experimental model in vital asymptomatic teeth allows variations, such as split-mouth design and cross-over designs, to be implemented efficiently. This renders it difficult, however, to synthesize the evidence using NMA because the independence assumption does not hold. Correlation between data can be adjusted by the standard approach, the reducing weight approach, and the adjusting variance approach [9].

Thus, this review aimed to evaluate the anesthetic efficacy of various LA in achieving pulpal anesthesia for vital asymptomatic teeth when administered through maxillary/mandibular buccal infiltrations or inferior alveolar nerve block (IANB). The review was intended to answer the following research question: In vital asymptomatic teeth, what is the most efficacious LA to achieve pulpal anesthesia?

MATERIALS AND METHODS

Scope of the review

The systematic review was reported according to the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) for Network Meta-Analyses (**Supplementary Table 1**) [10]. The PICOS framework was used to define the scope of the review.

Types of participants

Trials in healthy participants older than 16 years old were included. Trials involving medically compromised patients were excluded. The diagnostic terminology approved by the American Association of Endodontists and the American Board of Endodontics was used to guide the selection of the trials. We considered teeth to be vital and asymptomatic if the teeth tested in the studies had normal pulp (the pulp was free of symptom, and the tooth was responsive to pulp testing) and normal apical tissue (the tooth was not sensitive to percussion or palpation; intact lamina dura and uniform periodontal space were observed radiographically) [11]. Trials in which participants were taking medications that could alter pain sensation were excluded.

Types of interventions and comparisons

The teeth tested needed to be randomly allocated to receive an injection with one type of LA solution, with or without vasoconstrictor. The techniques of injection considered in this review include maxillary buccal infiltration, mandibular buccal infiltration, and the conventional IANB. In this review, an LA volume of 1.5 mL to 2.2 mL was defined as one cartridge and an LA volume of 3.0 mL to 4.4 mL was defined as 2 cartridges. Trials using LA volume less than 1.5 mL or more than 4.4 mL for each administration were excluded. Trials designed to test a combination of different LA solutions in a single administration, different routes of administration, supplemental injection, or computer-controlled LA delivery were excluded. Studies comparing various additives of LA, such as buffering and carbonating agents, opioids, steroids and other drugs were excluded.

Types of outcomes

The primary outcome of interest was pulpal anesthetic success, defined as the proportion of participants who did not respond to electric pulp testing (EPT) in the maximum setting. Studies not reporting the primary outcome were excluded.

Types of studies

Only RCTs comparing the administration of various solutions and volumes of LA were included. The design of the trials could be parallel-group design, crossover design, or split-mouth design. Observational studies, cluster-RCTs, and quasi-RCTs were excluded.

Study identification and search method

The National Library of Medicine Medical Subject Heading (MeSH) terms were identified and used to search for appropriate trials in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (via PubMed), and EMBASE databases from the inception of the databases to May 3, 2019. Language restriction was not applied. The detailed search strategies for each database are listed in **Supplementary Table 2**. Electronic searching of web archives for the Journal of Endodontics, International Endodontic Journal, and Anesthesia Progress was also performed. Subsequently, we manually scanned the reference lists of articles that met the inclusion criteria and published reviews on the topic. Additional

searches were also conducted on ClinicalTrials.gov and Google Scholar (in English) to ensure the identification of all trials.

Selection of studies and data extraction

Title and abstract screening, appraisal of the full-text articles, trial selection, and data extraction were carried out in duplicate by 2 independent investigators (A.L. and D.A.). At the end of each stage, the 2 investigators met to discuss. Any discrepancies were resolved by consensus between the investigators. Review Manager (RevMan 5, Cochrane Collaboration) was used to record details, such as characteristics of the trial participants, the tooth type, sample size, the type and volume of LA used, the definition of anesthetic success, the success rate, and the incidence of paresthesia. In trials with multiple arms or repeated measures, only data from the testing relevant to the research question were extracted.

Assessment of risk of bias

Two investigators (A.L. and D.A.) assessed the risk of bias for individual studies using the Cochrane Risk of Bias Tool, independently and in duplicate. Disagreements were resolved through discussion to achieve consensus. The methodological quality of the included articles was assessed to identify selection, performance, detection, attrition, and reporting biases [12].

Statistical analysis

Statistical analysis was performed using STATA version 15.0 (StataCorp LP, College Station, TX, USA). Trials with split-mouth or cross-over design were identified, and the adjusting variance approach was implemented to adjust for the dependency of observations within the same patient [9]. Network graphs were plotted for maxillary buccal infiltration, mandibular buccal infiltration, and IANB.

Using the network command in STATA, NMA was implemented with the random-effects model to synthesize both direct and indirect evidence from the included trials and derive the relevant estimates as odds ratios (ORs) with associated 95% confidence intervals (CIs). The design-by-treatment interaction model was fitted to check for overall consistency [13,14]. Loop inconsistency was assessed using the methods described by Lu and Ades [15]. Inconsistency between the direct and indirect evidence was evaluated using the side-splitting model [16].

The surface under the cumulative ranking (SUCRA) line was estimated to determine the ranking of the LA relative to one another. The higher the SUCRA value (reported in percentage), the greater the probability that the LA was of higher rank [17]. Funnel plots and Egger's test were used to assess small-study bias and publication bias.

Quality of evidence

Within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence of the NMA estimates were evaluated using the CINeMA web application (University of Bern, Bern, Switzerland) [18]. Indirectness was manually rated down when carious teeth were tested. Based on the CINeMA output and guidelines [18], the investigators discussed and achieved consensus on the overall confidence—*i.e.*, very low, low, moderate, or high. The overall confidence was downgraded according to the magnitude of the investigators' concerns.

RESULTS

The literature search yielded 1,678 potentially eligible reports, but only 42 were considered appropriate for this review (**Figure 1**). The reasons for exclusion for 51 full-text articles are listed in Table S3. The number of included trials and participants were as follows: i) maxillary buccal infiltration: 19 trials, 793 participants [19-37], ii) mandibular buccal infiltration: 10 trials, 465 participants [25,26,38-45], and iii) IANB: 16 trials, 477 participants [35,46-60].

The characteristics of the included studies are summarized in **Table 1**. Of the 42 articles selected, 2 [29,30] had an identical control arm; hence, these were analyzed as a single trial with 3 arms. Of a total of 41 trials, 2 had a parallel-group design [29,49], another 4 had a split-mouth design [25,26,35,48], and the remaining 35 had a crossover design [19-24,27,28,31-34,36-47,50-60]. The LA was tested with various tooth types, mostly in young adults. All the selected studies involved vital asymptomatic adult permanent teeth with established baseline responsiveness to electrical stimuli, but additional criteria (*e.g.*, free of caries, without large restorations, no periodontal diseases, no history of trauma, and no sensitivity) often apply. Similarly, all the included studies assessed the primary outcome using EPT, but some studies were more specific in their timeframe for measuring the primary outcome.

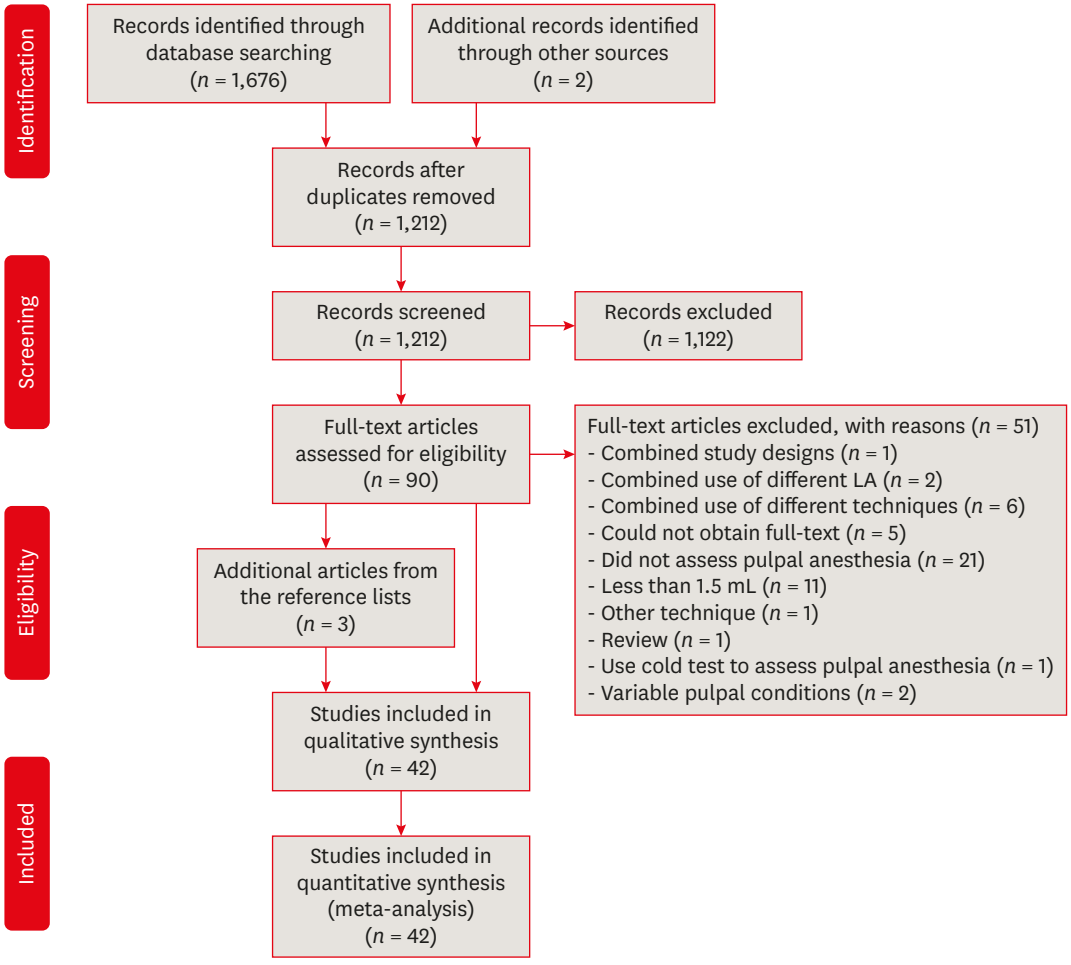

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analyses flow diagram.

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Table 1. Randomized controlled trials included in the network meta-analysis

Study	Design	Age (mean ± SD /SE or range)	Male: Female	Tooth type	Condition of tooth	Criteria for success	Interventions	LA (No., % success)
Aberg and Sydnes 1978 [19]	RCT, cross-over	22–29	10:8	Maxillary lateral incisors	Intact or, in a few cases, had minor restorations.	EPT. Successful tooth anesthesia.	Maxillary BI	1.8 mL of mepivacaine 1% plain (n = 18, 50%); 1.8 mL of mepivacaine 2% plain (n = 18, 83.3%); 1.8 mL of mepivacaine 3% plain (n = 18, 88.9%); 1.8 mL of mepivacaine 0.75% plain (n = 18, 27.8%)
Branco et al. 2006 [46]	RCT, cross-over	18–40	15:15	Mandibular second molar	Teeth tested were free of caries, large restorations, and periodontal disease, and that none had a history of trauma or sensitivity.	EPT. Every 2 min after injection, the same teeth were tested until there was no response to the maximum output of the pulp tester (2 consecutive reading, of 80 without response).	IANB	1.8 mL of bupivacaine 0.5% with 1:200,000 epinephrine (n = 30, 80%); 1.8 mL of levobupivacaine 0.5% with 1:200,000 epinephrine (n = 30, 76.7%)
Caldas et al. 2015 [20]	RCT, cross-over	24.3 ± 4.7	18:12	Maxillary canine	Teeth without decay or extensive restorations, traumas, endodontic treatment and responsive to electric stimulation.	EPT. Two consecutive lack of responses within the 10 initial min.	Maxillary BI	1.8 mL of lidocaine 2% with 1:100,000 epinephrine (n = 30, 100%); 1.8 mL of lidocaine 2% with 1:200,000 epinephrine (n = 30, 100%)
Costa et al. 2005 [21]	RCT, cross-over	18–31	5:15	Maxillary posterior teeth	Initial-stage occlusal caries or indication for occlusal sealant were selected.	EPT. As soon as the injection was completed, the tooth was pulp-tested every 20 secuntil no sensation was reported by the patient, even if the maximum stimulus was applied (350 V, level 80 of the pulp tester).	Maxillary BI	1.8 mL of lidocaine 2% with 1:100,000 epinephrine (n = 20, 100%); 1.8 mL of articaine 4% with 1:200,000 epinephrine (n = 20, 100%); 1.8 mL of articaine 4% with 1:100,000 epinephrine (n = 20, 100%)
Dagher et al. 1997 [47]	RCT, cross-over	32, 22–50	22:8	Mandibular first molar	Free of caries, large restorations, and periodontal disease, and that none had a history of trauma or sensitivity.	EPT. An 80 reading was achieved within 16 min and when this reading was sustained for the remainder of the 50-min test period.	IANB	1.8 mL of lidocaine 2% with 1:50,000 epinephrine (n = 30, 50%); 1.8 mL of lidocaine 2% with 1:100,000 epinephrine (n = 30, 63%); 1.8 mL of lidocaine 2% with 1:200,000 epinephrine (n = 30, 47%);
Donaldson et al. 1987 [48]	RCT, split-mouth	27.67 ± 7.99	11:29	Not reported	Teeth required restorative dental treatment. The sensation level of the test tooth was determined and recorded before treatment.	EPT. The probe indicator light blinks upon maximum output, which occurs when the tooth is anesthesized.	IANB	1.8 mL of prilocaine 4% with 1:200,000 epinephrine (n = 16, 100%); 1.8 mL of articaine 4% with 1:200,000 epinephrine (n = 16, 81.25%)
Ernberg and Kopp 2002 [49]	RCT, parallel	31.9, 18–43	22:8	Mandibular canines	Normal electrical pulp sensibility.	EPT. An electrical pulp tester was used to test the electrical pulp sensibility and pain thresholds.	IANB	1.8 mL of ropivacaine 0.2% plain (n = 10, 20%) 1.8 mL of ropivacaine 0.5% plain (n = 10, 10%) 1.8 mL ropivacaine 0.75% plain (n = 10, 70%)
Evans et al. 2008 [22]	RCT, cross-over	25, 20–36 24, 20–33	25:15 21:19	Maxillary lateral incisors & first molars	A visual and clinical examination was conducted to ensure that all teeth were free of caries, large restorations, crowns, and periodontal disease and that none had a history of trauma or sensitivity.	EPT. When 2 consecutive 80 readings with the pulp tester were obtained within 10 min after the infiltration.	Maxillary BI	1.8 mL of articaine 4% with epinephrine 1:100,000 (n = 80, 82.5%) 1.8 mL of lidocaine 2% with epinephrine 1:100,000 (n = 80, 67.5%)
Fernandez et al. 2005 [50]	RCT, cross-over	24, 20–30	26:13	Mandibular first molars	Clinical examinations indicated that all teeth were free of caries, large restorations, and periodontal disease; none had histories of trauma or sensitivity.	EPT. When 2 consecutive 80 readings were obtained within 15 min and the 80 reading was continuously sustained for 60 min.	IANB	1.8 mL of bupivacaine 0.5% with epinephrine 1:200,000 (n = 39, 46%) 1.8 mL of lidocaine 2% with epinephrine 1:100,000 (n = 39, 54%)
Franz-Montan et al. 2012 [23]	RCT, cross-over	23 ± 5, 18–44	20:20	Maxillary canine	The teeth tested had no history of trauma or sensitivity and were free of caries, large restorations, or periodontal disease.	EPT. A minimum of 10 min of pulpal anaesthesia.	Maxillary BI	1.8 mL of 0.5% ropivacaine plain (n = 40, 50%) 1.8 mL of ropivacaine 0.5% with epinephrine 1:200,000 epinephrine (n = 40, 75%) 1.8 mL of lidocaine 2% with 1:100,000 epinephrine (n = 40, 95%)

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Table 1. (Continued) Randomized controlled trials included in the network meta-analysis

Study	Design	Age (mean ± SD /SE or range)	Male: Female	Tooth type	Condition of tooth	Criteria for success	Interventions	LA (No., % success)
Gross et al. 2007 [24]	RCT, cross-over	24, 18–36 24, 18–36	20:13 20:12	Maxillary lateral incisors & first molar	A visual and clinical examination was conducted to ensure that all teeth were free of caries, large restorations, crowns, and periodontal disease, and that none had a history of trauma or sensitivity.	EPT. Obtaining 2 consecutive 80 readings with the pulp tester within 10 min.	Maxillary BI	1.8 mL of bupivacaine 0.5% with epinephrine 1:200,000 (n = 65, 70.8%) 1.8 mL of lidocaine 2% with epinephrine 1:100,000 (n = 65, 89.2%)
Haas et al. 1990 [25]	RCT, split-mouth	25, 22–32	Not reported	Maxillary and mandibular canines	Noncarious, non-restored teeth.	EPT. A median value of 80, which is the maximal EPS reading possible, for any triplicate recording at any one of the post-injection time-points.	Maxillary BI Mandibular BI	1.5 mL prilocaine 4% with epinephrine 1:200,000 (n = 20, 65%) 1.5 mL of articaine 4% with epinephrine 1:200,000 (n = 20, 65%) 1.5 mL prilocaine 4% with epinephrine 1:200,000 (n = 20, 50%) 1.5 mL of articaine 4% with epinephrine 1:200,000 (n = 20, 65%)
Haas et al. 1991 [26]	RCT, split-mouth	26, 23–41	Not reported	Maxillary and mandibular second molar	Noncarious, non-restored teeth.	EPT. A median value of 80, which is the maximal EPS reading possible, for any triplicate recording at any one of the post-injection time-points.	Maxillary BI Mandibular BI	1.5 mL prilocaine 4% with epinephrine 1:200,000 (n = 20, 90%) 1.5 mL of articaine 4% with epinephrine 1:200,000 (n = 20, 95%) 1.5 mL prilocaine 4% with epinephrine 1:200,000 (n = 19, 53%) 1.5 mL of articaine 4% with epinephrine 1:200,000 (n = 19, 63%)
Hinkley et al. 1991 [51]	RCT, cross-over	27, 23–42	19:11	Mandibular first molar	Clinical examinations indicated that all teeth were free of caries, large restorations, and periodontal disease, and that none had a history of trauma or sensitivity.	EPT. An 80 reading was achieved within 16 min and this reading was sustained for the remainder of the 50-min test period.	IANB	1.8 mL of prilocaine 4% with epinephrine 1:200,000 (n = 30, 46%) 1.8 mL of mepivacaine 2% with levonodefrin 1:20,000 (n = 30, 57%) 1.8 mL of lidocaine 2% with epinephrine 1:100,000 (n = 30, 54%)
Jaber et al. 2010 [38]	RCT, cross-over	24.4 ± 4.4	11:20	Mandibular incisors	Clinical examinations were performed to ensure that all test teeth were free of caries, large restorations, and periodontal disease, and that none had a history of trauma or sensitivity.	Recording the number of volunteers with no response to maximal pulp tester stimulation within 15 min and maintained for 45 min (defined as sustained anaesthesia).	Mandibular BI	1.8 mL of lidocaine 2% with epinephrine 1:100,000 (n = 31, 3.2%) 1.8 mL of articaine 4% with epinephrine 1:100,000 (n = 31, 45.2%)
Kanaa et al. 2006 [39]	RCT, cross-over	22.8 ± 2.1	15:16	Mandibular first molar	Vital. Baseline EPT established.	EPT. Absence of pulp sensation on 2 consecutive maximal pulp tester stimulations (80 A).	Mandibular BI	1.8 mL of articaine 4% with epinephrine 1:100,000 (n = 31, 64.5%) 1.8 mL of lidocaine 2% with epinephrine 1:100,000 (n = 31, 38.7%)
Katz et al. 2010 [27]	RCT, cross-over	25, 22–31 25, 22–33	25:5 20:10	Maxillary lateral incisor & first molar	A visual and clinical examination was conducted to ensure that all teeth were free of caries, large restorations, crowns, and periodontal disease, and that none had a history of trauma or sensitivity.	EPT. When 2 consecutive 80 readings with the pulp tester were obtained within 10 minutes after the infiltration.	Maxillary BI	1.8 mL of lidocaine 2% with epinephrine 1:100,000 (n = 60, 83.3%) 1.8 mL of prilocaine 4% with epinephrine 1:200,000 (n = 60, 91.7%) 1.8 mL of prilocaine 4% (n = 60, 81.7%)
Kennedy et al. 2001 [28]	RCT, cross-over	24, 18–35	20:20	Maxillary lateral incisor	Clinical examinations indicated that all teeth were free of caries, large restorations, and periodontal disease, and that none had a history of trauma or sensitivity.	EPT. When 2 consecutive 80 readings were obtained.	Maxillary BI	1.8 mL of 0.5% ropivacaine with 1:200,000 epinephrine (n = 40, 68%) 1.8 mL of 0.5% ropivacaine plain (n = 40, 75%) 1.8 mL of 0.5% bupivacaine with 1:200,000 epinephrine (n = 40, 80%)

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Table 1. (Continued) Randomized controlled trials included in the network meta-analysis

Study	Design	Age (mean ± SD /SE or range)	Male: Female	Tooth type	Condition of tooth	Criteria for success	Interventions	LA (No., % success)
Krzemiński et al. 2011 [29,30]	RCT, parallel	31.3 ± 7.4 25.1 ± 3.3 27.1 ± 5.6	14:16 15:15 15:15	Maxillary lateral incisor	The presence of maxillary incisor and canine teeth and confirmation that they had healthy pulps that responded to pulp testing.	EPT. The anaesthetic effect (total anaesthesia) was recorded when the tooth gave a negative response to the maximal stimulus of the electrical pulp tester (current intensity of 60 mA).	Maxillary BI	1.8 mL of articaine 4% with epinephrine 1:100,000 (n = 30, 100%) 1.8 mL of ropivacaine 0.5% plain (n = 30, 100%) 1.8 mL of lidocaine 2% with epinephrine 1:100,000 (n = 30, 100%)
Kämmerer et al. 2014 [31]	RCT, cross-over	20, 24–34	10:0	Maxillary central incisor	Vital maxillary central incisors without pathological findings, and without caries and/or prior filling therapy. The periodontium of each tooth had to be free from pathological signs as well.	EPT. The electronic threshold was measured continuously every minute until the maximal intensity (15 = 200 μA) was reached without volunteers' response.	Maxillary BI	1.7 mL of articaine 4% without epinephrine (n = 10, 40%) 1.7 mL of articaine 4% with epinephrine 1:100,000 (n = 10, 100%) 1.7 mL of articaine 4% with epinephrine 1:200,000 (n = 10, 100%) 1.7 mL of articaine 4% with epinephrine 1:300,000 (n = 10, 100%) 1.7 mL of articaine 4% with epinephrine 1:400,000 (n = 10, 100%)
Lawaty et al. 2010 [32]	RCT, cross-over	25, 22–31 24, 21–29	15:15 15:15	Maxillary central incisor and first molar	A visual and clinical examination was conducted to ensure that all teeth were free of caries, large restorations, crowns, and periodontal disease, and that none had a history of trauma or sensitivity.	EPT. When 2 consecutive 80 readings were obtained with the pulp tester.	Maxillary BI	1.8 mL of mepivacaine 2% with 1:20,000 levonordefrin (n = 60, 88.3%) 1.8 mL of lidocaine 2% with 1:100,000 epinephrine (n = 60, 86.7%)
Martin et al. 2011 [40]	RCT, cross-over	26, 20–45	43:43	Mandibular first molar	A visual and clinical examination was conducted to ensure that all teeth were free of caries, large restorations, crowns, and periodontal disease and that none had a history of trauma or sensitivity.	EPT. When 2 consecutive 80 readings with the pulp tester were obtained within 10 min of the initial injection.	Mandibular BI	1.8 mL of articaine 4% with epinephrine 1:100,000 (n = 86, 50%) 3.6 mL of articaine 4% with epinephrine 1:100,000 (n = 86, 70%)
Maruthingal et al. 2015 [41]	RCT, cross-over	18.2	7:25	Mandibular first molar	Having initial occlusal caries confirmed by intraoral periapical radiograph (incipient caries).	EPT. Two or more consecutive episodes of no sensation at maximum stimulation.	Mandibular BI	1.7 mL of lidocaine 2% with epinephrine 1:100,000 (n = 32, 53.1%) 1.7 mL of articaine 4% with epinephrine 1:100,000 (n = 32, 87.5%)
Mason et al. 2009 [33]	RCT, cross-over	25, 19–43 25, 20–42	15:15 16:14	Maxillary lateral incisor and first molar	A visual and clinical examination was conducted to ensure that all teeth were free of caries, large restorations, crowns, and periodontal disease and that none had a history of trauma or sensitivity.	EPT. When 2 consecutive 80 readings with the pulp tester were obtained within 10 min after the infiltration.	Maxillary BI	1.8 mL of lidocaine 2% with epinephrine 1:100,000 (n = 60, 98.3%) 1.8 mL of lidocaine 2% with epinephrine 1:50,000 (n = 60, 96.7%) 1.8 mL of mepivacaine 3% (n = 60, 93.3%)
McEntire et al. 2011 [42]	RCT, cross-over	26, 18–43	43:43	Mandibular first molar	A visual and clinical examination was conducted to ensure that all teeth were free of caries, large restorations, crowns, and periodontal disease and that none had a history of trauma or sensitivity.	EPT. When 2 consecutive 80 readings with the pulp tester were obtained within 10 min of the initial injection.	Mandibular BI	1.8 mL of articaine 4% with epinephrine 1:100,000 (n = 86, 67%) 1.8 mL of articaine 4% with epinephrine 1:200,000 (n = 86, 59%)
McLean et al. 1993 [52]	RCT, cross-over	28, 24–43	24:6	Mandibular first molar	Clinical examinations indicated that all teeth were free of caries, large restorations, and periodontal disease, and that none had a history of trauma or sensitivity.	EPT. An 80 reading was achieved within 16 min and this reading was sustained for the remainder of the 50-min test period.	IANB	1.8 mL of prilocaine 4% (n = 30, 57%) 1.8 mL of mepivacaine 3% (n = 30, 43%) 1.8 mL of lidocaine 2% with epinephrine 1:100,000 epinephrine (n = 30, 63%)

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Table 1. (Continued) Randomized controlled trials included in the network meta-analysis

Study	Design	Age (mean ± SD /SE or range)	Male: Female	Tooth type	Condition of tooth	Criteria for success	Interventions	LA (No., % success)
Mikesell et al. 2005 [53]	RCT, cross-over	28, 19–60	30:27	Mandibular first molar	Clinical examinations indicated that all teeth were free of caries, large restorations, and periodontal disease; none had histories of trauma or sensitivity.	EPT. When 2 consecutive 80 readings were obtained within 15 min and the 80 reading was continuously sustained for 60 min.	IANB	1.8 mL of articaine 4% with epinephrine 1:100,000 (n = 57, 40%) 1.8 mL of lidocaine 2% with epinephrine 1:100,000 (n = 57, 32%)
Mikesell et al. 2008 [34]	RCT, cross-over	26, 21–43	74:22	Maxillary lateral incisor, first premolar, first molar	A visual and clinical examination was conducted to ensure that all teeth were free of caries, large restorations, crowns, and periodontal disease and that none had a history of trauma or sensitivity.	EPT. If 2 consecutive 80 readings were recorded.	Maxillary BI	1.8 mL of lidocaine 2% with epinephrine 1:100,000 (n = 96, 99%) 3.6 mL of lidocaine 2% with epinephrine 1:100,000 (n = 96, 97.9%)
Moore et al. 2006 [54]	RCT, cross-over	30.4 ± 10.0, 19–60	36:27	Mandibular canine	No dental restorations, no gross caries and a normal EPT sensitivity value (10–50 units).	EPT. Three consecutive tests (at 30-sec intervals) above the maximum threshold (EPT ≥ 80), achieved in 10 min.	IANB	1.7 mL of articaine 4% with epinephrine 1:200,000 (n = 62, 54.8%) 1.7 mL of articaine 4% with epinephrine 1:100,000 (n = 62, 47.6%) 1.7 mL of articaine 4% plain (n = 62, 25.8%)
Nydegger et al. 2014 [43]	RCT, cross-over	26, 20–38	30:30	Mandibular first molar	Visual and clinical examinations were conducted before subject inclusion to ensure that all test teeth were free of caries, large restorations, crowns, and periodontal disease and that none had a history of trauma or sensitivity.	EPT. When 2 consecutive 80 readings with the pulp tester were recorded.	Mandibular BI	1.8 mL of 4% articaine with 1:100,000 epinephrine (n = 60, 55%) 1.8 mL of 4% lidocaine with 1:100,000 epinephrine (n = 60, 33%) 1.8 mL of 4% prilocaine with 1:200,000 epinephrine (n = 60, 32%)
Petersen et al. 1977 [55]	RCT, cross-over	23.3, 19–27	4:5	Mandibular canine	All teeth were vital. Baseline threshold value of the pulp reaction was tested before injection with an electric stimulator.	EPT. An analgesic effect was registered when the highest possible current strength (125 μA) failed to produce a reaction of the dental pulp, and the measurements were stopped when a reaction had been recorded for 3 consecutive periods.	IANB	1.8 mL of mepivacaine 2% with epinephrine 1:200,000 (n = 9, 88.9%) 1.8 mL of prilocaine 3% with felypressin 0.03 iu/mL (n = 9, 55.6%) 1.8 mL of mepivacaine 3% plain (n = 9, 77.8%) 1.8 mL of lidocaine 2% with epinephrine 1:80,000 (n = 9, 88.9%)
Robertson et al. 2007 [44]	RCT, cross-over	27, 19–51	26:34	Mandibular first molar	Clinical examinations indicated that all teeth were free of caries, large restorations and periodontal disease; none had histories of trauma or sensitivity.	EPT. When we obtained 2 consecutive readings of 80 with the electric pulp tester.	Mandibular BI	1.76 mL of lidocaine 2% with epinephrine 1:100,000 (n = 60, 57%) 1.76 mL of articaine 4% with epinephrine 1:100,000 (n = 60, 87%)
Teplitsky et al. 1987 [35]	RCT, split-mouth	22–33	Not reported	Maxillary and mandibular second premolar	The teeth to be tested were caries free, vital and without symptoms.	EPT. A reading of 80 was considered to be complete pulpal anesthesia corresponding with no patient response.	Maxillary BI IANB	1.8 mL of bupivacaine 0.5% with epinephrine 1:200,000 (n = 22, 50%) 1.8 mL of lidocaine 2% with epinephrine 1:100,000 (n = 22, 63.7%) 1.8 mL of bupivacaine 0.5% with epinephrine 1:200,000 (n = 22, 86.7%) 1.8 mL of lidocaine 2% with epinephrine 1:100,000 (n = 22, 80%)
Tortamano et al. 2013 [56]	RCT, cross-over	24.63, 18–40	15:15	Mandibular molar	Vital asymptomatic, diagnosed with occlusal caries in enamel, without restoration, pulpal calcification and periodontal disease (which were clinically and radiographically confirmed).	EPT. Two consecutive negative responses were used to stimulate the apparatus' maximum (80 μa).	IANB	1.8 mL of lidocaine 2% with epinephrine 1:100,000 (n = 30, 100%) 1.8 mL of articaine 4% with epinephrine 1:100,000 (n = 30, 100%) 1.8 mL of articaine 4% with epinephrine 1:200,000 (n = 30, 100%)

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Table 1. (Continued) Randomized controlled trials included in the network meta-analysis

Study	Design	Age (mean ± SD /SE or range)	Male: Female	Tooth type	Condition of tooth	Criteria for success	Interventions	LA (No., % success)
Tófoli et al. 2003 [57]	RCT, cross-over	23 ± 4, 20–35	7:13	Mandibular first premolar	Free of caries and restorations.	EPT. Period in which the subject had no response to maximal output of the pulp tester (80 reading).	IANB	1.8 mL of articaine 4% with epinephrine 1:200,000 (*n* = 20, 100%) 1.8 mL of articaine 4% with epinephrine 1:100,000 (*n* = 20, 100%)
Tófoli et al. 2011 [36]	RCT, cross-over	25.4 ± 5.2, 20–45	13:17	Maxillary canine	Vitals, free of caries, large restorations, periodontal disease, past endodontic treatment, and history of trauma or sensitivity.	EPT. When the maximum stimulation threshold produced by the instrument (80 readings/300 V) was reached, the tooth was considered anesthetized and the LP was obtained. If the electrical stimulation produced a response after 10 min, the tooth was considered not anesthetized.	Maxillary BI	1.8 mL of mepivacaine 2% with epinephrine 1:100,000 (*n* = 30, 100%) 1.8 mL of mepivacaine 3% plain (*n* = 30, 100%)
Vreeland et al. 1989 [58]	RCT, cross-over	25.5, 22–32	27:3	Mandibular first molar	Clinical examinations with an explorer and periodontal probe indicated that all experimental teeth were free of caries, large restorations, crowns, previous endodontic therapy, exposed dentin, or periodontal disease. After questioning the subjects, all teeth with a history of trauma or sensitivity were also eliminated.	EPT. Subjects who achieved an 80 reading within 16 min and continuously sustained this reading for 55 min.	IANB	1.8 mL of lidocaine 2% with epinephrine 1:100,000 (*n* = 30, 63.3%) 3.6 mL of lidocaine 2% with epinephrine 1:200,000 (*n* = 30, 63.3%) 1.8 mL of lidocaine 4% with epinephrine 1:100,000 (*n* = 30, 53.3%)
Wali et al. 2010 [59]	RCT, cross-over	28, 22–44	22:8	Mandibular first molar	Clinical examinations indicated that all teeth were free of caries, large restorations, and periodontal disease; none had histories of trauma or sensitivity.	EPT. When 2 consecutive 80 readings were obtained within 15 min, and the 80 reading was continuously sustained through the 60th min.	IANB	1.8 mL of lidocaine 2% with epinephrine 1:100,000 (*n* = 30, 43%) 1.8 mL of lidocaine 2% with epinephrine 1:50,000 (*n* = 30, 30%) 3.6 mL of lidocaine 2% with epinephrine 1:50,000 (*n* = 30, 40%)
Wiziack Zago et al. 2011 [37]	RCT, cross-over	25.41 ± 3.87, 19–33	15:17	Maxillary canine	All test and control teeth were responsive to electric stimulation (i.e., a pulp tester), had no history of trauma or sensitivity, and were free of caries, restorations, periodontal disease, and endodontic treatment.	EPT. Anesthesia was considered successful when the onset time was less than 10 min and the duration was at least 10 min.	Maxillary BI	1.8 mL of prilocaine 3% with felypressin 0.03 IU/mL (*n* = 32, 90.6%) 1.8 mL of prilocaine plain (*n* = 32, 71.9%)
Yared and Dagher 1997 [60]	RCT, cross-over	32, 22–50	22:8	Mandibular first molar	Clinical examinations indicated that all teeth were free of caries, large restorations, and periodontal disease and that none had a history of trauma or sensitivity.	EPT. If an 80 reading was achieved within 16 min and when this reading was sustained for the remainder of the 50-min test period.	IANB	3.6 mL of lidocaine 2% with epinephrine 1:50,000 (*n* = 30, 77%) 3.6 mL of lidocaine 2% with epinephrine 1:80,000 (*n* = 30, 93%) 3.6 mL of lidocaine 2% with epinephrine 1:100,000 (*n* = 30, 77%)
Yonchak et al. 2001 [45]	RCT, cross-over	26, 20–34	30:10	Mandibular lateral incisor	Clinical examinations indicated that all teeth were free of caries, large restorations, and periodontal disease and that none had a history of trauma or sensitivity.	EPT. When 2 consecutive 80 readings were obtained.	Mandibular BI	1.8 mL of lidocaine 2% with epinephrine 1:50,000 (*n* = 40, 43%) 1.8 mL of lidocaine 2% with epinephrine 1:100,000 (*n* = 40, 45%)

SD, standard deviation; SE, standard error; LA, local anesthesia; RCT, randomized controlled trial; BI, buccal infiltration; EPT, electric pulp testing; IANB, inferior alveolar nerve block.

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Of the 41 included trials, 18 had a low risk of bias, 17 had a moderate risk of bias, and 6 had a high risk of bias (**Supplementary Figures 1** and **2**). The forest plots indicated that most direct pairwise comparisons were informed by a single study (**Supplementary Figure 3**). When multiple studies were available for direct comparison, heterogeneity between studies was low ($p > 0.05$).

Based on the injection techniques, 3 network plots are presented (**Figure 2**). Each node represents a type of LA, with the size of the nodes indicating the number of patients assigned to this type of LA. Comparisons between LA are linked by a straight line. The thickness of the line represents the number of trials for each pair being compared. All interventions in the network for mandibular buccal infiltration could be included in the NMA. The network plot for maxillary buccal infiltration and IANB were partly disconnected, however, forming separate clusters. The minor cluster for maxillary buccal infiltration consists of prilocaine 3% plain and prilocaine 3% with felypressin, while the minor cluster for IANB consists of ropivacaine 0.2%, ropivacaine 0.5%, and ropivacaine 0.75%. Hence, these separate clusters were excluded from the NMA. In all 3 networks, lidocaine 2% with 1:100,000 epinephrine was the most universal LA compared.

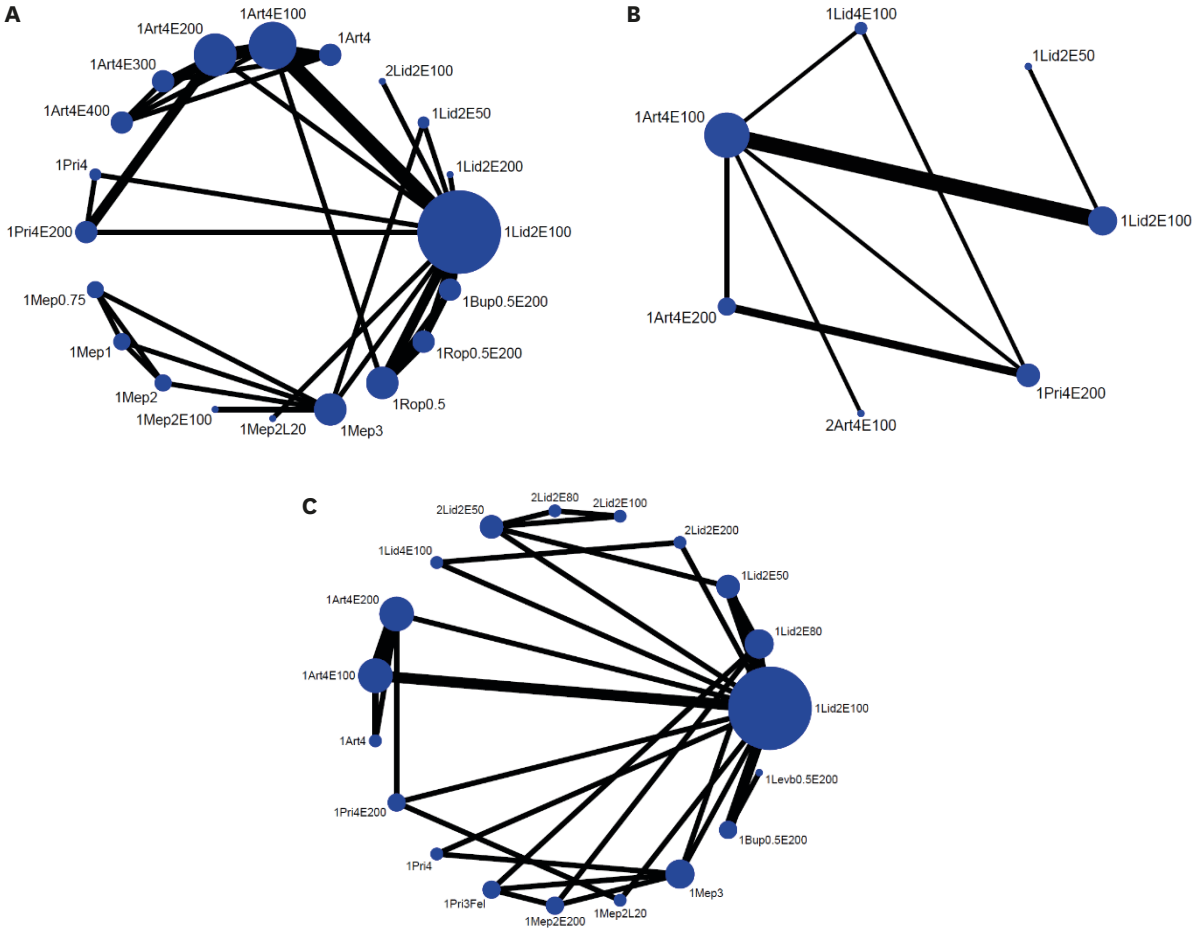

Figure 2. Network plots of local anesthetic solutions used for (A) maxillary infiltration, (B) mandibular infiltration, and (C) inferior alveolar nerve block. LAs forming a separate cluster from the main network are not displayed here. Abbreviation codes were used to represent the intervention. The first number indicates the number of cartridges used. This is followed by the type of LA (Art = articaine, Lid = lidocaine, Bup = bupivacaine, Rop = ropivacaine, Mep = mepivacaine, Pri = prilocaine, Lev = levobupivacaine) and its concentration (%). The third part denotes the vasoconstrictor (nil = plain, E = epinephrine, L = levonordefrin, Fel = felypressin) and its concentration (one in hundred thousand, *e.g.*, E100 = epinephrine 1:100,000 or tenth of iu/mL, *e.g.*, Fel3 = 0.03 iu/mL).
LA, local anesthesia.

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Wide CIs were noted in most of the cells in the league table (**Table 2**). For maxillary buccal infiltration using a single cartridge, articaine 4% with epinephrine 1:100,000 had higher odds of anesthetic success than lidocaine 2% with epinephrine 1:100,000 (OR, 2.11; 95% CI, 1.14–3.89). Long-acting LA, such as ropivacaine 0.5% plain, ropivacaine 0.5% with epinephrine 1:200,000, and bupivacaine 0.5% with epinephrine 1:200,000, were less efficacious than short- to medium-acting LA with a vasoconstrictor. Articaine 4% plain, mepivacaine 0.75% plain, and mepivacaine 1% plain, had lower odds of success than all other LA. For mandibular buccal infiltration, 2 cartridges of articaine 4% with epinephrine 1:100,000 were more efficacious than a single cartridge of various solutions. A single cartridge of articaine 4% with epinephrine 1:100,000 was more efficacious than the lidocaine or prilocaine solutions.

For IANB, articaine 4% plain was less efficacious than articaine 4% with epinephrine 1:200,000 (OR, 0.31; 95% CI, 0.15–0.65) and articaine 4% with epinephrine 1:100,000 (OR, 0.35; 95% CI, 0.17–0.74). Prilocaine 3% with felypressin was less efficacious than lidocaine 2% with epinephrine 1:80,000 (OR, 0.12; 95% CI, 0.02–0.69). Similarly, mepivacaine 3% plain recorded lower odds of anesthetic success than did lidocaine 2% with epinephrine 1:80,000 (OR, 0.29; 95% CI, 0.09–0.90).

In general, articaine with epinephrine dominated the ranking chart of LA when used as maxillary and mandibular buccal infiltration (**Table 3**). For IANB, lidocaine 2% with epinephrine 1:80,000 was ranked best when 2 cartridges were used and second best when one cartridge was used. In maxillary buccal infiltration, the ranking of 2 cartridges of lidocaine 2% with epinephrine 1:100,000 was lower than a single cartridge of the same LA (**Table 3**), but the OR for this pair included the null value (**Table 2**). In mandibular buccal infiltration, 2 cartridges of articaine 4% with epinephrine 1:100,000 ranked higher than a single cartridge of the same LA (OR, 2.31; 95% CI, 1.34–3.97). For IANB, the ranking of 2 cartridges of lidocaine 2% with epinephrine 1;80,000 was higher than the single cartridge, but the reverse pattern was observed for lidocaine 2% with epinephrine 1:100,000 and 1:50,000. Nonetheless, all 3 pairs of comparisons have ORs that include the null value.

For maxillary and mandibular buccal infiltrations, no gross inconsistency was detected when tested using the design-by-treatment interaction model, loop inconsistency model, or side-splitting model ($p > 0.05$). For IANB, statistical significance was not detected in the design-by-treatment interaction model or loop inconsistency model ($p > 0.05$). In the side-splitting model, inconsistency was detected between the direct and indirect evidence comparing single cartridges of lidocaine 2% with epinephrine 1:100,000 and prilocaine 4% with epinephrine 1:200,000 ($p = 0.049$). In addition, inconsistency was detected between the direct and indirect evidence comparing single cartridges of lidocaine 2% with epinephrine 1:100,000 and mepivacaine 2% with levonordefrin 1:20,000 ($p = 0.049$).

Publication bias and small-study effects were unlikely, as observed using funnel plots (**Supplementary Figure 4**) and Egger's graphs (**Supplementary Figure 5**). Statistical significance was not evident in Egger's tests for maxillary buccal infiltration, mandibular buccal infiltration, or IANB ($p > 0.05$). The estimates were derived from studies of variable risk of bias (**Supplementary Figure 6**). The quality concerns were mostly for imprecision (**Supplementary Table 4**).

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Table 2. The OR of pairwise meta-analysis (lower left) and network meta-analysis (upper right) for the anesthetic efficacy in vital asymptomatic teeth

Maxillary buccal infiltration																			
1Lid2E100	1.00 (0.03–30.65)	0.49 (0.06–4.29)	0.49 (0.06–4.09)	**0.07 (0.01–0.72)**	**2.11 (1.14–3.89)**	2.29 (0.69–7.63)	2.20 (0.10–49.44)	2.20 (0.10–49.35)	0.87 (0.39–1.97)	2.08 (0.82–5.23)	**0.01 (0.00–0.14)**	**0.03 (0.00–0.36)**	0.15 (0.01–1.99)	0.24 (0.00–12.39)	1.16 (0.46–2.98)	0.24 (0.03–1.72)	**0.13 (0.06–0.31)**	**0.27 (0.11–0.64)**	**0.35 (0.19–0.63)**
1.00 (0.03–30.65)	1Lid2E200	0.49 (0.01–28.22)	0.49 (0.01–27.61)	0.07 (0.00–4.46)	2.11 (0.07–68.17)	2.29 (0.06–86.28)	2.20 (0.02–224.54)	2.20 (0.02–224.28)	0.87 (0.03–29.42)	2.08 (0.06–71.91)	**0.01 (0.00–0.81)**	0.03 (0.00–2.06)	0.15 (0.00–10.88)	0.24 (0.00–44.35)	1.16 (0.03–40.51)	0.24 (0.00–12.39)	0.13 (0.00–4.53)	0.27 (0.01–9.27)	0.35 (0.01–11.16)
0.49 (0.06–4.29)		1Lid2E50	1.01 (0.05–20.74)	0.15 (0.01–3.46)	4.29 (0.45–40.70)	4.67 (0.39–55.56)	4.47 (0.10–198.37)	4.47 (0.10–198.09)	1.77 (0.18–17.95)	4.22 (0.40–44.50)	**0.02 (0.00–0.21)**	**0.06 (0.01–0.52)**	0.30 (0.03–2.89)	0.48 (0.01–20.40)	2.37 (0.22–25.11)	0.48 (0.11–2.20)	0.27 (0.03–2.77)	0.55 (0.05–5.69)	0.70 (0.07–6.65)
0.50 (0.06–4.09)			2Lid2E100	0.15 (0.01–3.31)	4.26 (0.47–38.43)	4.64 (0.41–52.70)	4.44 (0.10–191.26)	4.44 (0.10–190.98)	1.76 (0.18–16.97)	4.20 (0.42–42.11)	**0.02 (0.00–0.62)**	0.06 (0.00–1.59)	0.30 (0.01–8.52)	0.48 (0.01–42.51)	2.35 (0.23–23.77)	0.48 (0.03–8.70)	0.27 (0.03–2.62)	0.55 (0.06–5.38)	0.70 (0.08–6.28)
				1Art4	**29.07 (2.98–283.55)**	**31.65 (3.25–308.78)**	**30.33 (1.81–507.08)**	**30.33 (1.82–506.09)**	**12.04 (1.12–129.74)**	**28.65 (2.83–290.20)**	0.16 (0.01–4.80)	0.41 (0.01–12.25)	2.05 (0.06–65.41)	3.27 (0.03–317.02)	**16.08 (1.35–191.77)**	3.27 (0.16–67.95)	1.85 (0.16–21.16)	3.75 (0.32–43.43)	4.77 (0.45–51.03)
2.16 (1.16–4.05)				**30.33 (1.86–494.24)**	1Art4E100	1.09 (0.30–3.97)	1.04 (0.05–23.19)	1.04 (0.05–23.15)	0.41 (0.15–1.13)	0.99 (0.34–2.89)	**0.01 (0.00–0.07)**	**0.01 (0.00–0.19)**	0.07 (0.00–1.01)	0.11 (0.00–6.17)	0.55 (0.18–1.70)	**0.11 (0.01–0.90)**	**0.06 (0.02–0.18)**	**0.13 (0.05–0.37)**	**0.16 (0.07–0.38)**
1.00 (0.03–31.06)				**30.33 (1.86–494.24)**	1.00 (0.09–11.51)	1Art4E200	0.96 (0.04–21.29)	0.96 (0.04–21.26)	0.38 (0.11–1.34)	0.91 (0.36–2.29)	**0.00 (0.00–0.08)**	**0.01 (0.00–0.21)**	0.06 (0.00–1.13)	0.10 (0.00–6.46)	0.51 (0.11–2.33)	0.10 (0.01–1.05)	**0.06 (0.01–0.25)**	**0.12 (0.03–0.52)**	**0.15 (0.04–0.58)**
				30.33 (1.82–507.08)	1.00 (0.03–32.96)	1.00 (0.03–32.96)	1Art4E300	1.00 (0.03–33.59)	0.40 (0.02–9.50)	0.94 (0.04–21.58)	**0.01 (0.00–0.29)**	**0.01 (0.00–0.73)**	0.07 (0.00–3.89)	0.11 (0.00–16.57)	0.53 (0.02–13.69)	0.11 (0.00–4.33)	0.06 (0.00–1.53)	0.12 (0.00–3.12)	0.16 (0.01–3.74)
				30.33 (1.82–506.09)	1.00 (0.03–32.91)	1.00 (0.03–32.91)	1.00 (0.03–33.59)	1Art4E400	0.40 (0.02–9.48)	0.94 (0.04–21.54)	**0.01 (0.00–0.29)**	**0.01 (0.00–0.73)**	0.07 (0.00–3.88)	0.11 (0.00–16.55)	0.53 (0.02–13.67)	0.11 (0.00–4.32)	0.06 (0.00–1.52)	0.12 (0.00–3.12)	0.16 (0.01–3.74)
0.89 (0.39–2.04)									1Pri4	2.38 (0.92–6.13)	**0.01 (0.00–0.19)**	**0.03 (0.00–0.47)**	0.17 (0.01–2.58)	0.27 (0.00–15.44)	1.34 (0.39–4.63)	0.27 (0.03–2.32)	**0.15 (0.05–0.49)**	0.31 (0.10–1.02)	0.40 (0.14–1.09)
2.20 (0.81–5.95)						0.85 (0.31–2.32)			2.47 (0.93–6.55)	1Pri4E200	**0.01 (0.00–0.08)**	**0.01 (0.00–0.21)**	0.07 (0.00–1.12)	0.11 (0.00–6.64)	0.56 (0.15–2.10)	**0.11 (0.01–1.02)**	**0.06 (0.02–0.22)**	**0.13 (0.04–0.46)**	**0.17 (0.06–0.50)**
											1Mep0.75	2.60 (0.75–9.07)	13.00 (3.15–53.69)	20.80 (0.48–900.65)	**102.11 (6.85–1,522.34)**	**20.80 (4.30–100.64)**	11.73 (0.81–168.96)	**23.84 (1.64–346.35)**	**30.32 (2.25–409.33)**
											2.60 (0.75–9.07)	1Mep1	5.00 (1.27–19.70)	8.00 (0.19–340.41)	**39.27 (2.70–571.41)**	**8.00 (1.72–37.11)**	4.51 (0.32–63.40)	9.17 (0.65–129.97)	11.66 (0.89–153.50)
											13.00 (3.15–53.69)	**5.00 (1.27–19.70)**	1Mep2	1.60 (0.04–72.27)	7.85 (0.50–124.16)	1.60 (0.30–8.54)	0.90 (0.06–13.79)	1.83 (0.12–28.26)	2.33 (0.16–33.46)
														1Mep2E100	4.91 (0.08–286.16)	1.00 (0.03–30.64)	0.56 (0.01–32.14)	1.15 (0.02–65.68)	1.46 (0.03–79.61)
1.17 (0.46–2.98)															1Mep2L20	0.20 (0.02–1.83)	**0.11 (0.03–0.40)**	**0.23 (0.07–0.84)**	**0.30 (0.10–0.90)**
0.24 (0.03–1.72)		0.48 (0.11–2.20)									**20.80 (4.30–100.64)**	**8.00 (1.73–37.11)**	1.60 (0.30–8.54)	1.00 (0.03–30.65)		1Mep3	0.56 (0.07–4.85)	1.15 (0.13–9.96)	1.46 (0.18–11.56)
0.07 (0.02–0.27)					1.00 (0.02–52.04)												1Rop0.5	**2.03 (1.13–3.67)**	**2.58 (1.23–5.41)**
0.16 (0.04–0.66)																	**2.09 (1.16–3.79)**	1Rop0.5E200	1.27 (0.59–2.73)
0.38 (0.20–0.73)																	1.93 (0.78–4.66)	1.33 (0.54–3.32)	1Bup0.5E200
Mandibular buccal infiltration																			
1Lid2E100	0.90 (0.42–1.94)	2.02 (0.91–4.48)	**4.87 (2.94–8.06)**	**3.36 (1.68–6.72)**	**11.24 (5.37–23.55)**	1.90 (0.91–3.96)													
0.90 (0.42–1.94)	1Lid2E50	2.23 (0.74–6.75)	**5.39 (2.16–13.48)**	**3.72 (1.32–10.45)**	**12.44 (4.29–36.06)**	2.10 (0.73–6.07)													
		1Lid4E100	**2.41 (1.30–4.48)**	1.66 (0.81–3.43)	**5.57 (2.45–12.66)**	0.94 (0.50–1.77)													
4.87 (2.94–8.06)		2.44 (1.29–4.64)	1Art4E100	0.69 (0.43–1.11)	**2.31 (1.34–3.97)**	**0.39 (0.23–0.67)**													
			0.70 (0.41–1.21)	1Art4E200	**3.35 (1.63–6.88)**	0.57 (0.32–1.00)													
			2.31 (1.34–3.97)		2Art4E100	**0.17 (0.08–0.36)**													
		0.93 (0.48–1.80)	0.38 (0.20–0.72)	0.59 (0.27–1.29)		1Pri4E200													

(continued to the next page)

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Table 2. (Continued) The OR of pairwise meta-analysis (lower left) and network meta-analysis (upper right) for the anesthetic efficacy in vital asymptomatic teeth

Inferior alveolar nerve block																		
1Lid2E100	1.63 (0.71–3.70)	0.86 (0.45–1.64)	1.00 (0.39–2.55)	0.99 (0.25–3.89)	4.23 (0.76–23.61)	0.99 (0.42–2.34)	0.66 (0.26–1.66)	1.41 (0.36–5.49)	1.23 (0.53–2.85)	0.44 (0.13–1.48)	1.00 (0.38–2.65)	0.78 (0.31–1.95)	0.20 (0.03–1.10)	1.25 (0.13–11.77)	1.33 (0.51–3.45)	0.47 (0.20–1.13)	0.85 (0.39–1.85)	0.70 (0.18–2.66)
1.97 (0.81–4.83)	1Lid2E80	0.53 (0.23–1.23)	0.62 (0.18–2.14)	0.61 (0.13–2.84)	2.60 (0.41–16.68)	0.61 (0.20–1.85)	0.41 (0.12–1.40)	0.87 (0.19–3.99)	0.76 (0.24–2.35)	0.27 (0.06–1.11)	0.61 (0.17–2.26)	0.48 (0.15–1.59)	**0.12 (0.02–0.69)**	0.77 (0.08–7.37)	0.82 (0.23–2.92)	**0.29 (0.09–0.90)**	0.52 (0.16–1.66)	0.43 (0.09–2.10)
0.87 (0.46–1.64)	0.58 (0.24–1.41)	1Lid2E50	1.17 (0.37–3.64)	1.16 (0.29–4.57)	4.93 (0.88–27.69)	1.16 (0.48–2.77)	0.77 (0.25–2.38)	1.64 (0.38–7.18)	1.43 (0.51–4.06)	0.51 (0.13–1.97)	1.16 (0.36–3.81)	0.91 (0.30–2.76)	0.23 (0.04–1.38)	1.46 (0.15–14.50)	1.55 (0.49–4.94)	0.55 (0.19–1.60)	0.99 (0.36–2.75)	0.81 (0.18–3.63)
1.00 (0.40–2.48)			2Lid2E200	0.99 (0.19–5.20)	4.23 (0.60–29.98)	0.99 (0.28–3.54)	0.66 (0.26–1.66)	1.41 (0.27–7.35)	1.23 (0.35–4.33)	0.44 (0.09–2.03)	1.00 (0.26–3.86)	0.78 (0.21–2.90)	0.20 (0.03–1.40)	1.25 (0.11–14.21)	1.33 (0.35–5.06)	0.47 (0.13–1.70)	0.85 (0.25–2.87)	0.70 (0.14–3.57)
				2Lid2E100	4.26 (0.96–18.90)	1.00 (0.35–2.89)	0.67 (0.13–3.47)	1.42 (0.21–9.72)	1.24 (0.25–6.15)	0.44 (0.07–2.73)	1.01 (0.19–5.40)	0.79 (0.15–4.06)	0.20 (0.02–1.75)	1.26 (0.09–17.14)	1.34 (0.25–7.10)	0.48 (0.10–2.39)	0.85 (0.18–4.12)	0.70 (0.10–4.76)
				4.26 (0.98–18.57)	2Lid2E80	0.23 (0.05–1.04)	0.16 (0.02–1.10)	0.33 (0.04–2.97)	0.29 (0.04–1.97)	**0.10 (0.01–0.85)**	0.24 (0.03–1.71)	0.19 (0.03–1.29)	**0.05 (0.00–0.52)**	0.30 (0.02–4.92)	0.32 (0.04–2.25)	**0.11 (0.02–0.76)**	0.20 (0.03–1.33)	0.16 (0.02–1.46)
0.87 (0.36–2.12)		1.33 (0.54–3.32)		1.00 (0.36–2.82)	0.24 (0.05–1.02)	2Lid2E50	0.67 (0.19–2.35)	1.42 (0.29–7.06)	1.24 (0.37–4.11)	0.44 (0.10–1.95)	1.01 (0.27–3.70)	0.79 (0.23–2.75)	0.20 (0.03–1.33)	1.26 (0.12–13.68)	1.34 (0.37–4.84)	0.48 (0.14–1.61)	0.85 (0.27–2.73)	0.70 (0.14–3.45)
0.66 (0.27–1.62)			0.66 (0.27–1.62)				1Lid4E100	2.13 (0.41–11.01)	1.86 (0.53–6.48)	0.66 (0.14–3.04)	1.51 (0.39–5.78)	1.18 (0.32–4.33)	0.30 (0.04–2.10)	1.90 (0.17–21.35)	2.01 (0.54–7.57)	0.72 (0.20–2.54)	1.28 (0.38–4.29)	1.05 (0.21–5.36)
1.00 (0.03–30.65)								1Art4E200	0.87 (0.39–1.96)	**0.31 (0.15–0.65)**	0.71 (0.11–4.56)	0.56 (0.11–2.95)	0.14 (0.02–1.28)	0.89 (0.06–12.46)	0.95 (0.16–5.48)	0.34 (0.06–1.80)	0.60 (0.11–3.43)	0.49 (0.06–3.86)
1.45 (0.75–2.78)								0.76 (0.42–1.38)	1Art4E100	**0.35 (0.17–0.74)**	0.81 (0.20–3.31)	0.64 (0.18–2.25)	0.16 (0.02–1.10)	1.02 (0.09–11.27)	1.08 (0.29–4.10)	0.39 (0.11–1.34)	0.69 (0.20–2.44)	0.57 (0.11–3.01)
								0.28 (0.15–0.55)	**0.38 (0.20–0.74)**	1Art4	2.29 (0.41–12.69)	1.80 (0.38–8.44)	0.45 (0.05–3.79)	2.88 (0.22–37.37)	3.06 (0.60–15.50)	1.09 (0.23–5.10)	1.95 (0.40–9.52)	1.60 (0.23–10.97)
0.75 (0.30–1.87)								8.56 (0.54–135.83)			1Pri4E200	0.78 (0.21–2.94)	0.20 (0.03–1.41)	1.26 (0.11–14.33)	1.33 (0.52–3.45)	0.47 (0.13–1.70)	0.85 (0.27–2.70)	0.70 (0.14–3.42)
0.76 (0.41–1.86)												1Pri4	0.25 (0.04–1.53)	1.60 (0.16–16.05)	1.70 (0.46–6.30)	0.60 (0.25–1.49)	1.08 (0.33–3.55)	0.89 (0.18–4.46)
	0.16 (0.02–1.34)												1Pri3Fel	6.40 (0.73–55.98)	6.80 (0.95–48.63)	2.41 (0.47–12.54)	4.33 (0.65–28.60)	3.55 (0.40–31.47)
	1.00 (0.08–13.17)												6.40 (0.74–55.31)	1Mep2E200	1.06 (0.09–12.05)	0.38 (0.04–3.33)	0.68 (0.06–7.19)	0.56 (0.04–7.51)
1.16 (0.46–2.88)											1.54 (0.62–3.83)				1Mep2L20	0.36 (0.10–1.27)	0.64 (0.19–2.08)	0.52 (0.10–2.61)
0.44 (0.18–1.09)	0.44 (0.05–4.26)											0.59 (0.24–1.42)	2.80 (0.47–16.69)	0.44 (0.05–4.29)		1Mep3	1.79 (0.57–5.63)	1.47 (0.30–7.16)
0.84 (0.42–1.70)																	1Bup0.5E200	0.82 (0.28–2.44)
																	0.82 (0.28–2.39)	1Levb0.5E200

Ranges in parentheses are 95% confidence intervals. Comparisons between local anesthetic solutions should be read from left to right. The estimate of anesthetic efficacy between each pair is in the cell in common between the row-defining treatment and column-defining treatment. For pairwise meta-analysis, an OR more than 1 indicates the local anesthetic solution specified in the row is more efficacious than the local anesthetic solution specified in the corresponding column. For network meta-analysis, an OR more than 1 indicates that the local anesthetic solution specified in the column is more efficacious than the local anesthetic solution specified in the corresponding row. Bold fonts indicate OR ranges which do not include the null value (null OR = 1). Abbreviation codes were used to represent the intervention. The first number indicates the number of cartridges used. This is followed by the type of local anesthesia (Art = articaine, Lid = lidocaine, Bup = bupivacaine, Rop = ropivacaine, Mep = mepivacaine, Pri = prilocaine, Lev = levobupivacaine) and its concentration (%). The third part denotes the vasoconstrictor (nil = plain, E = epinephrine, L = levonordefrin, Fel = felypressin) and its concentration (one in hundred-thousandth, *e.g.*, E100 = epinephrine 1:100,00).
OR, odds ratio.

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Table 3. Relative ranking of local anesthesia

Relative ranking	Local anesthesia	SUCRA	Probability of ranked best	Mean rank
Maxillary buccal infiltration				
1	1Art4E200	84.6	11.2	3.9
2	1Art4E100	84.3	6.8	4
3	1Pri4E200	83.4	6	4.2
4	1Art4E400	77	26	5.4
5	1Art4E300	76.2	23.1	5.5
6	1Mep2L20	69.3	0.9	6.8
7	1Lid2E100	65.1	0	7.6
8	1Pri4	61.4	0.1	8.3
9	1Lid2E200	60.9	15.5	8.4
10	1Lid2E50	52.4	1.4	10
11	2Lid2E100	50.7	2.9	10.4
12	1Bup0.5E200	41.4	0	12.1
13	1Mep2E100	41	5.3	12.2
14	1Mep3	36.2	0.1	13.1
15	1Rop0.5E200	36	0	13.2
16	1Mep2	29.3	0.7	14.4
17	1Rop0.5	21.8	0	15.8
18	1Art4	17.8	0	16.6
19	1Mep1	9.2	0	18.3
20	1Mep0.75	1.9	0	19.6
Mandibular buccal infiltration				
1	2Art4E100	100	99.9	1
2	1Art4E100	82.1	0.1	2.1
3	1Art4E200	65.9	0	3
4	1Lid4E100	42.1	0	4.5
5	1Pri4E200	38.5	0	4.7
6	1Lid2E100	12.3	0	6.3
7	1Lid2E50	9	0	6.5
Inferior alveolar nerve block				
1	2Lid2E80	92.6	61.2	2.3
2	1Lid2E80	77.3	5.4	5.1
3	1Art4E200	68.5	10.1	6.7
4	1Mep2L20	68.1	3.6	6.7
5	1Art4E100	65.6	0.9	7.2
6	1Mep2E200	58.7	14.6	8.4
7	1Lid2E100	54.9	0	9.1
8	2Lid2E200	54.2	1.2	9.2
9	1Pri4E200	53.9	1	9.3
10	2Lid2E50	52.9	0.2	9.5
11	2Lid2E100	51.6	0.7	9.7
12	1Lid2E50	45	0.1	10.9
13	1Bup0.5E200	44.6	0	11
14	1Pri4	43.1	0.2	11.2
15	1Levb0.5E200	39.1	0.7	12
16	1Lid4E100	33.8	0.1	12.9
17	1Art4	20.5	0	15.3
18	1Mep3	18.5	0	15.7
19	1Pri3Fel	7	0	17.7

Abbreviation codes were used to represent the intervention. The first number indicates the number of cartridges used. This is followed by the type of local anesthesia (Art = articaine, Lid = lidocaine, Bup = bupivacaine, Rop = ropivacaine, Mep = mepivacaine, Pri = prilocaine, Lev = levobupivacaine) and its concentration (%). The third part denotes the vasoconstrictor (nil = plain, E = epinephrine, L = levonordefrin, Fel = felypressin) and its concentration (one in hundred-thousandth, *e.g.*, E100 = epinephrine 1:100,000).
SUCRA, surface under the cumulative ranking.

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DISCUSSION

Articaine 4% with epinephrine achieved greater pulpal anesthesia in vital asymptomatic teeth when delivered as maxillary or mandibular infiltration. Articaine is more lipid-soluble and has a fast onset [61]. When used in maxillary infiltration, the odds of achieving pulpal anesthesia were higher for articaine 4% with 1:100,000 epinephrine than with lidocaine 2% with 1:100,000 epinephrine. This concurs with earlier pairwise meta-analysis in teeth with irreversible pulpitis [62]. A statistically significant difference, however, was not apparent when these were compared with various solutions of lidocaine when used in IANB. The present findings also supported a common claim that articaine 4% with epinephrine 1:100,000 was more efficacious than other agents in mandibular infiltration. Further studies are needed, however, to evaluate whether mandibular infiltration using articaine 4% with epinephrine 1:100,000 can replace conventional IANB.

For IANB, lidocaine 2% with epinephrine 1:80,000 was ranked best when 2 cartridges were used and second when one cartridge was used. Most of the comparisons to lidocaine 2% with epinephrine 1:80,000, however, have CIs that include the null value. When only one cartridge of lidocaine was used, the efficacy of the LA did not differ statistically with different concentrations of epinephrine. In addition, a mixed pattern was shown for the SUCRA ranking, favoring different concentrations of epinephrine in different situations. Theoretically, epinephrine contributes to the vasoconstriction effect, thereby retaining the LA in the localized region and slowing down the metabolism of the LA [61]. This may lengthen the duration of action. However, a dose-response relationship in anesthetic success is unlikely [47].

Recent NMA has suggested that mepivacaine is better than lidocaine in eliciting pulpal anesthesia when delivered as IANB to teeth with irreversible pulpitis [8,63]. We could not conclude whether this is also true in vital asymptomatic teeth because the interventions in the present NMA are categorized by the type of anesthetic as well as its concentration of vasoconstrictor. The division into finer categories reduces the sample size in each group and therefore leads to imprecision. Nevertheless, finer categorization allows for comparisons of different formulations: *e.g.*, mepivacaine 2% with epinephrine ranked lower than lidocaine 2% with epinephrine 1:80,000 but higher than lidocaine 2% with epinephrine 1:100,000 and 1:50,000. Prilocaine and mepivacaine are agents with milder vasodilatory effects. Hence, several formulations without vasoconstrictor were available commercially. Nevertheless, the anesthetic success for these agents was generally poorer than the same agents with a vasoconstrictor.

Ropivacaine is a newer long-acting LA and is unavailable in dental cartridges [30]. Despite this, it is included in this NMA because NMA plays a crucial role in providing comparative evidence for new drugs before approval [64]. Ropivacaine was found to be less efficacious than most commercially available dental anesthetics.

Conflicting findings were found for the effect of doubling the volume of several LA. In irreversible pulpitis, increasing the volume of LA to more than one cartridge does not improve the success of IANB [8]. The additional volume may appear beneficial when profound anesthesia after the second injection is observed. This is, however, most likely due to the longer onset time of the first injection [65].

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In short, articaine remains a good choice for buccal infiltrations. Lidocaine 2% with epinephrine 1:80,000 ranked best for IANB, but wide CIs including null values were observed for most comparisons involving lidocaine 2% with epinephrine 1:80,000. The findings for IANB should be interpreted with caution, as inconsistency was detected in the side-splitting model. The main concern about using articaine is paresthesia [66].

Several limitations were noted in this review. While all of the studies included defined pulpal anesthesia as having no response upon maximal electrical stimulus, some authors further defined the onset and duration of no response. Ideally, a standardized measure should be used. The studies at the Ohio State University used the most comprehensive and consistent definition. For maxillary infiltration, anesthetic success was defined as the percentage of patients who showed no response to an EPT (2 consecutive 80 readings) within 10 minutes of the initial injection [22,24,27,33]. Anesthetic success for IANB was defined as the percentage of patients who showed no response to an EPT (2 consecutive 80 readings) within 15 minutes of injection and continuously sustained the 80 reading for 60 minutes [50,51,52,53,59]. In addition, criteria for slow onset and non-continuous pulpal anesthesia were listed in several studies [34,47,51,58,60]. Therefore, outcome measurement using the binary variable of success and failure is an oversimplification of the actual pharmacodynamics. Ultimately, the choice of LA is also dependent on the type of procedure being carried out, the length of time required for anesthesia, and the pharmacodynamics of each medication [67].

Confounding factors, such as route of administration, were noted before the commencement of the review. Hence, categorization based on the route of administration was planned. This reduces the heterogeneity among studies but results in a smaller number of studies in each category, yielding reduced statistical power for hypothesis testing and a larger variance of estimation. Further, some comparisons were informed only by the direct evidence of a single trial. Similarly, caution is warranted in the interpretation of the funnel plot and Egger's regression because there were only a few studies in each network.

In addition, the type of tooth tested varied among studies. This is a major concern for IANB, as explained in the central core theory. The fasciculi supplying molars are located at the periphery of the nerve and are exposed to a higher concentration of LA, while the fasciculi supplying the anterior teeth are located in the core of the nerve and are exposed to a lower anesthetic concentration [1].

Our assessment indicated that the quality of evidence was negatively affected by inconsistency and imprecision. The implications for future research are twofold. First, it suggests the need for additional large RCTs. Second, it emphasizes the importance of scientific rigor and standardized outcome measurements. To that end, we support using the standardized protocol developed by the Ohio State University and trial registration for RCTs testing LA in the future.

CONCLUSIONS

Articaine 4% with epinephrine is superior when maxillary or mandibular infiltration is required in vital asymptomatic teeth. Generally, LA without a vasoconstrictor has a lower success rate in achieving pulpal anesthesia. Doubling the volume of LA may not always be beneficial.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
PRISMA NMA checklist of items to include when reporting a systematic review involving a network meta-analysis

Click here to view

Supplementary Table 2
Search strategies

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Supplementary Table 3
Reasons of exclusion

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Supplementary Table 4
Confidence in the effect estimates of various local anesthetics based on the GRADE approach obtained from the CINeMA web application

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Supplementary Figure 1
Summary of risk of bias of included studies.

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Supplementary Figure 2
Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

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Supplementary Figure 3
Forest plots for (A) maxillary buccal infiltration, (B) mandibular buccal infiltration, and (C) inferior alveolar nerve block.

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Supplementary Figure 4
Begg's funnel plots for (A) maxillary buccal infiltration, (B) mandibular buccal infiltration, and (C) inferior alveolar nerve block.

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Supplementary Figure 5

Egger's regression for (A) maxillary buccal infiltration, (B) mandibular buccal infiltration, and (C) inferior alveolar nerve block.

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Supplementary Figure 6

Risk of bias bar charts for (A) maxillary buccal infiltration, (B) mandibular buccal infiltration, and (C) inferior alveolar nerve block. Each bar represents a relative treatment effect estimated from the networks. The width between white lines represents the percentage contribution of each study. The colours of each segment indicates the risk of bias for each study, which are low (green), moderate (yellow) and high (red) risk of bias.

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