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Efficacy and safety of mepivacaine compared with lidocaine in local anaesthesia in dentistry: a meta-analysis of randomised controlled trials

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The objective of the study was to assess the efficacy and safety of mepivacaine compared with lidocaine used in local anaesthesia in dentistry. Medline, Cochrane Central Register of Controlled Trials, EMBASE, Chinese BioMedical Literature Database, China National Knowledge Infrastructure and WHO International Clinical Trials Registry Platform were searched electronically. Relevant journals and references of studies included were hand-searched for randomised controlled trials comparing mepivacaine with lidocaine in terms of efficacy and safety. Twenty-eight studies were included, of which 15 had low risk of bias and 13 had moderate risk of bias. In comparison with 2% lidocaine with 1:100,000 adrenaline, 3% mepivacaine showed a lower success rate ($P = 0.05$), a shorter onset time of pulpal anaesthesia ($P = 0.0005$), inferior pain control during injection phase and superior inhibition of heart rate increase ($P < 0.0001$). In contrast, 2% mepivacaine with 1:100,000 adrenaline gave a higher success rate ($P < 0.00001$), a similar onset time of pulpal anaesthesia ($P = 0.34$) and superior pain control during injection phase ($P < 0.0001$); 2% mepivacaine with 1:20,000 levonordefrin had the same success rate ($P = 0.69$) and similar onset time of pulpal anaesthesia ($P = 0.90$). In addition, 3% mepivacaine had shorter onset time ($P = 0.004$), same level of success rate ($P = 0.28$) and similar pain control during injection and postinjection compared with 2% lidocaine with 1:50,000 adrenaline. Given the efficacy and safety of the two solutions, 2% mepivacaine with vasoconstrictors is better than 2% lidocaine with vasoconstrictors in dental treatment. Meanwhile, 3% plain mepivacaine is better for patients with cardiac diseases.

Key words: *Mepivacaine, lidocaine, local anaesthesia, meta-analysis, dentistry*

INTRODUCTION

Pain occurs throughout dental treatment, so good management of pain and anxiety is a key issue that can win a patient's trust[1]. An epidemiological study revealed that more than 50% of Americans avoid dental treatments because of fear of pain, and a similar figure was reported among Brazilians[2,3]. About 14% of 4- to 11-year-old Dutch children are dentally anxious, and the strongest fear is associated with pain[4]. Local anaesthesia is a principal way of preventing pain and discomfort in dental treatment[5].

Mepivacaine was first introduced into dentistry in 1960 as a 2% solution containing synthetic vasopressor levonordefrin, and in 1961 as a 3% solution without any vasoconstrictor. Lidocaine which was introduced first in 1943 has high efficacy, low allergenicity and minimal toxicity proven through clinical use and research; it shows higher anaesthetic efficacy only when combined with vasoconstrictors[6]. Mepivacaine has the same anaesthetic potency as lidocaine[7], but also has milder vasodilating ability, which leads to a longer duration of anaesthesia without a vasoconstrictor[8]. Mepivacaine is the third most widely used solution in dentistry only after articaine and lidocaine in some parts of the world[9]. In dentistry, mepivacaine is always available as a 3% solution without any vasoconstrictors or as a 2% solution with vasoconstrictors such as 1:20,000 levonordefrin and 1:100,000 adrenaline; lidocaine is always available as a 2% solution with 1:100,000 or 1:50,000 adrenaline[10].

Although several trials have been conducted to compare mepivacaine with lidocaine in dental treatment, their conclusions are somewhat controversial. Therefore, it is necessary to combine the results to obtain more precise evidence on the efficacy and safety of mepivacaine in comparison with lidocaine.

METHODS

A protocol that specified the method of the review was established in advance. Study selection, risk of bias assessment, and data extraction were conducted in duplicate by two trained reviewers. Disagreement between them was resolved through discussion, and the unresolved issues were brought to a third reviewer for consensus.

Inclusion criteria

Those trials that met the following criteria would be included:

- Randomised controlled or quasi-randomised designs which explore the efficacy and safety of mepivacaine solutions, including 3% mepivacaine, 2% mepivacaine with 1:20,000 levonordefrin and 2% mepivacaine with 1:100,000 adrenaline compared with lidocaine solutions, including 2% lidocaine with 1:100,000 adrenaline or 1:50,000 adrenaline in local anaesthesia of dentistry
- The outcome variables would include at least one of the following: success rate of anaesthesia (SRA), onset time of pulpal anaesthesia (OTP), pain ratings at injection phase (PTI), pain ratings at postinjection phase (PTP) and adverse events (AE).

Exclusion criteria

The following trials would be excluded:

- Review articles, cohort studies and other kinds of studies
- Trials involving participants who were hypersensitive to mepivacaine or lidocaine, or were pregnant, lactating, unreliable and unable to return for follow-up
- Trials involving participants who had a history of significant medical conditions, or who took any medication that may affect anaesthetic assessment
- Repetitive publications (only the best-described one was included).

Search strategy and study inclusion

The Sichuan University Electronic Databases including Medline (1946 to July 2013), Cochrane Central Register of Controlled Trials (CENTRAL, July 2013), EMBASE (via OVID, 1984 to July 2013) were searched without language limitation. The Chinese BioMedical Literature Database (1978 to July 2013) and China National Knowledge Infrastructure (1994 to July 2013) were searched for the related Chinese literatures which were not indexed in the above databases. Chinese and English journals related to local anaesthesia collected by the Medical Library of the University were handsearched. The references of the studies included were also retrieved. The World Health Organisation (WHO) International Clinical Trials Registry Platform was searched to trace ongoing clinical trials. Some experts in this field were communicated with by letter.

The searching strategies included MeSH terms such as 'mepivacaine', 'lidocaine', 'Anaesthesia, Local' and free text words. The Cochrane Highly Sensitive Search Strategies were combined to identify randomised trials.

Risk of bias assessment

Risk of bias assessment was performed using Cochrane Collaboration's tool, 2011, on the following seven domains: (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 and (7) other bias[11]. A trial would be considered as 'low risk' of bias if all the seven domains were judged as 'low risk', 'moderate risk' if any of the seven items was judged as 'unclear risk' or 'high risk' if any item was judged as 'high risk'.

The meta-analysis results were further assessed by GRADE which is short for Grading of Recommendations Assessment, Development and Evaluation on GRADEprofiler which is a software used to grade the quality of the evidence in the systematic reviews, and were scored as high, moderate, low, or very low[12].

Data extraction

A customised data extraction form was developed, including the following items: study designs, method of randomisation, concealment and blinding, demographic data, usage of the drugs, anaesthesia techniques, losses to follow-up and the reasons and the final outcomes.

Data analysis

REVIEW MANAGER 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was chosen for data analysis. The pooled results were expressed as relative risks (RRs) and its 95% confidence intervals (95% CIs) for dichotomous data or as mean difference (MD) along with its 95% CI for continuous data. The statistical significance of hypothesis test was set at $\alpha = 0.05$ (two-tailed z-tests). Heteroge-

neity was explored and if it was significant, causes of heterogeneity were analysed. A random-effects model instead of a fixed-effect model was be used and subgroup analysis conducted. Sensitivity analysis was used to test the stability of the results. Any data unable to be pooled was just described. Publication bias was detected by using funnel plots if there were about 10 studies[13,14]. For crossover or split-mouth trials, the carry-over/carry-across effect was assessed[15]. If carry-over/carry-across effect was considered a problem, the analysis was based on the first period; if not, we attempted to approximate a paired analysis following the handbook. If no crossover or split-mouth designs exist, the first period and second period were mixed and pooled with parallel groups expressed as odds ratio (OR) and 95% CI[15].

RESULTS

Results of the search and study inclusion

One hundred and seventy citations were obtained through the extensive searching. Screening of the titles and abstracts yielded 34 eligible studies and their full texts were retrieved. In total, 28 studies were included – 15 in English[5,16–29] and 13 in Chinese[30–42] (*Figure 1*).

Characteristics of the studies included

Of the 28 studies included, 16 were parallel designs[16–24,28,29] and 12 were crossover designs[5,25–27,30–42]. The washout periods of crossover designs were 1–3 weeks. The success of anaesthesia was defined in 10 studies[5,16–24]as equal or over 80 readings obtained with electronic pulpal tester (EPT) after injection, or as no pain or mild pain evaluated by visual analogue scale (VAS) or operators in other studies[25,26,30–42]. The pain ratings at injection and postinjection phases were evaluated by pain grades of four-point scale as no, mild, moderate and severe in seven studies[16,19,20,23,28,38,39] using (VAS)[20,28,38,39] or rating scales 0–3[16,19,23]. The other characteristics are presented in *Table 1*.

Risk of bias of studies included

Among the studies included, 15 had low risk of bias[5,16–24,27–31] and the other 13 had moderate risk of bias[25,26,32–42] (*Table 2*).

Efficacy and safety of mepivacaine compared with lidocaine

The parallel and crossover studies were mixed for meta-analyses because none of the 12 crossover studies reported the data of the first and second periods separately and none of them was suitable for a paired analysis[14].

Success rate

3% mepivacaine versus 2% lidocaine with 1:100,000 adrenaline

Ten studies compared 3% mepivacaine and 2% lidocaine with 1:100,000 adrenaline[5,16,17,19–21,23–26]. The results showed that 3% mepivacaine was significantly inferior to 2% lidocaine with 1:100,000 adrenaline (OR 0.71, 95% CI 0.51–1.00, $P = 0.05$) (*Figure 2a*). When anaesthetic techniques were considered, the OR was 0.94 (95% CI 0.14–6.29, $P = 0.95$) for

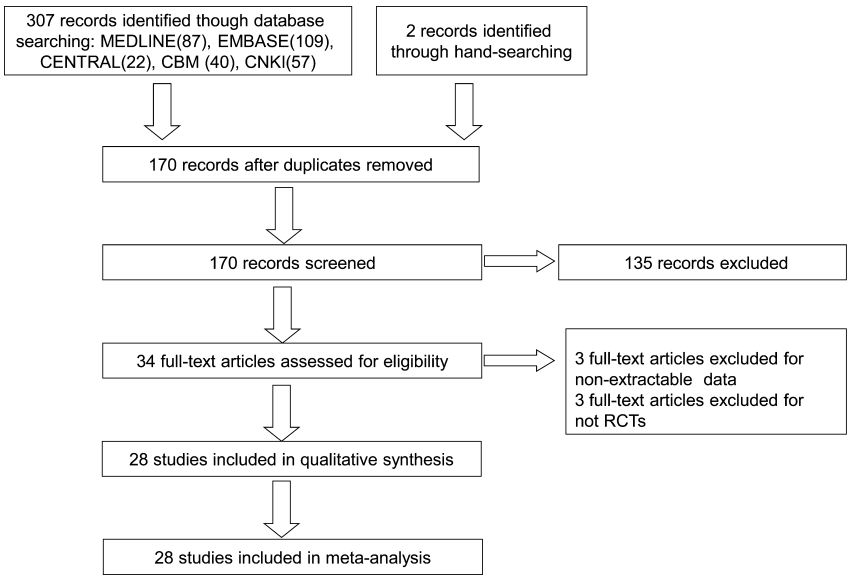


Figure 1. Flow diagram of the study inclusion. RCTs, randomised controlled trials.

Table 1 Characteristics of studies included

Study ID	Study design	Country	Sex (male/female)	Age	Methods (comparison)	Anaesthesia technique	Dosage (experiment/control)	Recording time	Outcome
Abdulwahab[5]	Crossover	USA	6/12	18–65	3% Mepivacaine with 2% lidocaine + 1:100,000 adrenaline in mandibular first molars	Infiltration	0.9 ml	Every minute for the first 20 minutes after injection using EPT	SRA
Schleder[16]	Crossover	USA	40/35	20–31	3% Mepivacaine with 2% lidocaine + 1:100,000 adrenaline in mandibular first premolar	Periodontal ligament injection	1.82 ml	2,4,10,30,45 minutes using EPT	SRA, PTI, AE
Mason[17]	Crossover	USA	31/29	19–43	3% Mepivacaine with 2% lidocaine + 1:100,000 adrenaline/2% lidocaine + 1:50,000 adrenaline in maxillary lateral incisor and first molars	Infiltration	1.8 ml	3-min cycles for 60 minutes at 1 minutes after injection using EPT	SRA, OTP
Lawary[18]	Crossover	USA	30/30	21–31	2% Mepivacaine + 1:20,000 levonordefrin with 2% lidocaine + 1:100,000 adrenaline in maxillary teeth	Infiltration	1.8 ml	2-minute cycles for 60 minutes at 1 minute after injection using EPT	SRA
Berberich[19]	Crossover	USA	34/6	23–33	3% mepivacaine with 2% lidocaine + 1:100,000 adrenaline/2% lidocaine + 1:50,000 adrenaline in maxillary teeth	Intraoral, infraorbital nerve block	Unclear	4-minute cycles for 60 min at 1–4 min after injection using EPT	SRA, PTI, PTP, OTP
Forloine[20]	Crossover	USA	27/23	18–57	3% mepivacaine with 2% lidocaine + 1:100,000 adrenaline in maxillary teeth	Maxillary block	3.6 ml	4-minute cycles for 60 minutes at 1–4 minutes after injection using EPT	SRA, PTI, PTP, AE
McLean[21]	Crossover	USA	24/6	24–43	3% Mepivacaine with 2% lidocaine + 1:100,000 adrenaline in mandibular teeth	IANB	1.8 ml	3-minute cycles for 50 minutes at 1–3 minutes after injection using EPT	SRA, OTP
Hinkley[22]	Crossover	USA	19/11	23–42	2% Mepivacaine + 1:20,000 levonordefrin with 2% lidocaine + 1:100,000 adrenaline in mandibular teeth	IANB	1.8 ml	3-minute cycles for 50 minutes at 1–3 minutes after injection using EPT	SRA, OTP
Replogle[23]	Crossover	USA	25/17	18–39	3% Mepivacaine with 2% lidocaine + 1:100,000 adrenaline in mandibular molars	IO	1.8 ml	2-minute cycles for 60 minutes at 1–2 minutes after injection using EPT	SRA, PTI, PTP
Burns[24]	Cross-over	USA	20/20	19–47	3% Mepivacaine with 2% lidocaine + 1:100,000 adrenaline in maxillary central incisors, lateral incisors and canines using computer-assisted injection system	P-ASA	1.4 ml	4-minute cycles for 72 minutes at 1–4 minutes after injection using EPT	SRA
Bradley[25]	Parallel	Australia	131/128	5–14	3% Mepivacaine with 2% lidocaine + 1:100,000 adrenaline in maxillary and mandibular teeth	Infiltration and IANB	1.8 ml & 0.8–3.6 ml	Unclear	SRA
Cohen[26]	Parallel	USA	Unclear	Unclear	3% Mepivacaine with 2% lidocaine + 1:100,000 adrenaline in mandibular teeth diagnosed with irreversible pulpitis	IANB	1.8 ml	1 minute after injection using DDM	SRA
Kramp[27]	Parallel	USA	Totally 150	Unclear	2% Mepivacaine + 1:20,000 levonordefrin with 2% lidocaine + 1:100,000 adrenaline in maxillary and mandibular teeth	Infiltration and IANB	0.3–0.6 ml for infiltration and 1.8 ml for IANB	Unclear	PTI

Table 1 continued

Study ID	Study design	Country	Sex (male/female)	Age	Methods (comparison)	Anaesthesia technique	Dosage (experiment/control)	Recording time	Outcome
Nusstein[28]	Crossover	USA	20/20	18–65	3% Mepivacaine with 2% lidocaine + 1:100,000 adrenaline in maxillary and mandibular teeth using the Wand Plus system	P-ASA	1.4 ml	4-minute cycles for 72 minutes after injection using the EPT	PTI, PTP, AE
Replogle[29]	Crossover	USA	25/17	18–39	3% Mepivacaine with 2% lidocaine + 1:100,000 adrenaline	IO	1.8 ml	2-minute cycles for 30 minutes after injection using EPT	AE
Shi[30]	Parallel	China	55/72	20–65	2% Mepivacaine + 1:100,000 adrenaline with 2% lidocaine + 1:100,000 adrenaline in maxillary and mandibular teeth	Infiltration	1.8 ml	1, 3, 5 minutes after injection using the EPT	SRA, AE, OTP
Chen[31]	Parallel	China	11/7	18–60	Compared 2% mepivacaine + 1:100,000 adrenaline with 2% lidocaine + 1:100,000 adrenaline in maxillary teeth diagnosed with pulpitis or deep caries	Infiltration	1.8 ml	At 1, 3, 5 minutes after injection using the EPT	SRA, AE, OTP
Wu[32]	Parallel	China	17/43	12–70	2% Mepivacaine + 1:100,000 adrenaline with 2% lidocaine + 1:100,000 adrenaline in maxillary and mandibular teeth diagnosed with irreversible pulpitis	Infiltration and IANB	1.8 ml/5.0 ml	Unclear	SRA
Li[33]	Parallel	China	38/32	60–72	2% Mepivacaine + 1:100,000 adrenaline with 2% lidocaine + 1:100,000 adrenaline in maxillary and mandibular teeth diagnosed with irreversible pulpitis	Infiltration	1.8 ml/5.0 ml	7 minutes after injection	SRA, AE
Dong[34]	Parallel	China	73/134	Mean 37.4	2% Mepivacaine + 1:100,000 adrenaline with 2% lidocaine + 1:100,000 adrenaline in maxillary molars diagnosed with acute pulpitis, chronic pulpitis.	Infiltration and IANB	1.8 ml/5.0 ml	Unclear	SRA
Liu[35]	Parallel	China	39/41	23–62	2% Mepivacaine + 1:100,000 adrenaline with 2% lidocaine + 1:100,000 adrenaline in maxillary and mandibular teeth that need pulp therapy or extraction	Infiltration and IANB	1.7 ml/5.0 ml	Unclear	SRA
Xing[36]	Parallel	China	Unclear	Unclear	2% Mepivacaine + 1:100,000 adrenaline with 2% lidocaine + 1:100,000 adrenaline in maxillary and mandibular teeth diagnosed with irreversible pulpitis or periodontal disease	Infiltration and IANB	0.9–1.8 ml/5.0 ml	At 1, 2, 5 minutes after injection	SRA
Luo[37]	Parallel	China	372/0	20–40	2% Mepivacaine + 1:100,000 adrenaline with 2% lidocaine + 1:100,000 adrenaline in maxillary molars that need extraction	Infiltration and maxillary block	1.8 ml/5.0 ml	Unclear	SRA
Ge[38]	Parallel	China	Totally 57	Unclear	2% Mepivacaine + 1:100,000 adrenaline with 2% lidocaine + 1:100,000 adrenaline in mandibular molars diagnosed with chronic pulpitis	Infiltration and IANB	1.8 ml/5.0 ml	Unclear	SRA, PTI

Table 1 continued

Study ID	Study design	Country	Sex (male/female)	Age	Methods (comparison)	Anaesthesia technique	Dosage (experiment/control)	Recording time	Outcome
Xuan[39]	Parallel	China	51/45	20–60	2% Mepivacaine + 1:100,000 adrenaline with 2% lidocaine + 1:100,000 adrenaline in maxillary and mandibular teeth that need prosthodontic therapy	Infiltration and IANB	1.8 ml/4.0 ml	Unclear	SRA, PTI
He[40]	Parallel	China	151/241	12–70	2% Mepivacaine + 1:100,000 adrenaline with 2% lidocaine + 1:100,000 adrenaline in maxillary and mandibular teeth diagnosed with irreversible pulpitis	Infiltration and IANB	1.8 ml/5.0 ml	Unclear	SRA, AE
Zhou[41]	Parallel	China	43/57	23–76	2% mepivacaine + 1:100,000 adrenaline with 2% lidocaine + 1:100,000 adrenaline in mandibular teeth that need pulp therapy or extraction	IANB	1.5 ml/5.0 ml	Unclear	SRA
Jin[42]	Parallel	China	Totally 360	6–78	2% mepivacaine + 1:100,000 adrenaline with 2% lidocaine + 1:100,000 adrenaline in maxillary and mandibular teeth diagnosed with pulpitis or tooth trauma	Infiltration and IANB	1.8 ml/5.0 ml	Unclear	SRA

IANB, inferior alveolar nerve block; SRA, success rate of anaesthesia; OTP, onset time of pulpal aesthesia; PTI, pain ratings for injection phase; PTP, pain ratings for postinjection phase; AE, adverse events; IO, intraosseous injection; P-ASA, palatalanterior superior alveolar injection.

Table 2 Risk of bias assessment of studies included

Study ID	1	2	3	4	5	6	7	Risk of bias of studies
Abdulwahab[5]	L	L	L	L	L	L	L	L
Schleder[16]	L	L	L	L	L	L	L	L
Mason[17]	L	L	L	L	L	L	L	L
Lawary[18]	L	L	L	L	L	L	L	L
Berberich[19]	L	L	L	L	L	L	L	L
Forloine[20]	L	L	L	L	L	L	L	L
McLean[21]	L	L	L	L	L	L	L	L
Hinkley[22]	L	L	L	L	L	L	L	L
Replogle[23]	L	L	L	L	L	L	L	L
Burns[24]	L	L	L	L	L	L	L	L
Bradley[25]	U	U	L	U	L	L	U	M
Cohen[26]	U	U	U	U	L	L	U	M
Kramp[27]	L	L	L	L	L	L	L	L
Nusstein[28]	L	L	L	L	L	L	L	L
Replogle[29]	L	L	L	L	L	L	L	L
Shi[30]	L	L	L	L	L	L	L	L
Chen[31]	L	L	L	L	L	L	L	L
Wu[32]	L	U	U	U	U	U	U	M
Li[33]	U	U	U	U	U	U	U	M
Dong[34]	L	U	U	U	U	L	U	M
Liu[35]	U	U	U	U	U	U	U	M
Xing[36]	U	U	U	U	U	U	U	M
Luo[37]	U	U	U	U	U	U	U	M
Ge[38]	U	U	U	U	U	U	U	M
Xuan[39]	U	U	U	U	U	U	U	M
He[40]	U	U	U	U	U	U	U	M
Zhou[41]	L	U	U	U	U	U	U	M
Jin[42]	U	U	U	U	U	U	U	M

L, means low risk of bias; U, means unknown risk of bias; M, means moderate risk of bias.

infiltrations[5,17] and 0.78 (95% CI 0.57–1.05, $P = 0.10$) for nerve blocks[19–21,24,26]. When jaws were considered, the OR was 0.83 (95% CI 0.57–1.20; $P = 0.31$) for maxillary regions[17,19,20,24,25] and 0.69 (95% CI 0.39–1.21, $P = 0.20$) for mandibular regions[5,16,21,23,25,26].

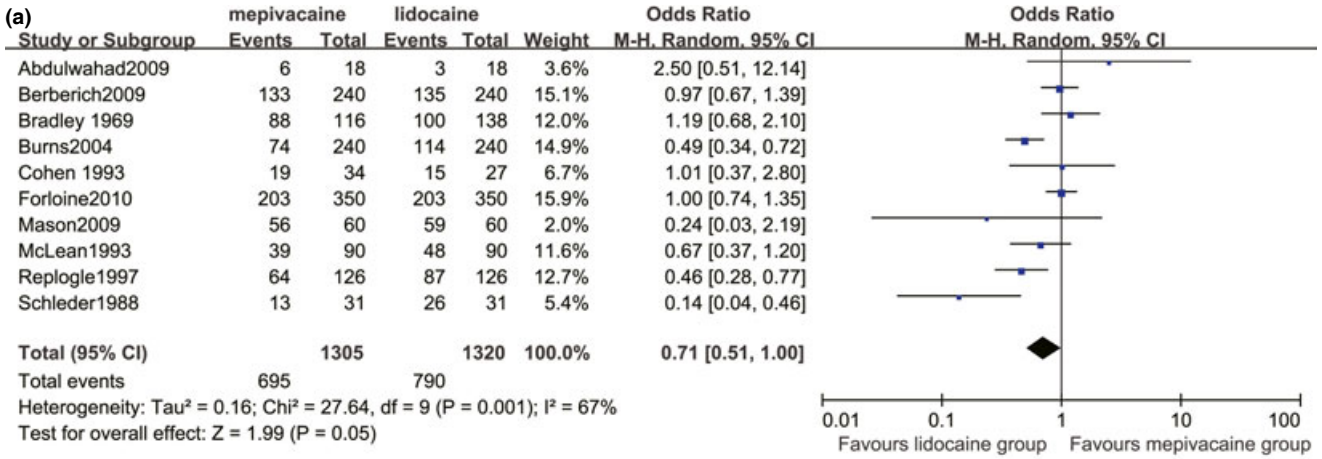
The funnel plot was symmetrical, indicating a low possibility of publication bias for this meta-analysis (*Figure 3a*). The strength of evidence of this outcome was moderate.

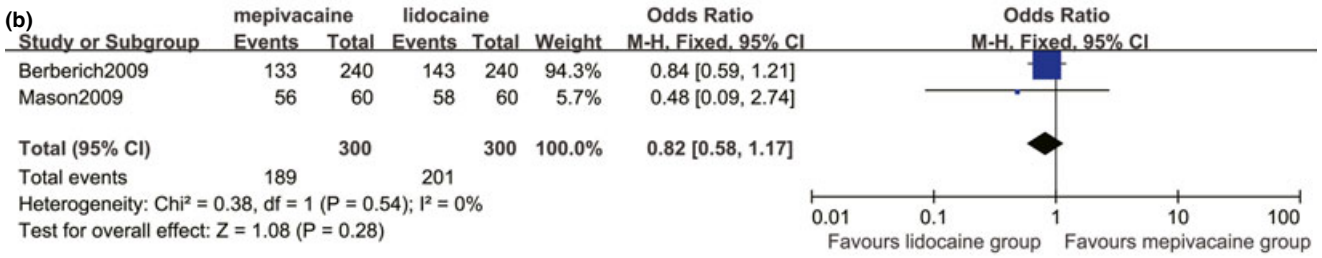
3% mepivacaine versus 2% lidocaine with 1:50,000 adrenaline

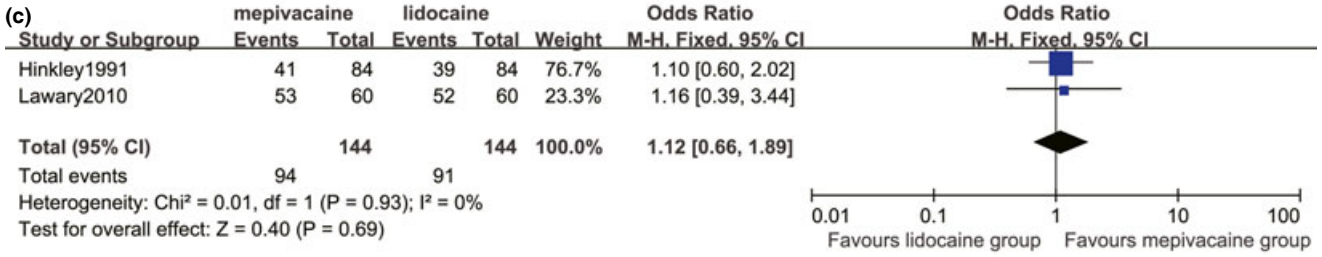
Two studies compared 3% mepivacaine and 2% lidocaine with 1:50,000 adrenaline[17,19]. The outcome showed no significant difference between the two groups (OR 0.82, 95% CI 0.58–1.17, $P = 0.28$) (*Figure 2b*).

2% mepivacaine with 1:20,000 levonordefrin versus 2% lidocaine with 1:100,000 adrenaline

Two studies compared 2% mepivacaine with 1:20,000 levonordefrin and 2% lidocaine with 1:100,000 adrenaline[18,22]. There was no statistical significance between the two groups (OR 1.12, 95% CI 0.66–1.89, $P = 0.69$) (*Figure 2c*).







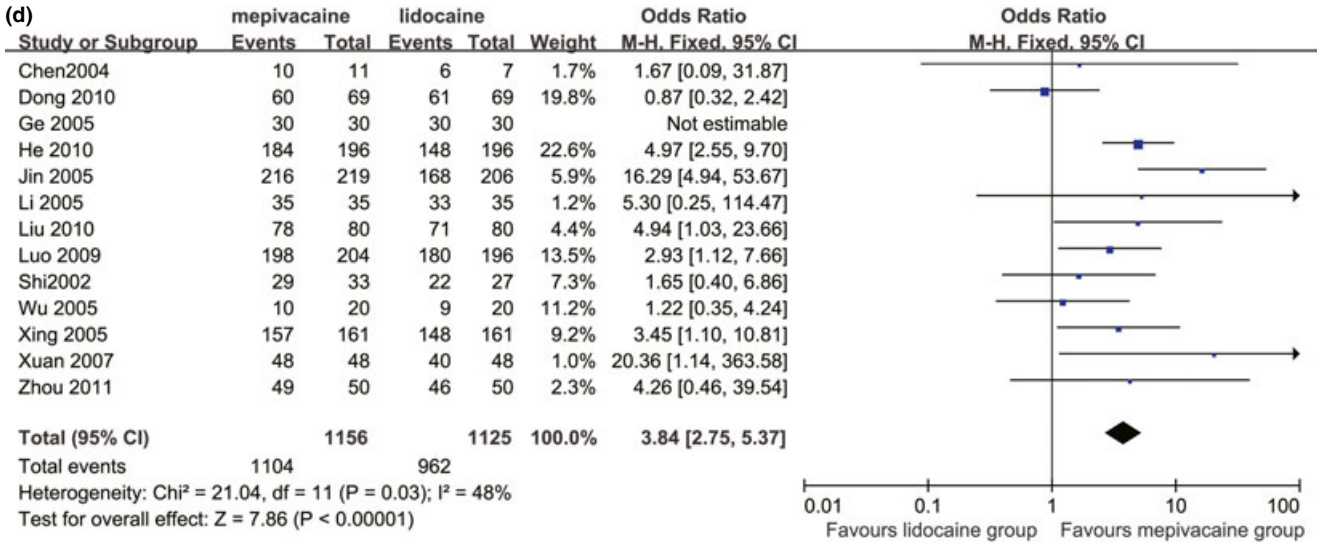


Figure 2. Meta-analyses of success rate of local anaesthesia in comparing 3% mepivacaine with 2% lidocaine with 1:100,000 adrenaline (a), 3% mepivacaine with 2% lidocaine with 1:50,000 adrenaline (b), 2% mepivacaine with 1:20,000 levonordefrin with 2% lidocaine with 1:100,000 adrenaline (c) and 2% mepivacaine with 1:100,000 adrenaline with 2% lidocaine with 1:100,000 adrenaline (d).

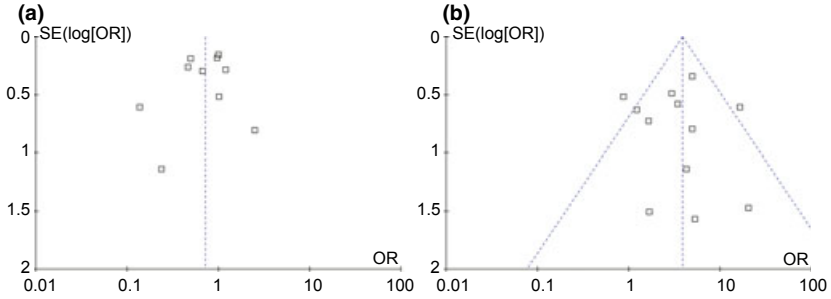


Figure 3. Funnel plots for comparing 3% mepivacaine with 2% lidocaine with 1:100,000 adrenaline (a) and 2% mepivacaine with 1:100,000 adrenaline with 2% lidocaine with 1:100,000 adrenaline (b) in success rate of local anaesthesia.

Table 3 Meta-analysis outcomes in onset time of pulpal anaesthesia

Comparison	Number of studies included	Mean difference (95% CI)	*P*	Heterogeneity (I^2) %
3% Plain mepivacaine *versus* 2% lidocaine with 1:100,000 adrenaline	3[17,19,21]	−1.13 (−1.77–0.49)	0.0005	0
3% Plain mepivacaine *versus* 2% lidocaine with 1:50,000 adrenaline	2[17,19]	−0.83 (−1.40–0.26)	0.004	0
2% Mepivacaine with 1:20,000 levonordefrin *versus* 2% lidocaine with 1:100,000 adrenaline	1[22]	0.20 (−2.87–3.27)	0.90	_
2% Mepivacaine with 1:100,000 adrenaline *versus* 2% lidocaine with 1:100,000 adrenaline	2[30,31]	−0.19 (−0.57–0.20)	0.34	0

2% mepivacaine with 1:100,000 adrenaline versus 2% lidocaine with 1:100,000 adrenaline

Thirteen studies compared 2% mepivacaine with 1:100,000 adrenaline and 2% lidocaine with 1:100,000 adrenaline[30–42]. Mepivacaine was significantly superior to lidocaine when both were combined with 1:100,000 adrenaline (OR 3.84, 95% CI 2.75–5.37, $P < 0.00001$) (*Figure 2d*). When anaesthetic techniques were considered, OR was 2.07 (95% CI 0.65–6.58, $P = 0.22$) for infiltrations[21,30,33] and 4.26 (95% CI 0.46–39.54, $P = 0.20$) for block[41]. When jaws were considered, OR was 1.76 (95% CI 0.93–3.34, $P = 0.08$) for maxillary regions[31,33,34,37] and was 0.77 (95% CI 0.38–1.56, $P = 0.47$) for mandibular regions[33,38,41].

The funnel plot

The funnel plot is also symmetrical and thus bias of publication was unlikely for the meta-analysis (*Figure 3b*). The strength of this outcome was also moderate.

Onset time of pulpal anaesthesia

In comparison with 2% lidocaine plus 1:100,000 adrenaline, 3% plain mepivacaine had a shorter onset time of pulpal anaesthesia while 2% mepivacaine with 1:20,000 levonordefrin or with 1:100,000 adrenaline both had similar time of onset. In comparison with 2% lidocaine with 1:50,000 adrenaline, 3% plain mepivacaine had shorter onset time of pulpal anaesthesia (*Table 3*).

Pain ratings for injection phase

Five studies used this variable and divided the injection phase into three sections (i.e. needle insertion, needle placement and solution deposition)[16,19,20,23,28]. The combined results showed that 3% mepivacaine was inferior to 2% lidocaine with 1:100,000 adrenaline in terms of the percentage of patients who felt no pain or mild pain during needle insertion and solution deposition, but there was no intergroup difference during needle placement (*Table 4*). In addition, there was no significant difference between 3% mepivacaine and 2% lidocaine with 1:50,000 adrenaline in terms of the percentage of patients who felt no pain or mild pain during solution deposition[19]. Another two studies[38,39] comparing 2% mepivacaine with 1:100,000 adrenaline with 2% lidocaine with 1:100,000 adrenaline were pooled and the outcome showed that the results in the mepivacaine group were superior to the lidocaine group in terms of the percentage of patients who felt no pain or mild pain during injection phase (*Figure 4*).

Pain ratings for postinjection phase

Pain on postinjection phase was recorded in day 0, day 1, day 2 and day 3 after injection in four studies[19,20,23,28]. The pooled results of these studies showed no intergroup difference in the percentage of

Table 4 Meta-analysis outcomes comparing 3% mepivacaine with 2% lidocaine with 1:100,000 adrenaline in pain ratings of injection phase and postinjection phase

	Time	Number of studies included	Odds ratio (95% CI)	*P*	Heterogeneity (I^2) %
Injection phase	Needle insertion	4[16,20,23,28]	0.50 (0.26 0.96)	0.04	0
	Needle placement	2[20,28]	1.20 (0.67 2.15)	0.55	0
	Solution deposition	5[16,19,20,23,28]	0.50 (0.29 0.87)	0.01	0
Postinjection phase	Day 0	4[19,20,23,28]	1.00 (0.53 1.89)	1.00	0
	Day 1	4[19,20,23,28]	0.78 (0.39 1.56)	0.48	0
	Day 2	4[19,20,23,28]	1.86 (0.61 5.73)	0.28	0
	Day 3	4[19,20,23,28]	1.00 (0.22 4.48)	1.00	0

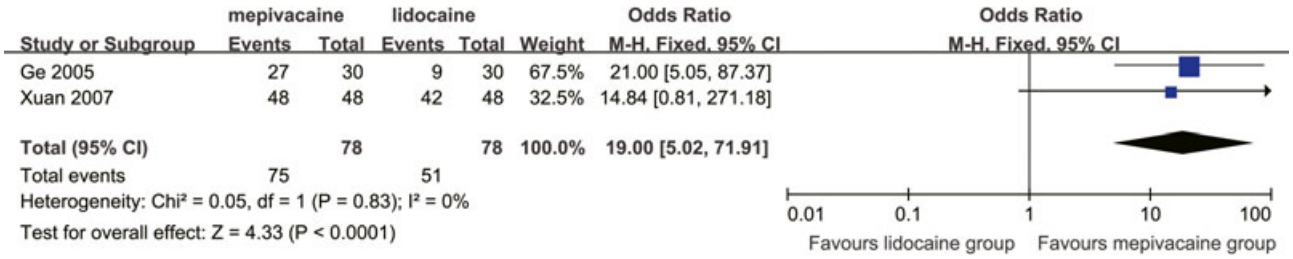


Figure 4. Meta-analysis comparing 2% mepivacaine with 1:100,000 adrenaline with 2% lidocaine with 1:100,000 adrenaline in pain ratings during injection phase.

Table 5 Percentage, number and odds ratio of subjects who experienced adverse events

Adverse events	Studies included	Percentage and number of events in mepivacaine group %	Percentage and number of events in lidocaine group %	Odds ratio (95% CI)	*P*
Diplopia	Forloine[20]	16 (8/50)	12 (6/50)	1.40 (0.45 4.37)	0.57
Increase in heart rate	Forloine[20]	0 (0/50)	30 (15/50)	0.01 (0.00 0.09)	<0.0001
	Replogle[29]	0 (0/42)	67 (28/42)		
Mandibular lip numbness	Forloine[20]	26 (13/50)	32 (16/50)	0.75 (0.31 1.78)	0.51
Incisive papilla swelling or soreness	Nusstein[28]	20 (8/40)	28 (11/40)	0.66 (0.23 1.86)	0.43
Temporary anaesthesia/ paraesthesia of incisive papilla	Nusstein[28]	12 (5/40)	18 (7/40)	0.67 (0.19 2.33)	0.53
Thermal pulpal sensitivity	Nusstein[28]	2 (1/40)	2 (1/40)	1.00 (0.06 16.56)	1.00
Ulcerations	Nusstein[28]	5 (2/40)	0 (0/40)	5.26 (0.24 113.11)	0.29
Hyperaemia and soreness of injection site	Chen[31]	9 (1/11)	0 (0/7)	2.14 (0.08 60.17)	0.65
Dizzy and syncope	Shi[30]	2 (1/66)	2 (1/61)	0.48 (0.09 2.66)	0.59
	Li[33]	0 (0/35)	3 (1/35)		
	He[40]	0 (0/196)	1 (1/196)		
Herpes-like lesions	Schleder[16]	3 (1/31)	10 (3/31)	0.31 (0.03 3.17)	0.32
Haematoma of interproximal papillae	Schleder[16]	3 (1/31)	0 (0/31)	3.10 (0.12 79.04)	0.49

patients who felt no pain or mild pain on day 0 to day 3 in those receiving 3% mepivacaine or 2% lidocaine with 1:100,000 adrenaline (*Table 4*). In addition, there was no statistically significant difference in the percentage of patients who felt no pain or mild pain during the postinjection phase with either 3% mepivacaine or 2% lidocaine with 1:50,000 adrenaline[19].

Adverse events

Eight studies[16,20,28–31,33,40] reported adverse events, which were evenly distributed in both groups except for a significant increase in heart rate in those receiving 2% lidocaine with 1:100,000 adrenaline compared with those receiving 3% mepivacaine (OR 0.01, 95% CI, 0.00–0.09, $P < 0.0001$)[20,29] (*Table 5*).

DISCUSSION

When the results involving 1:100,000 adrenaline were combined in both groups, the success rate of mepivacaine increased dramatically and exceeded that of lidocaine (3.84 *vs.* 1). The presence of adrenaline in local anaesthetic solutions was confirmed to be beneficial with regard to duration, depth of anaesthesia, reduction of bleeding and systemic toxicity of the anesthetics[43]. Mepivacaine has milder vasodilating ability than lidocaine, which might explain why with

the same vasoconstrictor, mepivacaine has dramatically superior effect to that of lidocaine. This advantage leads to broad application of mepivacaine as a local anaesthetic in dentistry in China, while it has seldom been used in Western dentistry up to now.

In addition, the milder vasodilating ability of mepivacaine does facilitate the usage of higher concentrations of plain mepivacaine. Although the success rate of 3% plain mepivacaine was nearly 30% lower in comparison with lidocaine with 1:100,000 adrenaline, the depth of local anaesthesia could satisfy the demand for pain control in those with cardiovascular diseases. Although the meta-analysis shows that 3% mepivacaine had a similar success rate to that of 2% lidocaine with 1:50,000 adrenaline, this was mainly because of data insufficiency.

Mepivacaine with 1:20,000 levonordefrin had the same level of success rate in comparison with 2% lidocaine with 1:100,000 adrenaline. In Western clinical practice, levonordefrin is commonly used as a vasoconstrictor with mepivacaine in a concentration of 1:20,000 in local anaesthesia[10,18]. It is believed from molecular structures and clinical observations that adrenaline at 1/100,000 had similar effect on local anaesthesia as did levonordefrin at 1/20,000[10]. Nevertheless, a conclusion derived from this review was that mepivacaine with levonordefrin and lidocaine with adrenaline showed the same level of effect. This might be ascribed to a chance effect because only two studies were included. In terms of safety, Guilielmo *et al*[44] demonstrated no significant difference in increasing heart rate between 2% mepivacaine with 1:20,000 levonordefrin and 2% lidocaine with 1:100,000 adrenaline after intra-osseous injection of 1.8 ml in both groups. That is, 1:20,000 levonordefrin may have similar efficacy and safety as 1:100,000 adrenaline.

What should be mentioned is the difference in the methods of assessment of the success of anaesthesia used in the trials. Because the anaesthesia of soft tissues is not a stable predictor for profound pulpal anaesthesia and painless operations[45], we focused on trials in which the presence or absence of pulpal anaesthesia was evaluated by using EPT, VAS and patients' feelings and expressions. In terms of teeth with vital pulp, anaesthetic success is often defined as the percentage of participants who achieve two consecutive EPT readings of 80 within 15 minutes after administration of anaesthetic and sustain this lack of responsiveness continuously for 60 minutes. However, as for symptomatic teeth, a lack of response to EPT may not guarantee that a tooth is experiencing profound pulpal anaesthesia, mainly because of the complex mechanism of neuroinflammatory and neuropulpal interactions, which still need to be clarified[46]. Therefore, VAS and the patients' intraoperative feelings and expressions are used to evaluate the success of an anaesthetic.

The 3% mepivacaine had shorter onset time in pulpal anaesthesia than 2% lidocaine with epinephrine, which was in agreement with other reports[47]. The time of onset of anaesthesia is directly related to the rate of epineural diffusion correlated with the percentage of drug in the base form, which is proportional to the pK_a of that agent. The 3% plain mepivacaine had pK_a of 7.6, while lidocaine with epinephrine had pK_a of 7.9[10].

Evidence in this review shows that in the injection phase and postinjection phase, the 3% mepivacaine groups suffered more pain than the 2% lidocaine with 1:100,000 epinephrine group during needle insertion and solution deposition, but there was no significant difference during needle placement or from day 0 to day 3 postinjection. During the injection, pain could result from mechanical trauma of needle during insertion, or from the sudden distension of the tissues caused by a rapid insertion of the solution and the chemical stimulation of the first few drops of the local anesthetics[48,49]. The lipid solubility of lidocaine is four times as high as mepivacaine[10]. That is, lidocaine, with slightly higher lipid solubility, is regarded as an effective topical anaesthetic and used widely in various operations in dentistry[10]. Therefore, lidocaine can be infiltrated to regional mucosa more easily than mepivacaine[50]. During the injection phase, the first few drops were penetrated more rapidly when lidocaine was used, and the regional tissue was anesthetised more rapidly in the lidocaine group while the sudden stress of regional space was lower. This might explain why the lidocaine group experienced less pain than the mepivacaine group during injection. In clinical practice some improvements could be made to relieve pain during the injection of mepivacaine, such as use of a smaller syringe needle, slower injection velocity, use of binding cartridges upon injection of mepivacaine or the use of the topical anaesthesia before injection. Furthermore, computer-controlled local anaesthetic delivery (C-CLAD), which has a slow and stable rate of delivering agents, might be used for ensuring less pain and more comfort in local anaesthesia in dentistry[10]. However, the 2% mepivacaine with 1:100,000 epinephrine groups suffered from less pain than the 2% lidocaine with 1:100,000 epinephrine groups during the injection phase, probably because of the presence of adrenaline in the mepivacaine, which is proved to have the functions of pain control and increasing depth of anaesthesia[10,43].

In terms of safety, results from two studies[20,29] indicated that 3% mepivacaine was superior to 2% lidocaine with 1:100,000 epinephrine in inhibiting an increase in heart rate. This can be explained by the fact that adrenaline as a vasoconstrictor in lidocaine can stimulate the cardiac and central nervous systems

and may increase heart rate especially when it is used excessively, which may be related to the β-activity of adrenaline[10]. The anaesthetic techniques used in the two studies were maxillary nerve block and intraosseous injection, respectively. In addition, 3% mepivacaine was also superior to 2% lidocaine with 1:100,000 epinephrine when the two anaesthetic techniques were considered separately. The maximum adrenaline dose used in local anaesthesia of dentistry is recommended to be 0.2 mg per appointment for a normal healthy patient (American Society of Anesthesiologists Physical Status classification system 1: ASA 1), or 0.04 mg per appointment for patients with clinically significant cardiovascular disease (ASA 3 or 4).[10] With increased levels of adrenaline in the blood, cardiac dysrhythmias become more common. There was no evidence showing any significant difference in other adverse events between the two solutions. In conclusion, 3% plain mepivacaine was safer than 2% lidocaine with 1:100,000 epinephrine.

Although the studies included had low to moderate risk of bias, there was still some bias in the reviewing process. The number of studies included in some meta-analyses was small, which might lead to bias of outcome. Parallel trials and crossover trials were mixed in meta-analysis because of imperfect data reporting in the studies, which might cause deviation in the outcomes. The diversity of the studies, small sample size and unexplained statistical heterogeneity limit the overall conclusions, which call for future studies to obtain more stable outcomes.

We hope that more higher-quality studies comparing 2% mepivacaine and epinephrine with 2% lidocaine and epinephrine, 2% mepivacaine and levonordefrin with 2% lidocaine and 1:100,000 epinephrine), and 3% mepivacaine with 2% lidocaine and 1:50,000 epinephrine can be conducted to further evaluate the efficacy and pain control during injection phase and postinjection phase between mepivacaine and lidocaine. In addition more randomised controlled trials could be done to evaluate any adverse events.

In summary the clinical evidence tells us that:

- 2% mepivacaine with 1:100,000 adrenaline is superior in increasing the success rate of local anaesthesia and pain control during the injection phase and has similar onset time of pulpal anaesthesia and safety in comparison with 2% lidocaine with 1:100,000 epinephrine
- 2% mepivacaine with 1:20,000 levonordefrin has the same level of success and a similar onset time of pulpal anaesthesia compared with 2% lidocaine with 1:100,000 epinephrine
- 3% mepivacaine has shorter onset time of pulpal anaesthesia and greater safety, but is inferior in increasing success rate and pain control during injection, in comparison with 2% lidocaine with 1:100,000 epinephrine, especially for patients with cardiovascular diseases
- 3% mepivacaine has the same level of success, similar pain control during injection and postinjection phases and shorter onset time of pulpal anaesthesia, compared with 2% lidocaine with 1:50,000 epinephrine.

In conclusion, given the efficacy and safety of the two solutions, 2% mepivacaine with vasoconstrictors is better than 2% lidocaine with epinephrine in dental treatment, and 3% plain mepivacaine is better for patients with cardiac diseases. However, more studies are still needed to make a definitive conclusion.

Conflicts of interest

None declared.

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