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REVIEW

Efficacy of local anaesthetic solutions on the success of inferior alveolar nerve block in patients with irreversible pulpitis: a systematic review and network meta-analysis of randomized clinical trials

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Abstract

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The management of pain during root canal treatment is important. The aim of this systematic review and network meta-analysis was to identify the anaesthetic solution that would provide the best pulpal anaesthesia for inferior alveolar nerve blocks (IANB) treating mandibular teeth with irreversible pulpitis. Two electronic databases (PubMed and Scopus) were searched to identify studies up to October 2018. Randomized clinical trials comparing at least two anaesthetic solutions (lidocaine (lignocaine), articaine, bupivacaine, prilocaine or mepivacaine) used for IANB for treatment of irreversible pulpitis were included. The revised Cochrane risk of bias tool for randomized trials was used to assess the quality of the included studies. Pairwise meta-analysis, network meta-analysis using a random-effects model, and SUCRA ranking were performed. The network meta-analysis estimated the probability of each treatment performing best. The quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations approach. In total, 11 studies (n = 750) were included in the meta-analysis. The network meta-analysis revealed that only mepivacaine significantly increased the success rate of IANB compared to lidocaine (RR, 1.42 [95% CI 1.04–1.95]). However, no significant differences in the success rate of IANB were observed between mepivacaine and other anaesthetic agents (articaine and bupivacaine). Of all anaesthetic agents, mepivacaine (SUCRA = 0.81) ranked first in increasing the success rate of IANB, followed by prilocaine (SUCRA = 0.62), articaine (SUCRA = 0.54), bupivacaine (SUCRA = 0.41) and lidocaine (SUCRA = 0.13). The overall quality of evidence was very low to moderate. In conclusion, based on the evidence from the randomized clinical trials included in this review, mepivacaine with epinephrine demonstrated the highest probability of providing effective pulpal anaesthesia using IANB for teeth with irreversible pulpitis compared to prilocaine, articaine, bupivacaine and lidocaine. Further, high-quality clinical trials are needed to support the conclusion of this review.

Keywords: inferior alveolar nerve block, irreversible pulpitis, network meta-analysis, systematic review.

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Introduction

Patients may perceive root canal treatment as painful if inadequate pulpal anaesthesia was achieved, especially during access and instrumentation. This can lead to an increase in fear and anxiety, potentiate medical problems, prolong treatment time and may cause the operator to be seen as inefficient (Wong & Lytle 1991). Root canal treatment of teeth with irreversible pulpitis and symptomatic apical periodontitis was demonstrated to be more painful than treating teeth with pulpal necrosis or asymptomatic apical periodontitis. Greater pain levels were reported for teeth in the mandible compared to the maxilla (Segura-Egea *et al.* 2009). The inferior alveolar nerve block (IANB) has been shown to be the most preferred technique to anaesthetize mandibular teeth suffering from irreversible pulpitis. Its failure was estimated to range between 43% and 83% (Reisman *et al.* 1997, Nusstein *et al.* 1998, Kennedy *et al.* 2003, Lindemann *et al.* 2008, Fowler *et al.* 2016, Aggarwal *et al.* 2017). Thus, the pain-free treatment of mandibular posterior teeth diagnosed with irreversible pulpitis is often challenging for the clinician (Parirokh & Abbott 2014, Abbott & Parirokh 2018).

Supplemental techniques, such as buccal infiltration (Aggarwal *et al.* 2009), periodontal ligament injection (Kim 1986), intraosseous anaesthesia (Nusstein *et al.* 2003), as well as oral premedication (Nagendrababu *et al.* 2018, Pulikkotil *et al.* 2018), have all been suggested to increase the success of anaesthesia for the treatment of mandibular teeth. However, it would be beneficial if the IANB itself, as the primary anaesthesia, could be more effective, for example by identifying the anaesthetic solution with the highest probability of success. Various anaesthetic solutions have been suggested to achieve successful pulpal anaesthesia by means of the IANB for the treatment of irreversible pulpitis, including lidocaine, articaine, bupivacaine and mepivacaine (Kung *et al.* 2015, Aggarwal *et al.* 2017, Vieira *et al.* 2018). Several meta-analyses were conducted to identify the best suitable solution; however, contradictory conclusions were reported. Kung *et al.* (2015) and Brandt *et al.* (2011) revealed no difference in the anaesthetic success rate for the IANB between lidocaine and articaine, particularly in cases of irreversible pulpitis, whereas Su *et al.* (2016) demonstrated that articaine had a greater anaesthetic effect compared to lidocaine. Su *et al.* (2014), however, demonstrated that mepivacaine had a greater anaesthetic effect compared to lidocaine, given the same amount of vasoconstrictor. Recently, Vieira *et al.* (2018) concluded that mepivacaine and lidocaine had similar anaesthetic efficacy for IANB in teeth with irreversible pulpitis. Moreover, three RCTs reported no difference in anaesthetic efficacy between lidocaine and bupivacaine (Sampaio *et al.* 2012, Parirokh *et al.* 2015, Aggarwal *et al.* 2017). Hence, the dental practitioner may be unclear regarding the selection of the best anaesthetic solution when performing root canal treatment on mandibular teeth with irreversible pulpitis.

To address this knowledge gap, a systematic review with a network meta-analysis approach was undertaken. Whilst a meta-analysis compares two interventions, a network meta-analysis allows for the comparison of more than two interventions, including direct and indirect comparisons of individual interventions and a ranking according to their probability of having beneficial effects (Kiefer *et al.* 2015, Tonin *et al.* 2017). Hence, a network meta-analysis has been considered as the highest level of evidence in decision-making (Roever & Biondi-Zoccai 2016) and for treatment guidelines (Leucht *et al.* 2016). The aim of the current systematic review was to identify the best anaesthetic solution for IANB for mandibular teeth with irreversible pulpitis.

Methods

Protocol and registration

This review followed the PRISMA extension statement for reporting systematic reviews incorporating network meta-analyses of healthcare interventions (Hutton *et al.* 2015). The protocol of the review study design was registered in the PROSPERO database (CRD42018103351).

Research question

The research question was formulated based on participants, interventions, comparisons, outcomes and study design (PICOS) format: 'Which is the most effective local anaesthetic solution for IANBs for treating teeth with irreversible pulpitis based on data from randomized clinical trials?'

Search strategy and inclusion criteria

A literature search was performed in two databases, PubMed and Scopus, using the search terms;

((((((((Anesthetic) OR Anaesthetic) OR lidocaine) OR lignocaine) OR articaine) OR bupivacaine) OR mepivacaine) OR prilocaine)) AND ((irreversible pulpitis) OR Inferior alveolar nerve block) until October 2018. The search was supplemented from the reference lists of included studies, published reviews and textbooks. Following the initial search, two independent reviewers (VN, SP) screened the title/abstract for eligible studies followed by full-text reading and any disagreement was resolved by a third reviewer (AS). The authors were contacted for missing information in the published studies. Randomized clinical trials with the following characteristics were included: adult patients undergoing root canal treatment in mandibular teeth with irreversible pulpitis, studies with at least two anaesthetic solutions (lidocaine (lignocaine), articaine, bupivacaine, prilocaine or mepivacaine) and anaesthetic solutions used for IANB for mandibular teeth with irreversible pulpitis. Studies that assessed the anaesthetic effect of IANB supplemented by infiltration anaesthesia and studies that used premedication to increase the success rate of IANB were excluded.

Outcome measure

Success of anaesthesia was assessed during access opening and pulpectomy in mandibular teeth diagnosed with irreversible pulpitis.

Data extraction

A data extraction form was created for entering the following information: name of the first author, year, country, age, gender, type of tooth treated, local anaesthetic solutions used, number of participants and anaesthetic success rate. Two independent reviewers (VN and SP) collected and entered the information and any disagreements in data extraction were resolved by a third reviewer (AS).

Quality assessment

The Cochrane risk of bias tool for randomized trials (RoB 2.0) (Higgins *et al.* 2016) was used to assess the quality of included studies. Two independent reviewers (VN and SP) assessed the quality of the studies. Any disagreements were resolved by the third reviewer (AS). Quality was categorized into ‘low’, ‘some concerns’, or ‘high risk of bias’ based on defined criteria on selected domains of randomization, deviations from intended interventions, missing outcome data, outcome measurement and selective reporting of results. Overall quality was assessed based on the scores in individual domains. When all the key domains had low risk of bias (good quality), the overall quality was of low risk of bias. When at least one domain was of some concerns, the overall quality was some concerns. A study was of high risk of bias in overall quality when at least one key domain of bias was associated with a high risk.

Statistical analysis

Risk ratio (RR) and 95% confidence intervals were used as summary statistics. Direct evidence was estimated by pairwise meta-analysis using a random-effects model. Heterogeneity was assessed by I^2 statistics; an I^2 statistic greater than 50% was interpreted as evidence of significant heterogeneity. Direct and indirect evidence was combined by performing a random-effects network meta-analysis (frequentist approach) using either a consistency or an inconsistency model (Veroniki *et al.* 2013). To find any disagreements between the direct and indirect evidence, a network inconsistency assumption was evaluated by using a design-by-treatment interaction approach (global inconsistency) (Bucher *et al.* 1997). Ranking of the various anaesthetic solutions was based on their efficacy by using SUCRA (surface area under the cumulative ranking) curves, with higher SUCRA scores nearing one (range 0–1) demonstrating higher efficacy (Salanti *et al.* 2011). Sensitivity analysis was performed by excluding high risk of bias studies. Additional analysis was performed with studies including molars only. Publication bias was assessed by plotting comparison-adjusted funnel plots. All analyses and plotting of charts were executed using Stata version 14.1 (StataCorp, College Station, TX, USA).

Rating the quality of evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) (GRADEpro GDT: GRADEpro Guideline Development Tool [Software], McMaster University, 2015 (developed by Evidence Prime, Inc.)) was used to objectively rate the quality of evidence obtained by the analysis, and it was adapted to the network meta-analysis. The quality of evidence was rated as ‘high’, ‘moderate’, ‘low’ and ‘very low’ (Puhan *et al.* 2014).

Results

Search results

The entire search process followed to identify the studies is shown in Fig. 1. The initial search identified 1259 studies from databases but 1246 studies were excluded after screening the title and/or abstract review. In total, 13 studies were selected for full-text assessment. After full-text assessment, two studies were excluded because supplemental buccal infiltration was administered with the IANB in any group (Ashraf *et al.* 2013, Monteiro *et al.* 2015). A total of 11 studies (Claffey *et al.* 2004, Tortamano *et al.* 2009, Cunha *et al.* 2011, Poorni *et al.* 2011, Sampaio *et al.* 2012, Ahmad *et al.* 2014, Sood *et al.* 2014, Parirokh *et al.* 2015, Allegretti *et al.* 2016, Visconti *et al.* 2016, Aggarwal *et al.* 2017) were included in the present systematic review and network meta-analysis.

Characteristics of the included studies

Detailed characteristics of the included studies are depicted in Table 1. The total number of participants in the included studies was $n = 750$. The age of the participants ranged between 18 and 57 years and included both sexes. Both mandibular molars and pre-molars had been included. Five anaesthetic solutions with vasoconstrictor were evaluated in this review. The four anaesthetic agents of lignocaine/lidocaine, articaine, bupivacaine and mepivacaine used in the selected studies contained epinephrine as the vasoconstrictor whilst prilocaine was added with felypressin as the vasoconstrictor.

Risk of bias assessment

The quality assessment of the included studies is shown in Table S1. Amongst the 11 studies included, only three studies (Claffey *et al.* 2004, Cunha *et al.* 2011, Ahmad *et al.* 2014) were 'High ROB' due to bias in measurement of the outcome, whereas other eight studies (Tortamano *et al.* 2009, Poorni *et al.* 2011, Sampaio *et al.* 2012, Sood *et al.* 2014, Parirokh *et al.* 2015, Allegretti *et al.* 2016, Visconti *et al.* 2016, Aggarwal *et al.* 2017) were assessed as 'Low ROB'.

Pairwise meta-analysis

The forest plots of pairwise meta-analyses are shown in Figure S1. The pairwise meta-analyses revealed that articaine (RR, 1.16 [95% CI 1.02, 1.32]) and mepivacaine (RR, 1.46 [95% CI 1.04, 2.07]) had significantly higher success rates in IANB anaesthesia of teeth with irreversible pulpitis compared to lidocaine. No significant difference was observed for bupivacaine and prilocaine when compared to lidocaine. Similarly, no significant difference was observed for mepivacaine, bupivacaine and prilocaine when compared to articaine.

Network meta-analysis

Figure 2 shows the network plot from trials evaluating five anaesthetic solutions (lignocaine/lidocaine, articaine, bupivacaine, prilocaine and mepivacaine). The results of the network meta-analysis and standard pairwise meta-analysis on success of IANB anaesthesia from all trials are shown in Fig. 3. The results of the network meta-analysis (estimated RR and SUCRA ranks) for anaesthetic solutions on IANB success rate including all trials are shown in Table S2. SUCRA ranking curves for the anaesthetic success rate of IANB are shown in Figure S2. The primary network meta-analysis of all trials (11 RCTs) demonstrated that the use of mepivacaine with epinephrine significantly ($P = 0.03$) increased the success of IANB for root canal treatment of teeth with irreversible pulpitis compared to lidocaine with epinephrine (RR, 1.42 [95% CI 1.04–1.95]; SUCRA = 0.81). No significant difference was observed in comparing other anaesthetic solutions (articaine vs. bupivacaine, articaine vs. mepivacaine, articaine vs. prilocaine, articaine vs. lidocaine, bupivacaine vs. mepivacaine, bupivacaine vs. lidocaine, bupivacaine vs. lidocaine, mepivacaine vs. prilocaine and prilocaine vs. lidocaine). Figure 4 shows the ranking plot for the success of IANB anaesthesia amongst the five anaesthetic solutions. The intervention of mepivacaine with epinephrine was ranked first, followed by prilocaine, articaine, bupivacaine and lidocaine. Subgroup analysis of studies including only molars (Figure S3a) demonstrated similar results to the primary analysis. A separate analysis for pre-molars could not be performed due to the limited number of studies. The results of sensitivity analysis performed by excluding high risk of bias trials (Figure S3b) revealed no significant difference amongst the various anaesthetic solutions.

Network consistency and small study effects

The assessment of the overall inconsistency for the success rate of IANB with various anaesthetic solutions in a primary network analysis and sensitivity analysis are shown in Table S3. A global inconsistency test by

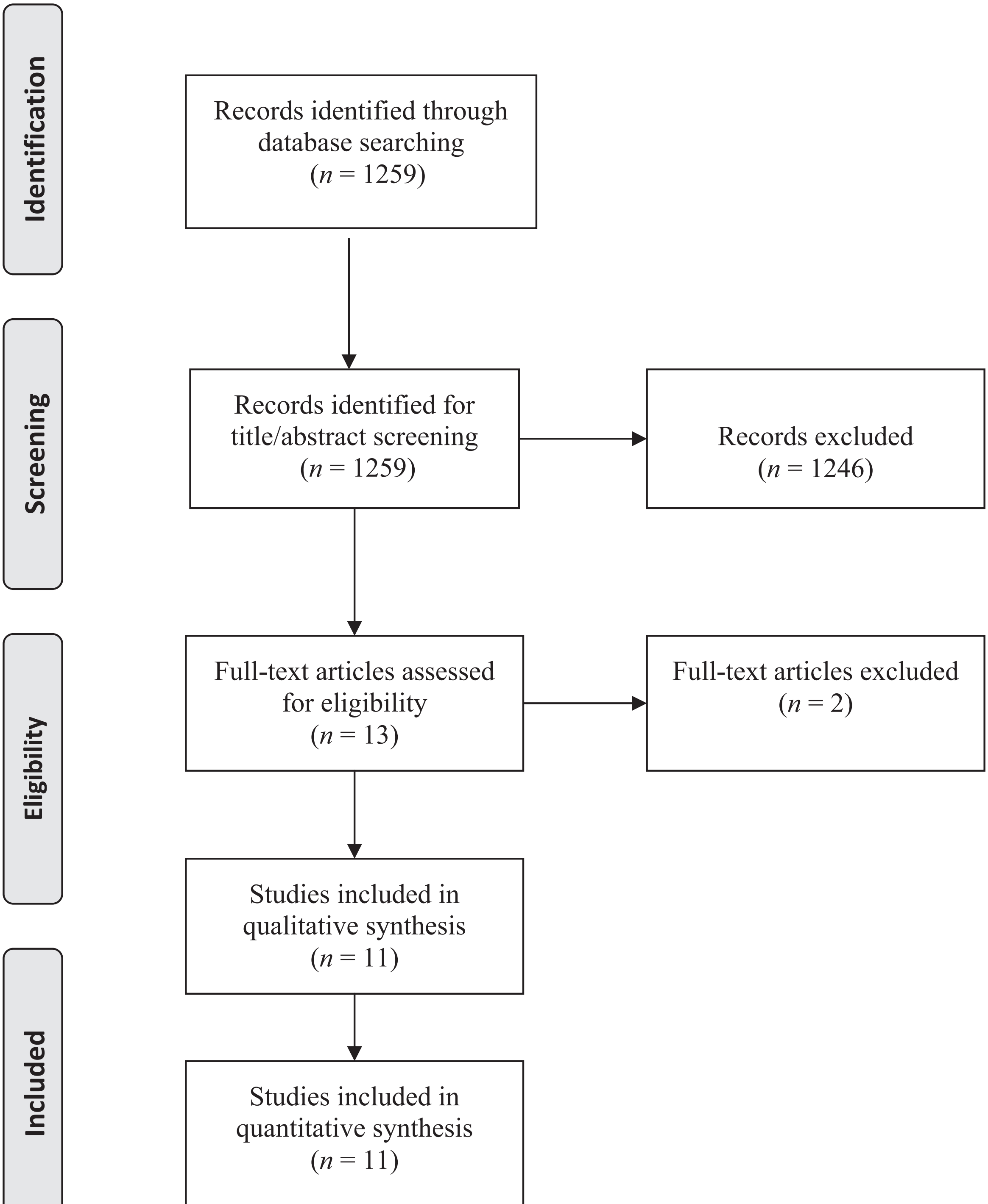

Figure 1 PRISMA search process.

fitting design-by-treatment in the inconsistency model showed no inconstancy for the outcome in both primary and sensitivity analyses (Table S3). No evidence of small study effects was observed for network meta-analysis from the comparison-adjusted funnel plots (Figure S4).

Table 1 Characteristics of the included studies

S no	Author (year)	Age (mean ± SD)	Gender (*n*) (M, F)	Local anaesthetic agents	Tooth type	Total number of samples (*n*)	Success (*n*)
1	Aggarwal *et al.* (2017)	37 ± 8.3	22, 9	1.8 mL of 2% lidocaine with 1 : 200 000 epinephrine	1st, 2nd mandibular molar	31	7
		34 ± 6.5	16, 14	1.8 mL of 4% articaine with 1 : 100 000 epinephrine		30	10
		38 ± 4.25	19, 11	1.8 mL of 0.5% bupivacaine with 1 : 2 000 000 epinephrine		30	5
2	Visconti *et al.* (2016)	26 ± 10	3, 18	1.8 or 3.6 mL of 2% mepivacaine with 1 : 100 000 epinephrine	1st, 2nd and 3rd mandibular molar	21	13
		28 ± 11	6, 16	1.8 or 3.6 mL of 2% lidocaine with 1 : 100 000 epinephrine		21	9
3	Allegretti *et al.* (2016)	NR	12, 10	3.6 mL of 4% articaine with 1 : 100 000 epinephrine	Mandibular molar	22	14
			9, 13	3.6 mL of 2% lidocaine with 1 : 100 000 epinephrine		22	12
			6, 16	3.6 mL 2% mepivacaine with 1 : 100 000 epinephrine		22	16
4	Parirokh *et al.* (2015)	26.7 ± 7.2	15, 14	1.8 mL of 2% lidocaine with 1 : 80 000 epinephrine	Mandibular molar	30	7
		26.7 ± 8.6	9, 21	1.8 mL of 0.5% bupivacaine with 1 : 200 000 epinephrine		30	6
5	Ahmad *et al.* (2014)[a]	NR	NR	2% lidocaine with 1 : 200 000 epinephrine	Mandibular pre-molar and molar	15	6
				2% lidocaine with 1 : 80 000 epinephrine		15	9
				4% articaine with 1 : 100 000 epinephrine		15	13
6	Sood *et al.* (2014)	26.46	20, 30	1.8 mL of 4% articaine with 1 : 100 000 epinephrine	1st, 2nd, 3rd mandibular molar and 1st, 2nd pre-molar	50	44
		28.9	27, 33	1.8 mL of 2% lidocaine with 1 : 80 000 epinephrine.		50	41
7	Sampaio *et al.* (2012)	29.4	16, 19	3.6 mL of 0.5% bupivacaine with 1 : 200 000 epinephrine	1st, 2nd mandibular molar	35	28
		32.3		3.6 mL of 2% lidocaine with 1 : 100 000 epinephrine		35	22
8	Cunha *et al.* (2011)	NR	19, 41	3.6 mL of 4% articaine with 1 : 100 000 epinephrine	Mandibular molar	15	7
				3.6 mL of 2% lidocaine with 1 : 100 000 epinephrine		15	3
				3.6 mL of 3% prilocaine with 0.03 IU felypressin		15	7
				3.6 mL of 2% mepivacaine with 1 : 100 000 epinephrine		15	8
9	Poorni *et al.* (2011)	24.40 ± 4.19	28, 24	1.8 mL of 4% articaine with 1 : 100 000 adrenaline	Mandibular molar	52	39
		24.13 ± 4.21	32, 20	1.8 mL of 2% lidocaine with 1 : 100 000 adrenaline		52	36
10	Tortamano *et al.* (2009)	29.9	10, 10	3.6 mL of 4% articaine with 1 : 100 000 epinephrine	1st, 2nd and 3rd mandibular molar, 2nd pre-molar	20	13
		34.1	6, 14	3.6 mL of 2% lidocaine with 1 : 100 000 epinephrine		20	9
11	Claffey *et al.* (2004)	31 ± 8.3	13, 24	2.2 mL of 4% articaine with 1 : 100 000 epinephrine	1st, 2nd mandibular molar and 1st, 2nd pre-molar	37	9
		31 ± 8.0	12, 23	2.2 mL 2% lidocaine with 1 : 100 000 epinephrine		35	8

[a]Volume of anaesthetic solution not reported.

GRADE summary of evidence

Quality of evidence for effect estimates from primary network meta-analysis comparing anaesthetic solutions is shown in Table S4. Overall, the evidence was of moderate (mepivacaine vs. lidocaine, articaine vs. lidocaine, bupivacaine vs. articaine, mepivacaine vs. articaine and bupivacaine vs. lidocaine) to very low quality (prilocaine vs. lidocaine, articaine vs. prilocaine and mepivacaine vs. prilocaine).

Discussion

The pairwise meta-analysis conducted in this review revealed that the use of articaine increased the IANB success compared to lidocaine. The results of the present review were similar to the results by Su *et al.* (2016) but did not concur with that of the review by Kung *et al.* (2015). Both those studies evaluated the IANB in combination with other supplemental injection techniques such as maxillary buccal infiltration or the Gow-Gates block variation. From the results of the pairwise meta-analysis in this review, mepivacaine increased the success rate of IANB significantly compared to lidocaine; however, this was in disagreement with Vieira *et al.* (2018). A likely reason for this discrepancy between the two investigations may be the inclusion of the study by Cohen *et al.* (1993) in the review by Vieira *et al.* (2018), which was excluded in the present investigation due to differences in the study eligibility criteria. In Cohen *et al.* (1993), the anaesthetic effect with regard to pulpal anaesthesia was assessed by cold testing with dichlorodifluoromethane and not by a pain-free access

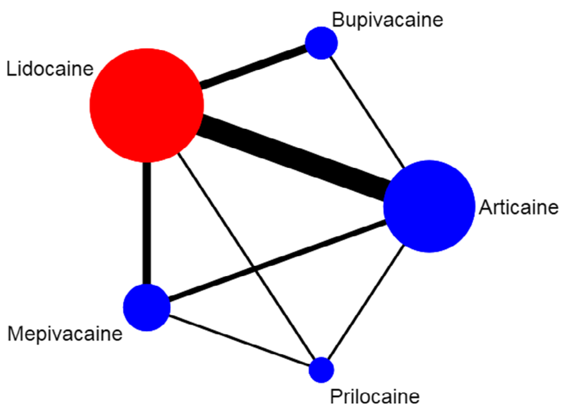

Figure 2 Network plot of five anaesthetic agents on the success rate of inferior alveolar nerve block. The size of the nodes corresponds to the number of trials. The width of the lines corresponds to the number of trials comparing the connected anaesthetic agents. Lidocaine (red colour node) is the most frequent comparator across the studies.

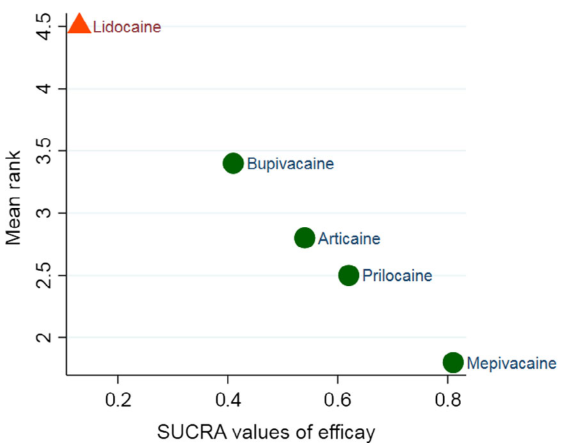

Figure 4 Ranking plots for network meta-analysis for five anaesthetic agents on the success rate of inferior alveolar nerve block.

Articaine	2.00 (0.78, 5.26)	0.88 (0.61, 1.25)	1.00 (0.47, 2.15)	**1.16 (1.02, 1.32)**
1.08 (0.71,1.63)	**Bupivacaine**	NA	NA	1.18 (0.89, 1.56)
0.85 (0.62,1.16)	0.79 (0.49,1.27)	**Mepivacaine**	1.13 (0.56, 2.33)	**1.46 (1.04, 2.07)**
0.91 (0.46,1.79)	0.85 (0.39,1.84)	1.08 (0.55,2.11)	**Prilocaine**	2.33 (0.74, 7.35)
1.21 (0.99,1.47)	1.12 (0.80,1.56)	**1.42 (1.04,1.95)**	1.32 (0.66,2.63)	**Lidocaine**

Figure 3 Pairwise (upper right portion) and network (lower left portion) meta-analytic results comparing the five anaesthetic agents for the success rate of inferior alveolar nerve block. Outcomes are expressed as RRs (95% confidence intervals). For the pairwise and network meta-analyses, a RR more than 1 indicates that the treatment specified in the column is more efficacious. Comparison between treatments should read from row to column. Blue-shaded results indicate statistical significance.

preparation or pulpectomy, which was the reason for exclusion in the present investigation.

From the results of the primary network meta-analysis of all trials (11 RCTs), mepivacaine with epinephrine significantly increased the success of IANB for root canal treatment of teeth with irreversible pulpitis compared to lidocaine with epinephrine ($P = 0.03$). SUCRA ranking showed that in both primary network meta-analysis (including all trials), sensitivity analysis (excluding high risk of bias trials) and subgroup analysis (including trails with only molars), mepivacaine ranked first. However, no difference was observed amongst articaine, bupivacaine and lidocaine. The level of evidence using GRADE methodology adapted for network meta-analysis showed very low-to-moderate quality for the comparison of the anaesthetic solutions.

Three studies (Claffey *et al.* 2004, Cunha *et al.* 2011, Ahmad *et al.* 2014) were rated as 'high ROB' due to serious bias in outcome measurement. Blinding of the examiner(s) is important to prevent bias in assessment of the outcome as knowledge of the intervention status can affect the recording of the outcome data. In three studies (Claffey *et al.* 2004, Cunha *et al.* 2011, Ahmad *et al.* 2014), allocation concealment was not performed. Randomization with allocation concealment in a study is important to prevent selection bias. Randomization creates opportunities for all eligible subjects to be part of the test or control group whilst allocation concealment of the sequencing prevents any bias by the operator or the participant. In all the 11 included studies, the administration of anaesthesia (intervention) and assessment of anaesthetic efficacy (outcome) were carried out in the same visit. Hence, there were no dropouts due to the type of study design and therefore no potential of bias.

The results of this network meta-analysis indicate that mepivacaine with epinephrine may be more suitable than the other anaesthetic solutions tested for achieving pulpal anaesthesia by IANB for the treatment of irreversible pulpitis. It performed better than, in descending order, articaine, bupivacaine and lidocaine. This validated information may be useful for the clinician. The practicing dentist may want to avoid supplemental techniques for certain patients, for example for those with anxiety of intraosseous or intraligamentary anaesthesia, or may want to increase the probability of successful pulpal anaesthesia by choosing a more effective anaesthetic solution. Whilst articaine also proved to be more effective than lidocaine or bupivacaine, it was shown, together with prilocaine, to be associated with significantly increased rates of paraesthesia (Haas & Lennon 1995, Gaffen & Haas 2009), and an increased risk of methemoglobinemia (Haas 2002). On the other hand, according to Su *et al.* (2014), mepivacaine has a reduced vasodilating ability compared to lidocaine, which might explain why having the same vasoconstrictor content, a superior effect compared to lidocaine can be observed. Mepivacaine may thus present a valuable alternative. It is already widely used in China (Su *et al.* 2014), yet remains one of the least common dental local anaesthetic solutions in the Western world (Gaffen & Haas 2009). Nevertheless, lidocaine will still not be outdated, as, together with prilocaine, it so far remains the only pregnancy category B anaesthetic, with all others considered category C (Haas 2002). The use of bupivacaine has been associated with risk of cardiac and central nervous system toxicity (Naguib *et al.* 1998). The use of local anaesthetic should be guided by proper case selection, anaesthetic technique and dose to minimize the risk of complications.

Strength

The included studies were conducted in various countries, including Brazil, Canada, India, Iran and the United States. The age of the included patients ranged from 18 to 57 years of both genders. Hence, the results of this systematic review should be applicable to a wide population range and applicable to the anaesthetic efficacy in mandibular teeth with irreversible pulpitis. The review included randomized clinical trials, which provide a higher level of evidence. Registration of the *a priori* protocol of the review in the PROSPERO database and reviewing by two independent examiners during the search and data extraction process was important to ensure the quality of the review. Sensitivity analysis was performed by excluding high ROB trials which confirmed the validity of the primary results.

Limitations

Prilocaine was included in the systematic review as it is an effective and widely used anaesthetic solution. However, results comparing prilocaine versus lidocaine, articaine versus prilocaine or mepivacaine versus prilocaine have to be reviewed with caution, as the sample size of the prilocaine group is very low

($n = 15$) in comparison with the other anaesthetic solutions, which may lead to skewed observations. From a critical perspective, this network meta-analysis could not evaluate the influence of the quantity of anaesthetic solutions (1.8, 2.2 mL or 3.6 mL) and vasoconstrictors, that both varied amongst the included studies. This was not done due to the limited number of studies and study subjects available. Another important confounding factor that could influence anaesthetic efficacy was the different degrees of preoperative pain status. Aggarwal *et al.* (2015) compared the influence of the degree of preoperative pain (mild, moderate and severe) on the anaesthetic success of IANB and revealed that there was a significant difference between the mild and severe preoperative pain groups and positive correlation between preoperative pain and intraoperative pain. Additional analysis based on preoperative pain status was not possible because of the limited number of studies.

Conclusion

The results of network meta-analysis including all trials revealed that mepivacaine with epinephrine performed better than lidocaine with epinephrine in achieving higher IANB success rate in teeth with irreversible pulpitis and also ranked higher amongst other anaesthetic solutions. However, the network meta-analysis including only low risk of bias studies revealed no difference amongst the four anaesthetic solutions. Future high-quality randomized clinical trials are needed to confirm the results of our review.

Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Risk of bias assessment for included studies

Table S2 Results of network meta-analysis: primary analysis including all the studies

Table S3 Results of network meta-analysis: primary analysis and Sensitivity analysis

Table S4 GRADE Summary of evidence

Figure S1 Forest plots of pairwise meta-analysis.

Figure S2 SUCRA ranking curves for primary analysis.

Figure S3 a) Network plot of four anaesthetic agents on the success rate of inferior alveolar nerve block including studies with only molars. b) Network plot of four anaesthetic agents on the success rate of inferior alveolar nerve block excluding high risk of bias studies.

Figure S4 Comparison-adjusted funnel plot from the network meta-analysis.