



Interventions for anesthetic success in symptomatic irreversible pulpitis: A network meta-analysis of randomized controlled trials

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Background: Local anesthetics alone or in combination with adjuncts, such as oral medications, have routinely been used for pain control during endodontic treatment. The best clinical choice amongst the vast numbers of agents and techniques available for pain control for irreversible pulpitis is unclear. This network meta-analysis combined the available evidence on agents and techniques for pulpal anesthesia in the maxilla and mandible, in order to identify the best amongst these approaches statistically, as a basis for future clinical trials.

Methods: Randomized trials in MEDLINE, DARE, and COCHRANE databases were screened based on inclusion criteria and data were extracted. Heterogeneity was assessed and odds ratios were used to estimate effects. Inconsistencies between direct and indirect pooled estimates were evaluated by H-statistics. The Grading of Recommendation, Assessment, Development, and Evaluation working group approach was used to assess evidence quality.

Results: Sixty-two studies (nine studies in the maxilla and 53 studies in the mandible) were included in the meta-analysis. Increased mandibular pulpal anesthesia success was observed on premedication with aceclofenac + paracetamol or supplemental 4% articaine buccal infiltration or ibuprofen+paracetamol premedication, all the above mentioned with 2% lignocaine inferior alveolar nerve block (IANB). No significant difference was noted for any of the agents investigated in terms of the success rate of maxillary pulpal anesthesia.

Conclusion: Direct and indirect comparisons indicated that some combinations of IANB with premedication and/or supplemental infiltration had a greater chance of producing successful mandibular pulpal anesthesia. No ideal technique for maxillary anesthesia emerged. Randomized clinical trials with increased sample size may be needed to provide more conclusive data. Our findings suggest that further high-quality studies are required in order to provide definitive direction to clinicians regarding the best agents and techniques to use for mandibular and maxillary anesthesia for irreversible pulpitis.

Keywords: Pain; Pulpitis; Root Canal Therapy.



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INTRODUCTION

Pain management is requisite for successful dental treatment. Local anesthetics alone or in combination with other agents are often used during endodontic treatment

of irreversible pulpitis [1,2]. Inflammatory mediators in pulpitis provoke pain responses and inflammation and successful anesthesia is achieved in less than 20% of cases under these circumstances [3]. Systematic reviews and meta-analysis have previously compared articaine and lignocaine [4,5], the effect of pre-operative analgesics

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and those of inferior alveolar nerve block (IANB) [6,7], IANB with different agents and techniques [8], and the effect of supplemental infiltration [9]. The diversity of these reviews does not identify any single best agent and technique for the maxilla and mandible, and anesthetic failure has been a recurring concern. Consequently, clinicians have little evidence by which to direct care, and may resort to trial and error. Such inadequate pain control can lead to avoidance of dental care and fear of dental treatment.

Unfortunately, results from different meta-analysis fail to point to the best amongst various tested agents. Lignocaine, which has been commercially available for more than 60 years and is commonly used, has been reported to be more successful when used with supplemental articaine infiltration [10,11]. However, articaine infiltration alone also produced successful anesthesia in individual studies [11-13]. Oral administration of non-steroidal anti-inflammatory drugs (NSAIDs) with lignocaine inferior alveolar block (IANB) has also been shown to improve anesthetic success [6,7]. Although patient-related factors, such as medical conditions, medications for systemic conditions, anatomical factors, and psychological factors, such as fear and anxiety [1-3] play an important role, the agent and the technique that was used successful in the majority of the population should be the first option adopted by clinicians, to produce more predictable results.

In comparison to traditional meta-analysis, network meta-analysis (NMA) may offer improved understanding of the best agents and techniques to use for anesthesia for irreversible pulpitis. The NMA principle is used for direct as well as indirect comparisons between multiple treatments from individual trials, using the common comparator principle [14]. The methodology of NMA provides a means to gain insight into relations and comparisons among randomized controlled trials [14,15]. Hence, we performed an NMA to combine the available evidence on agents and techniques that produce successful pulpal anesthesia in the maxilla and mandible, in order to identify the best amongst these statistically,

to form the basis for future clinical trials.

METHODS

1. Information sources and search strategy

The protocol for this review was registered with PROSPERO (registration number CRD42017057700). A literature search was conducted in Medline (through PubMed), Cochrane CENTRAL, and Google Scholar databases, up to April 1, 2017. The search strategy used was (((irreversible pulpitis) AND (endodontic (treatment OR therapy) OR root canal OR pulp therapy)) AND pain) AND (local (anesthesia OR anaesthesia))). Only studies published in English language were considered. The reference lists from the identified articles were manually screened to identify other eligible studies. Manual searches were also conducted to identify missed studies. Two authors carried out independent search and retrieved appropriate articles.

2. Eligibility criteria

The criteria for inclusion were randomized controlled trials conducted in adult patients of any age and sex, with any tooth/teeth diagnosed with symptomatic irreversible pulpitis, based on subjective methods such as a pain scale and/or objective testing, using heat, cold, or electric pulp testing, and requiring endodontic treatment. Studies comparing different local anesthetic agents; techniques of administration; combination of local anesthetics with other orally administered medications, such as analgesics, nitrous oxide, acupuncture, or others were included. Traditional subjective methods of testing success of anesthesia included testing lip numbness, responsiveness of the mucosa to needle sticks, or simply commencing with the treatment and looking for a pain response [12,13]. Although objective methods, such as electric and heat/cold pulp testing are more reliable, they are more commonly used as diagnostic aids [1-4]. The primary outcome in the present meta-analysis was “no” or “mild” pain during endodontic access or canal preparation,

measured using a visual analog scale (VAS), which is also subjective, or objective negative testing, using a pulp tester. This outcome was adopted as this was the primary outcome in the majority of the included studies. Studies conducted in children, pregnant and lactating women, patients with medical conditions, anxious patients on anti-anxiety medications, patients on any other medications interfering with the action of local anesthetics or the drugs administered were excluded.

3. Study procedure and statistical considerations

After a thorough literature search by both investigators independently, a pre-tested data extraction form was created and the following data were extracted from each eligible study: trial site, year, trial methods, participants, interventions, and outcomes. Disagreement between the investigators was resolved through discussion to consensus. The present review and NMA is presented as per the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [16]. Risk-of-bias of the included randomized trials was assessed using the Cochrane risk-of-bias tool [17]. Heterogeneity between directly compared studies was assessed using Chi-square and I^2 tests. The inverse variance heterogeneity model was used, as it does not require any assumptions and is more robust than the random-effects model for both direct and indirect comparisons. Direct comparison estimates were derived by pooling the data from studies that compared the same intervention. Indirect comparison pooled estimates were derived by pooling the data between the studies through a common comparator. The entire NMA was carried out using MetaXL. Odds ratios and 95% confidence intervals were used to estimate effects, as the outcome is a categorical variable. Inconsistencies between the direct and indirect pooled estimates were evaluated by H-statistics, wherein a value of < 3 was considered as minimal, 3–6 as modest, and > 6 as gross inconsistency. The Grading of Recommendation, Assessment, Development and Evaluation (GRADE) working group approach was used to assess the quality of evidence [17].

RESULTS

1. Search results

Sixty-two studies were considered for inclusion [18-79]; 53 studies involving 4465 patients investigated the mandible [18-70], eight studies involving 442 patients investigated the maxilla [71-78], and one study [79] involving 51 patients included both maxillary and mandibular teeth. One study [48] was excluded because of disconnected network (the treatments included in this study [48] did not form a connected network, such that there was a path from each treatment to every other treatment within the whole network), and hence 61 studies were included in the final meta-analysis. The detailed search results are presented in Figure 1. Key characteristics of the included studies are represented in Table 1. Risk-of-bias assessment demonstrated low risk in all domains for most of the studies (Fig. 2).

2. Direct comparison: Pooled results for mandibular anesthetic techniques

The pooled estimates (odds ratio) for comparison of different anesthetic techniques with 2% lignocaine IANB in the mandible are presented in Figure 3. The estimates are arranged in a forest plot from the top to bottom in decreasing order of outcome success. Increased likelihood of success was observed with

- pre-medication with aceclofenac + paracetamol (odds ratio: 2.09 [95% confidence interval, CI: 0.99, 4.42]) before administering 2% lignocaine IANB
- 2% lignocaine IANB + 4% articaine buccal infiltration (BI) (2.36 [1.38, 4.03])

Other significant interventions that performed better than 2% lignocaine IANB alone include: 2% lignocaine Gow-Gates IANB (2.43 [1.10, 5.34]); mannitol + 2% lignocaine IANB (2.47 [1.08, 5.61]); 2% lignocaine IANB + BI + lingual infiltration (LI) (2.55 [1.12, 5.84]); etodolac + paracetamol before 2% lignocaine IANB (2.57 [1.14, 5.80]); nitrous oxide with 2% lignocaine IANB (2.57 [1.12, 5.90]). Other interventions (Fig. 3) also showed significant pooled

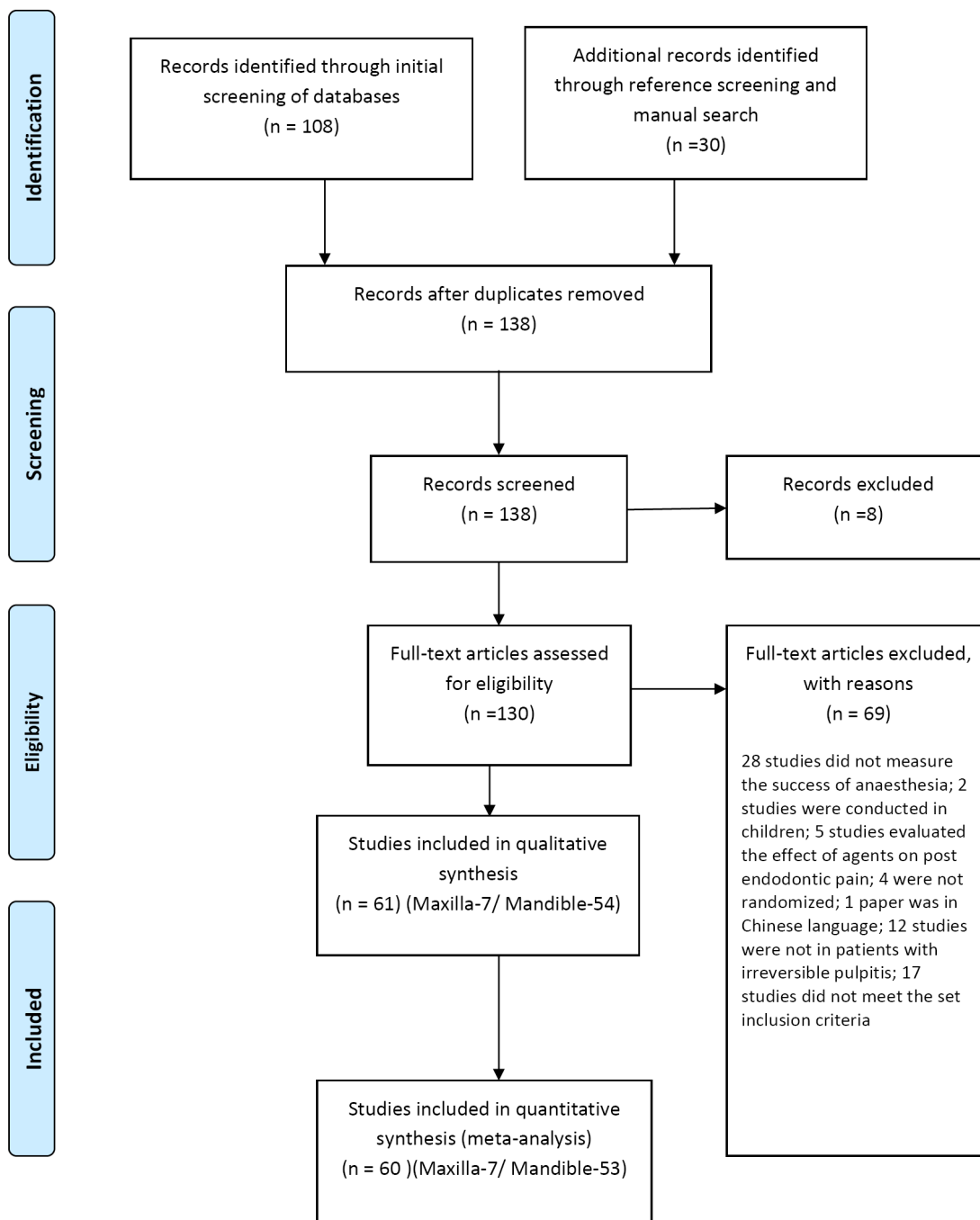


Fig. 1. PRISMA flow diagram

estimates; however, they were considered less precise due to their wider confidence intervals.

3. Indirect comparison: Pooled results for mandibular anesthetic techniques

The indirect comparison pooled estimates were derived using common comparator principle and are shown in

Figure 4. The chances of increased success of anesthesia were observed with:

- pre-medication with ibuprofen + paracetamol before 2% lignocaine IANB (2.1 [1.02, 4.33])
 - pre-medication with aceclofenac + paracetamol (2.23 [1.06, 4.72]) before 2% lignocaine IANB
- Other interventions that performed better than 2%

Table 1. Key characteristics of included studies

Study NO	First author, year [reference]	Sample size/ population	Area of anesthesia	Symptomatic/ Asymptomatic	Intervention	Comparator	Anesthetic agent used	Definition for anesthetic success
Studies in the mandible								
1	Click V, 2015 [18]	98	Mandibular molar or premolar	Symptomatic	60 patients received Gow-Gates and BNB	38 patients received Akinosi Vazirani and BNB	2% lignocaine with 1:100 000 epinephrine	access and instrument the tooth with no or mild pain, using VAS scale
2	Aggarwal, 2010 [19]	76	Mandibular molar	Symptomatic	27 patients received Gow-Gates, 25 received Vazirani-Akinosi	24 patients received IANB	4% articaine with 1:100 000 epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale
3	Matthews, 2009 [20]	78	Mandibular molar or premolar	Symptomatic	55 patients received IAN and long buccal and supplemental BI	23 patients received IANB and long buccal	2% lignocaine with 1:100 000 epinephrine. Supplemental BI with 4% articaine with 1:100 000 epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale
4	Aggarwal, 2011 [21]	98	Mandibular molar	Symptomatic	24 patients supplemental BI articaine with 1:100 000 ephinephrine. 26 patients with 1 mL/30 mg of ketorolac tromethamine 24 patients with 1 mL/4 mg of dexamethasone.	4% 24 patients did not receive any supplemental infiltrations	All patients received IANB with 2% lignocaine with 1:200 000 epinephrine	No pain or weak/mild pain during access and instrumentation using VAS scale
5	Razavian, 2013 [22]	40	Mandibular posterior tooth	Symptomatic	20 patients received X tip IO injection	20 patients received IANB	2% lignocaine with 1:100 000 epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale
6	Webster, 2016 [23]	175	Mandibular molar or premolar	Symptomatic	75 patients received conventional IANB and intraseptal 1.4 mL 4% articaine with 1:100 000 epinephrine	100 patients received IANB	2% lignocaine with 1:100 000 epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale
7	Reisman, 1997 [24]	86	Mandibular molar or premolar	Symptomatic	42 patients received IANB and IO of 1.8 ml of 3% mepivacaine	44 patients received IANB	2% lignocaine with 1:100 000 epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale
8	Pairokh, 2014 [25]	69	Mandibular molar	Mentioned as asymptomatic but included patients with prolonged response to cold test. Hence considered symptomatic	33 patients received IANB followed by BI and intraligamentary	36 patients received IANB	2% lignocaine with 1/80 000 epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale
9	Aggarwal, 2009 [26]	87	Mandibular molar	Symptomatic	62 patients received IANB. 31 patients received supplemental infiltrations of 2% articaine with 1:200 000 epinephrine, and 31 patients received infiltrations of 2% lignocaine with 1:200 000 epinephrine	25 patients received IANB	2% lignocaine with 1:200 000	No pain or weak/mild pain during access and instrumentation, using VAS scale
10	Pairokh, 2010 [27]	82	Mandibular molar	Symptomatic	55 patients received IANB and BI	27 patients received IANB	2% lignocaine with 1:100 000 epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale
11	Kanaa, 2012 [28]	100	Mandibular molar or premolar	Symptomatic	25 patients received IANB and BI of 4% articaine with epinephrine 1:100 000 25 patients received IANB with periodontal ligament infiltration 25 patients received IANB with IO	25 patients received IANB	2.0 mL of 2% lignocaine with 1:80,000 epinephrine	No response to the maximum stimulation (reading of 80) with the pulp tester

12	Aggarwal, 2014 [29]	63	Mandibular molar	Symptomatic	31 patients received IANB 2% lignocaine with 1:80 000 epinephrine	32 patients received IANB 2% lignocaine with 1:200 000 epinephrine	Lignocaine	Pulp access and canal instrumentation into the apical third with no or mild pain
13	Shadmehr, 2016 [30]	100	Mandibular molar	Symptomatic	50 received 2% lignocaine with clonidine IANB	50 received 2% lignocaine with epinephrine 1:80 000 IANB	2% lignocaine	Ability to penetrate dentine, enter the pulp and advance instruments into the coronal part of the canal pulp without pain (VAS score of zero) or mild pain
14	Stanley, 2012 [31]	100	Mandibular molar or premolar	Symptomatic	50 patients received nitrous oxide/oxygen 6 L/min flow rate of 100% oxygen and IANB	50 patients received room air/oxygen and IANB	3.6 ml of 2% lidocaine with 1:100 000 epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale
15	Jalali, 2015 [32]	40	Mandibular molar	Symptomatic	20 patients received acupuncture and IANB	20 patients received IANB only	2% lignocaine with 1:80 000 epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale
16	Shetty, 2015 [33]	100	Mandibular premolar or molar	Symptomatic	50 patients received 1 mL magnesium sulfate USP 50% and IANB	50 patients received 1 mL distilled water (placebo) and IANB	2% lignocaine with 1/80000 epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale
17	Kreimer, 2012 [34]	106	Mandibular molar or premolar	Symptomatic	56 patients received 5 mL, 63.6 mg of lignocaine with 31.8 mg epinephrine plus 1.82 mL of 0.5 mol/L mannitol or 3-mL containing 76.4 mg of lignocaine with 36 mg epinephrine plus 1.1 mL of 0.5 mol/L mannitol	50 patients received the same without mannitol	Lignocaine with epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale
18	Schellenberg, 2015 [35]	100	Mandibular molar or premolar	Symptomatic	50 patients received IANB buffered with 0.18 mEq/mL sodium bicarbonate	50 patients received IANB	4% lignocaine with 1:100 000	No pain or weak/mild pain during access and instrumentation using VAS scale
19	Saatchi, 2016 [36]	100	Mandibular first molar	Symptomatic	50 patients received standard IANB and BI with sodium bicarbonate	50 patients received IANB	2% lignocaine with 1:80 000 epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale
20	Saatchi, 2015 [37]	80	Mandibular posterior tooth	Symptomatic	40 patients received 0.18 mL 8.4% sodium bicarbonate (8.4% weight/volume, 50 mEq/50 mL buffered IANB	40 patients received 0.18 mL of sterile distilled water with IANB	2% lidocaine with 1:80 000 epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale
21	Dou L, 2013 [38]	80	Mandibular molar	Symptomatic	40 patients received IANB and BI of 0.9 mL of 4% articaine with 1:100 000 epinephrine	40 patients received IANB and BI and LI of 0.9 mL of 4% articaine with 1:100 000 epinephrine	2% lignocaine containing 1:100 000 epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale
22	Shahi, 2013 [39]	165	Mandibular molar	Mentioned as asymptomatic but included patients with prolonged response to cold test. Hence considered symptomatic	55 patients received 0.5 mg dexamethasone and 55 patients received 400 mg ibuprofen and IANB and BI	55 patients received placebo of lactose powder and IANB and BI	2% lignocaine containing 1:80000 epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale
23	Shantiaee, 2016 [40]	69	Mandibular first molar	Symptomatic	23 patients received 7.5 mg of meloxicam; 23 patients received 600 mg of ibuprofen and IANB	23 patients received placebo and IANB	2% lignocaine and 1:100 000 epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS

24	Aggarwal, 2010 [41]	69	Mandibular molar	Symptomatic	22 patients received 300 mg of ibuprofen, 23 patients received 10 mg of ketorolac and IANB	24 patients received placebo starch capsules and IANB	1.8 mL of 2% lignocaine with 1:200 000 epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale
25	Jena, 2013 [42]	100	Mandibular posterior teeth	Symptomatic	20 patients received ibuprofen (600 mg), 20 patients ketorolac (10 mg), 20 patients combination of etodolac with paracetamol (400 mg + 500 mg) and 20 patients combination of aceclofenac with paracetamol (100 mg + 500 mg) and IANB	20 patients were administered placebo with sugar coated pills and IANB	IANB 2% lignocaine with 1:200 000 epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale
26	Parirokh, 2010 [43]	150	Mandibular first and second molar	Symptomatic	50 patients received 600 mg ibuprofen and 60 patients received 75 mg indomethacin And IANB	50 patients received placebo of lactose powder and IANB	2% lignocaine with 1/80000 IANB	No pain or weak/mild pain during access and instrumentation, using VAS scale
27	Simpson, 2011 [44]	100	Mandibular molar or premolar	Symptomatic	50 patients received either 800 mg ibuprofen or 1000 mg acetaminophen and IANB and BI	50 patients received Placebo, IANB and BI	2% lignocaine with 1:100 000	No pain or weak/mild pain during access and instrumentation, using VAS scale
28	Fullmer, 2014 [45]	100	Mandibular molar or premolar	Symptomatic	50 patients received 1000 mg acetaminophen plus 10 mg hydrocodone and IANB	50 patients received placebo an IANB	2% lignocaine with 1:100 000	No pain or weak/mild pain during access and instrumentation, using VAS scale
29	Ianiro, 2009 [46]	40	Mandibular molar	Symptomatic	14 patients received 1,000 mg of acetaminophen only, 13 patients received a combination of 1,000 mg of acetaminophen and 600 mg of ibuprofen and IANB	13 patients received placebo and IANB	2% lignocaine with 1:100 000 epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale
30	Lindemann, 2008 [47]	58	Mandibular molar or premolar	Symptomatic	30 patients received sublingual triazolam 0.25 mg	28 patients received Placebo	2% lignocaine with 1:100 000 epinephrine IANB	No pain or weak/mild pain during access and instrumentation using VAS scale
31	Bigby, 2007 [48]	50	Mandibular posterior teeth	Symptomatic	25 patients received 36 mg meperidine and IANB	25 patients received IANB	36 mg of lignocaine with 18 g of epinephrine	No pain or weak/mild pain during access and instrumentation using VAS scale
32	Akhlagi, 2016 [49]	40	Mandibular molar	Symptomatic	20 received IANB and BI of 0.9 mL articaine. After 5 minutes, 20 patients received supplemental BI of 30 mg/mL ketorolac tromethamine	20 received the same and BI with normal saline	4% articaine 1:100 000 epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale
33	Yadav, 2015 [50]	150	Mandibular first and/or second molar	Symptomatic	75 patients received standard IANB using 1.8 mL 4% articaine with 1:100 000 epinephrine	75 patients received standard IANB using 2% lignocaine with 1:80,000 epinephrine	Lignocaine and articaine	no pain or weak/mild pain during access and instrumentation using VAS scale
34	Saha, 2016 [51]	126	Mandibular posterior teeth	Symptomatic	Oral 10 mg ketorolac or 50 mg diclofenac, 84 patients received standard IANB	Oral placebo 42 patients received standard IANB injections	2% lignocaine containing 1:200 000 epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale
35	Khademi, 2012 [52]	60	Mandibular molar	Symptomatic	30 patients 0.5 mg of alprazolam and IANB	30 patients received placebo and IANB	2% lignocaine with 1:100 000 epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale
36	Pedro-Munoz, 2016 [53]	42	Mandibular molar	Symptomatic	21 received submucosal 50 mg tramadol and IANB	21 received placebo and IANB	4% articaine with 1:100 000 epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale
37	Rodriguez Wong, 2016 [54]	56	Mandibular molar	Symptomatic	28 patients received IANB with tramadol 50 mg	28 patients received IANB	mepivacaine 2% 1 : 100 000 epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale

38	Prasanna, 2011 [55]	114	Mandibular molar	Symptomatic	38 patients received Oral diclofenac and 38 received lornoxicam and IANB	38 patients received placebo and IANB	2% lignocaine epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale
39	Sood, 2014 [56]	100	Mandibular molar	Symptomatic	50 patients received 4% Articaine with 1:100 000 epinephrine	50 patients received 2% lignocaine with 1:80,000 epinephrine	Articaine and lignocaine IANB	No pain or weak/mild pain during access and instrumentation, using VAS scale
40	Tortamano,2009 [57]	40	Mandibular molar	Symptomatic	20 patients received IANB of 4% articaine with 1:100 000 epinephrine	20 patients received IANB of 2% lignocaine with 1:100 000 epinephrine	Articaine and lignocaine IANB	No pain or weak/mild pain during access and instrumentation, using VAS scale
41	Claffey, 2004 [58]	72	Mandibular molar or premolar	Symptomatic	37 patients received 4% articaine with 1:100 000 epinephrine IANB	35 patients received 2% lignocaine with 1:100 000 epinephrine IANB	Articaine and lignocaine IANB	No pain or weak/mild pain during access and instrumentation, using VAS scale
42	Allegretti, 2016 [59]	66	Mandibular posterior teeth	Symptomatic	22 patients each received IANB of 4% or 2% mepivacaine with 1:100 000 epinephrine	22 patients received IANB 2% lignocaine with 1:100 000 epinephrine	Articaine, lignocaine or mepivacaine	No pain or weak/mild pain during access and instrumentation, using VAS scale
43	Ahmad, 2014 [60]	45	Mandibular posterior teeth	Symptomatic	15 patients received 2% lignocaine with 1:80,000 epinephrine 15 patients received 4% Articaine with 1:100000 epinephrine	15 patients received 2% lignocaine with 1:200000 epinephrine	Articaine or lignocaine IANB on pain, supplementary BI with same	absence of pain after the administration of BI
44	Poorni, 2011 [61]	156	Mandibular molar	Symptomatic	52 patients received IANB with 4% articaine with 1:100 000 epinephrine 52 patients received additional BI	52 patients received IANB with 2% lignocaine with 1:100 000 epinephrine	Articaine and lignocaine	No pain or weak/mild pain during access and instrumentation, using VAS scale
45	Sherman, 2008 [62]	40	Maxillary molar	Symptomatic	20 patients received 1.7 mL of articaine by a Gow-Gates or maxillary infiltration	20 patients received 1.8 mL of lignocaine by Gow-Gates block or maxillary infiltration	Articaine and lignocaine	No pain or weak/mild pain during access and instrumentation, using VAS scale
46	Rogers, 2014 [63]	100	Mandibular molar	Symptomatic	74 patients received IANB and supplemental BI using articaine or lignocaine	26 patients received IANB	4% articaine with 1:100 000 epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale
47	Monteiro, 2014 [64]	50	Mandibular molar	Symptomatic	30 patients received IANB and BI of 4% articaine with 1 : 100 000	20 patients received IANB.	2% lignocaine with 1:100 000 epinephrine	Ability to access and instrument the tooth with no pain or no more than mild pain
48	Bigby, 2006 [65]	49	Mandibular posterior teeth	Symptomatic	39 patients received IANB and long buccal injections	10 patients received IANB	4% articaine with 1:100 000 epinephrine	No or mild pain upon endodontic access or initial Instrumentation
49	Fan, 2009 [66]	60	Mandibular first molar	Symptomatic	30 IANB and additional BI	30 IANB and additional PDL injections	4% articaine/HCl with epinephrine 1:100 000	No pain or weak/mild pain during access and instrumentation using VAS scale
50	Visconti, 2016 [67]	43	Mandibular molar	Symptomatic	21 patients received IANB 2% mepivacaine	22 patients received IANB 2% lignocaine	Mepivacaine and lignocaine	Accessed the pulp chamber without the patient reporting pain
51	Sampaio, 2012 [68]	70	Mandibular molar	Symptomatic	35 patients received 0.5% bupivacaine with 1:200 000 epinephrine IANB	35 patients received 2% lignocaine with 1:100 000 epinephrine IANB	Bupivacaine and lignocaine	Accessed the pulp chamber without the patient reporting pain
52	Singla, 2015 [69]	147	Mandibular first or second molar	Symptomatic	73 patients received standard IANB and 1.8 ML BI	74 patients received standard IANB and 3.6 mL BI	4% articaine with 1:100 000 epinephrine	No pain or weak/mild pain during access and instrumentation, using VAS scale

53	Abazarpoor, 2015 [70]	80	Mandibular first molar	Symptomatic	40 patients received 3.6 mL articaine IANB	40 patients received 1.8 mL articaine IANB	4% articaine with 1:100 000 epinephrine	Ability to undertake pulp access and canal instrumentation into the apical third with no or mild pain
Studies in the maxilla								
1	Aggarwal, 2011 [71]	61	Maxillary first molar	Symptomatic	28 patients received PSA	33 patients received BI	2% lignocaine with 1:200 000 epinephrine	No pain or weak/mild pain during access and instrumentation using VAS
2	Mehrvarzfar, 2014 [72]	61	Maxillary molars	Symptomatic	31 patients received local infiltration and 0.8 mL of fentanyl (40 µg).	30 patients received local infiltration and sterile normal saline solution	2% lignocaine, containing 1:80000 epinephrine	2 consecutive negative reading of EPT (maximum 80)
3	Elsharawy, 2007 [73]	40	Maxillary molars	Symptomatic	20 patients received infiltration and intraligamental 0.4 mL fentanyl 0.05 mg/ml	20 patients received infiltration and intraligamental mepivacaine	1.8 mL of 2% mepivacaine with 1:200 000 epinephrine	Success was recorded as "none" or "mild" pain.
4	Atasoy, 2014 [74]	50	Maxillary first molar	Symptomatic	25 patients received 4% articaine HCl + 1:100 000 epinephrine infiltration	20 patients received 4% articaine HCl + 1:100 000 Epinephrine bitartrate infiltration	Articaine	Successful pulpal anesthesia.
5	Srinivasan, 2009 [75]	40	Maxillary posterior tooth	Symptomatic	20 patients received 4% articaine with epinephrine 1:100 000 infiltration	20 patients received 2% lignocaine with epinephrine 1:100 000 infiltration	Articaine and lignocaine	No pain or weak/mild pain during access and instrumentation using VAS scale
6	Hosseini, 2016 [76]	40	Maxillary first molar	Symptomatic	20 patients received BI of 1.8 mL of 4% articaine with 1:100000 epinephrine	20 patients received BI of 1.8 mL 2% lignocaine with 1:80000 epinephrine	Articaine	Absence of pain or mild discomfort
7	Ramachandran, 2012 [77]	100	Maxillary first molar	Symptomatic	Premedication with 1000 mg of paracetamol or 800 mg of ibuprofen, 100 mg aceclofenac and infiltration	Premedication with placebo and infiltration	2% lignocaine with epinephrine 1:200 000	Absence of pain during access preparation and root canal instrumentation
8	Kanna 2012 [78]	50	Maxillary teeth	Symptomatic	2.0 mL 4% articaine with 1:100 000 epinephrine BI	2% lidocaine with 1:80,000 epinephrine BI	Articaine and lignocaine	No response was obtained to the maximum stimulation (80 reading) of the pulp tester
Study of both maxillary and mandibular teeth								
1	Nusstein, 1998 [79]	51	Mandibular or maxillary molar or premolar	Symptomatic	26 patients received IANB or BI in addition to IO	25 received conventional IANB or BI	2% lignocaine with 1:100 000 epinephrine.	No pain or weak/mild pain during access and instrumentation using VAS scale

IANB—inferior alveolar nerve block; BNB—buccal nerve block; BI—buccal infiltration; LI—lingual infiltration; VAS—visual analog scale; IO—intra-osseous; PSA—posterior superior alveolar

lignocaine IANB alone were 2% lignocaine Gow-Gates IANB (2.43 [1.10, 5.34]); mannitol with 2% lignocaine IANB (2.47 [1.08, 5.61]); 4% articaine BI with 2% lignocaine IANB (2.54 [1.49, 4.32]); nitrous oxide with CIANB (2.57 [1.12, 5.9]). The estimates of other interventions are presented in Figure 4. Although significant, they were considered less precise given their wider confidence intervals. Mild inconsistencies were observed for the pooled estimates between direct and indirect comparisons, with H values ranging between 1

and 1.5. Similarly, mild-to-moderate heterogeneity was observed.

4. Indirect comparison: Pooled results for maxillary anesthetic techniques

The indirect pooled estimates for the following interventions in comparison with 2% lignocaine BI in the maxilla is shown in Figure 5: adjuvant intra-osseous 2% lignocaine; and 4% articaine BI and adjuvant fentanyl. No significant difference in the success rate of maxillary

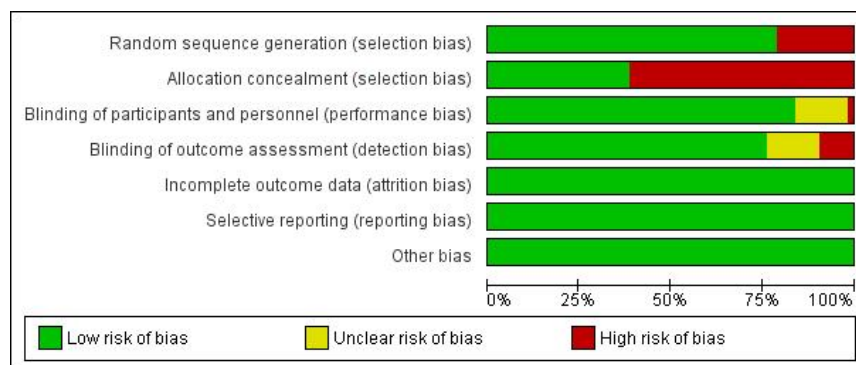


Fig. 2. Risk-of-bias of included studies.

anesthesia was observed with any of the above-mentioned approaches. Direct comparison was not attempted because of the small number of available studies. Mild to moderate heterogeneity was observed between direct and indirect comparisons using H-statistics and I^2 tests. This indicated that the results obtained were dependable.

5. Grading the evidence

Grading of the evidence for key comparisons was carried out based on the assessment of indirectness, inconsistency, publication bias, and imprecision of the estimates. Very low quality of evidence was observed due to serious limitations in the precision of the estimates and because publication bias could not be assessed (Table 2).

DISCUSSION

This NMA attempted to identify the best agent and technique for successful local anesthesia in the maxilla and mandible in adult patients with symptomatic irreversible pulpitis undergoing endodontic treatment. The results indicated that premedication with ibuprofen + paracetamol, or aceclofenac + paracetamol before IANB, or 2% lignocaine IANB + 4% articaine BI, produced the most successful anesthesia in the mandible. No significant difference in the success rate of maxillary anesthesia was noted with the approaches tested due to the low number of available studies.

Reports indicate that the most commonly used,

conventional lignocaine IANB failed at a rate of 15–50% [13]. The most common cause of failure was poor injection technique, followed by technical errors and anatomical variability, infection and inflammation, pathological processes, and psychological causes, such as fear, apprehension, or anxiety [1,13].

Although Gow–Gates and Akinosi–Vazirani techniques showed varied anesthetic success compared with IANB in previous studies [80–82], results from the present meta-analysis showed that the Gow–Gates approach performed better than the Akinosi technique or conventional IANB. This variability can be attributed to the experience of the dentist administering the nerve block. Most dentists do not adopt this technique due to inadequate training and experience [81]. Overall, the Gow–Gates technique has been proven to have a higher likelihood of success in patients with varied anatomy, when performed by a skilled dentist. A recent study also reported increased success with a combination of the Gow–Gates technique and conventional IANB [83]. Results from previous randomized trials did not indicate significant differences in pain during injection using these techniques [83]. Other reported advantages of the adjuvant techniques, such as the Gow–Gates and Akinosi techniques, include a lower incidence of positive aspiration and decreased problems related to accessory innervation [80–83].

The use of supplemental buccal, lingual, intraosseous, and intraligamentary infiltrations as a means to deal with collateral nerve supply have also been tested in various

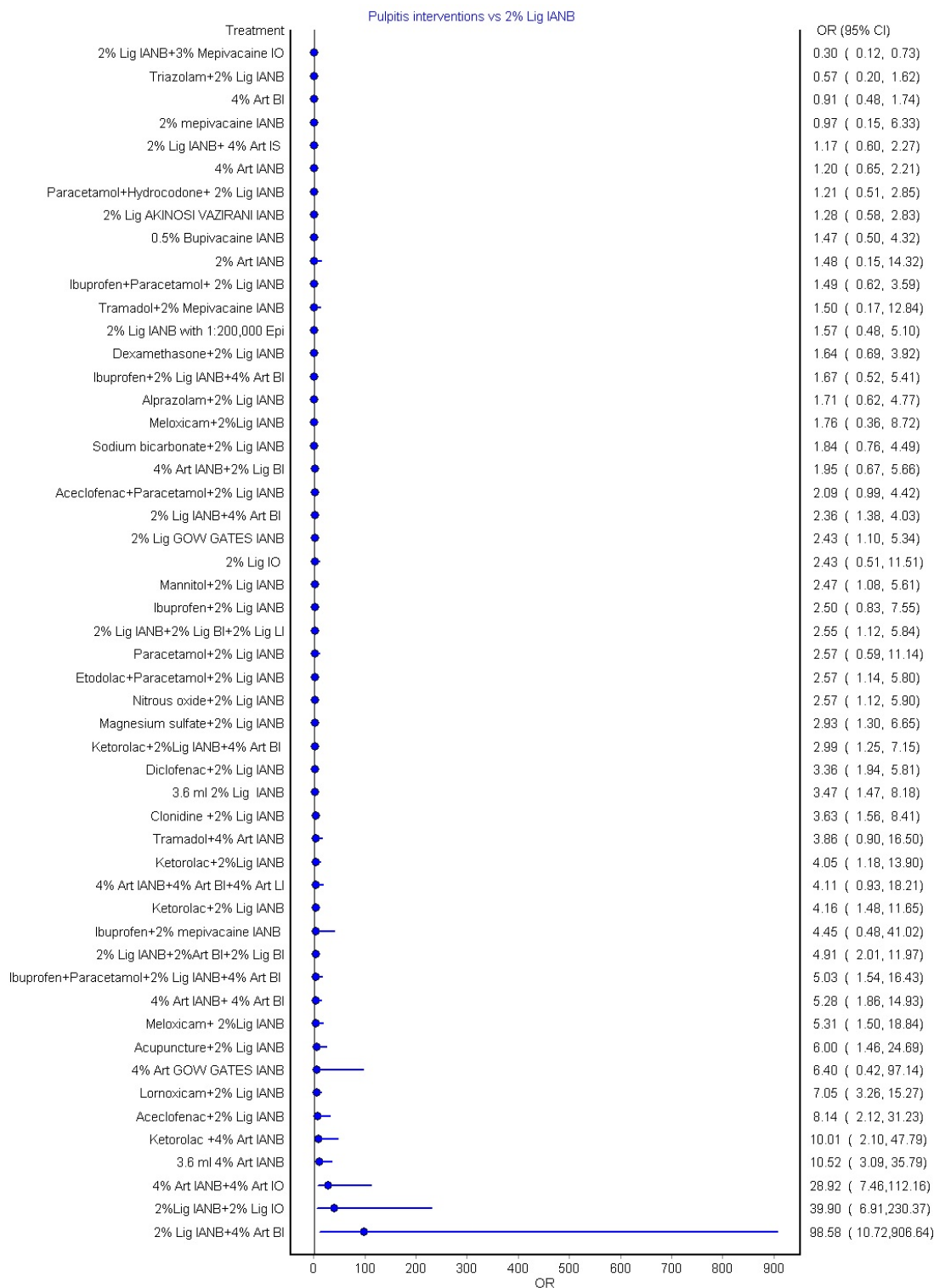


Fig. 3. Forest plot for direct comparison of treatments in the mandible

randomized controlled trials, and results from pooled estimates indicate higher success [84]. Pooled results from the present review also indicate that supplemental

infiltration produced better success rates. Specifically, the most successful anesthesia was produced with supplemental 4% articaine BI, followed by 2% lignocaine BI

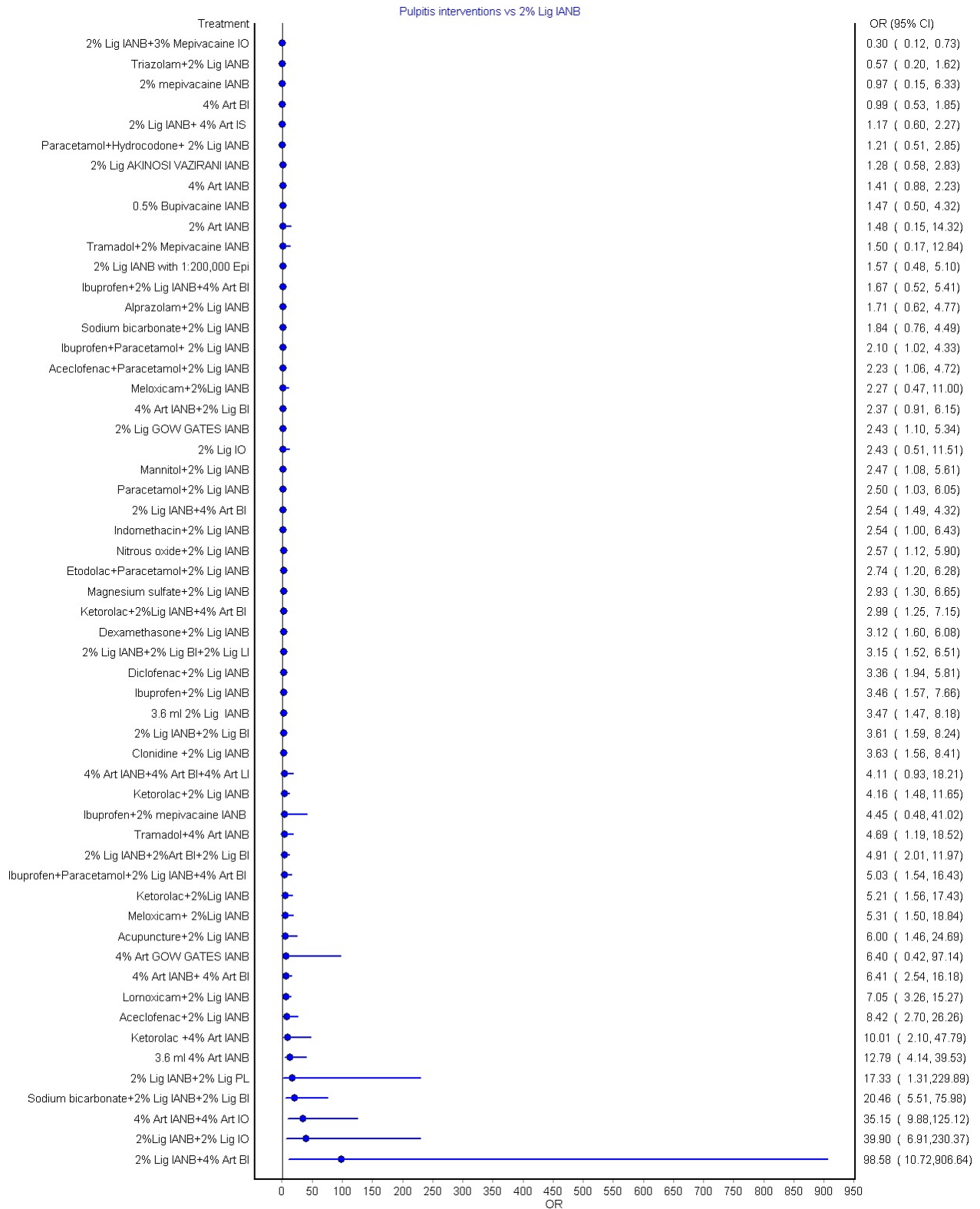


Fig. 4. Forest plot for indirect comparison of treatments in the mandible

and LI in the mandible. Infiltration alone has been recommended in the anterior mandibular region because

of the particular disadvantages of bilateral administration of blocks [84-87]. There is a paucity of data from

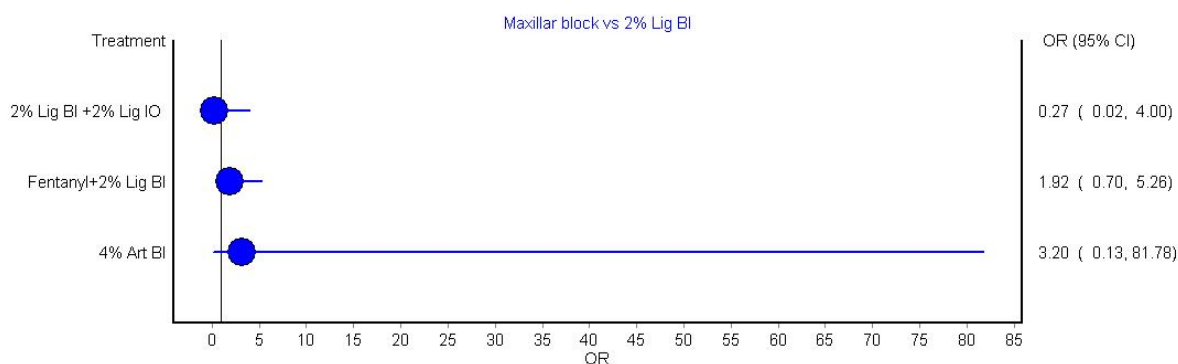


Fig. 5. Forest plot for indirect comparison of treatments in the maxilla

Table 2. Grading the quality of evidence for key comparisons using 2% lignocaine IANB for the success of anesthesia

Outcomes	Illustrative comparative risks (95% confidence intervals)		Odds ratio (95% confidence intervals)	Quality of the evidence (GRADE)
	Assumed risk ¹	Corresponding risk		
Premedication with combined ibuprofen and paracetamol	348 per 1000	522 per 1000 (328 to 685)	2.1 [1.02, 4.33]	⊕⊖⊖⊖ very low ^{2, 3, 4}
2% lignocaine Gow-Gates	348 per 1000	564 per 1000 (383 to 743)	2.43 [1.1, 5.34]	⊕⊖⊖⊖ very low ^{2, 3, 4}
Premedication with paracetamol	348 per 1000	580 per 1000 (332 to 752)	2.5 [1.03, 6.05]	⊕⊖⊖⊖ very low ^{2, 3, 4}
Adjuvant 4% articaine BI	348 per 1000	581 per 1000 (432 to 683)	2.54 [1.49, 4.32]	⊕⊖⊖⊖ very low ^{2, 3, 4}
Adjuvant 2% lignocaine BI and 2% lignocaine LI	348 per 1000	639 per 1000 (464 to 754)	3.12 [1.6, 6.08]	⊕⊖⊖⊖ very low ^{2, 3, 4}
Premedication with ibuprofen	348 per 1000	634 per 1000 (460 to 808)	3.46 [1.57, 7.66]	⊕⊖⊖⊖ very low ^{2, 3, 4}
Premedication with ketorolac	348 per 1000	710 per 1000 (459 to 905)	5.21 [1.56, 17.43]	⊕⊖⊖⊖ very low ^{2, 3, 4}

1—Assumed risk was the median control group risk across the studies

2—Downgraded one level as publication bias could not be assessed

3—Downgraded one level for imprecision of the estimates, as evident by the wider confidence intervals

4—Downgraded one level for low sample size

Very low quality: Marked uncertain about the estimate.

randomized controlled trials on the use of infiltration alone in the anterior mandible. Most dentists consider supplemental infiltration as a means to manage the collateral nerve supply, as well as in cases of block failure, according to the studies included in the present review [21,22,32].

The commonly tested agents in the studies were articaine and lignocaine. Other agents, such as bupivacaine and mepivacaine, were tested in very few trials. Results from previous studies did not show significant differences between articaine and lignocaine IANB alone [4,5], although supplemental articaine infiltration was shown to

produce significant success [4,5]. Similar results were obtained in the present NMA, probably because most trials concentrated on articaine and lignocaine only. The safety profile of these drugs was reported to be similar, although articaine caused greater injection pain scores [4,5]. Other local anesthetic agents need to be studied in detail in randomized controlled trials to warrant any conclusion.

A meta-analysis on the success of IANB for teeth with irreversible pulpitis concluded that premedication with NSAIDs before IANB increased the efficacy of anesthesia [7]. Results from the present NMA specifically indicate

that the combination of ibuprofen + paracetamol and aceclofenac + paracetamol premedication before IANB produced the most successful anesthesia, as compared to the injection techniques alone. Other drugs that were used alone or in combination were piroxicam, naproxen, diclofenac, steroids, and benzodiazepines, prescribed 1 hour before the block. However, premedication with drugs has been tested mainly before IANB, and not in combination with any other techniques. The effect of premedication using oral drugs as a supplemental technique for pain control in irreversible pulpitis requires further investigation.

Most of the studies in the review used infiltration with or without an intraosseous injection technique. No conclusive evidence is available from the present review, mainly due to the limited number of available studies. Individual study results indicated that dentists preferred infiltration techniques in the maxilla, due to the cancellous nature of the bone, covered by a thin cortical plate, which allows easier penetration of the anesthetic solution. Furthermore, maxillary blocks were technique-sensitive [86]. This is probably the reason for fewer available clinical trials on block anesthesia in the maxilla [86]. There is a need for future studies on different anesthetic agents and techniques to allow a firm conclusion to be drawn.

The study was limited by the small sample sizes in the included studies for evaluation of each of the interventions tested, which is evident from the wider confidence intervals. Increased sample sizes in the individual trials would likely narrow the confidence interval and provide a more compelling conclusion. This NMA suggested that future clinical trials should make a strong effort to increase sample size. Given the quality of evidence and the limitations of the individual studies, the pooled data obtained via NMA does not provide confident, conclusive guidance for clinicians. Although the literature indicates that the efficacy of anesthesia differs between symptomatic and asymptomatic pulpitis [87], this was not tested in the present review. All included trials addressed symptomatic pulpitis cases only.

Publication bias could not be assessed, and other variables, such as psychological profile and characteristics of healthcare facilities, which may impact the outcome measures, were not considered.

In conclusion, the use of premedication with ibuprofen and paracetamol, or aceclofenac and paracetamol, prior to conventional 2% lignocaine IANB, or supplemental 4% articaine BI may produce the most successful anesthesia for mandibular teeth with irreversible pulpitis. This meta-analysis could not identify the most favorable technique in the maxilla, because of limited number of available studies. NMA is a powerful tool that can help to identify the best possible technique by using mixed treatment comparisons in cases of limited clinical trials. This NMA suggested that IANB with lignocaine alone may be unlikely to produce effective anesthesia in symptomatic irreversible pulpitis in the mandible, and that supplemental injections or premedication may improve the anesthetic success. Future randomized control trials should focus on the overall quality of the study, with larger sample sizes, which will more likely produce definitive conclusions.

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 Muneera Alsobaiei: Conceptualization, Data curation, Formal analysis, Methodology, Resources, Supervision, Visualization
 Kannan Sridharan: Conceptualization, Data curation, Software, Supervision, Writing - original draft, Writing - review & editing

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