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Efficacy of Combined Versus Supplementary Injection Techniques With Inferior Alveolar Nerve Block for Mandibular Molars With Symptomatic Irreversible Pulpitis: A Systematic Review and Network Meta-Analysis

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ABSTRACT

Background: Achieving effective anaesthesia in mandibular molars with symptomatic irreversible pulpitis is challenging. Various strategies involving the inferior alveolar nerve block (IANB) have been investigated, such as supplementing with additional injections after IANB failure (SUPP) or combining injections with IANB as primary injections (COMB). However, studies directly comparing SUPP and COMB are still lacking.

Objectives: This study aims to assess and compare the anaesthetic effectiveness of different IANB strategies—SUPP and COMB—in mandibular posterior teeth with symptomatic irreversible pulpitis using a systematic review and network meta-analysis.

Method: A comprehensive search was conducted in the PubMed, Embase, Cochrane Library, CINAHL and Scopus databases to identify relevant studies up to October 2024. Eligible randomised clinical trials (RCTs) were analysed using pairwise meta-analysis and network meta-analysis with a random-effects model to estimate treatment effects. Results were reported as risk ratios (RRs) with 95% confidence intervals (CIs) and surface under the cumulative ranking curve (SUCRA) values. The quality of the evidence was assessed using the CINeMA (Confidence in network meta-analysis) software (University of Bern, Bern, Switzerland).

Results: A total of 28 studies involving five interventions were identified. Compared with IANB alone, both SUPP (RR = 2.02; 95% CI: 1.55–2.30; SUCRA: 85.1%) and COMB (RR = 1.86; 95% CI: 1.50–2.30; SUCRA: 64.9%) significantly improved anaesthetic success. However, there was no significant difference in effectiveness between SUPP and COMB.

Conclusion: The quality of evidence ranging from low to high suggests that both SUPP and COMB are comparable in anaesthetic efficacy during endodontic treatment of mandibular molars with symptomatic irreversible pulpitis. However, both SUPP and COMB strategies showed significantly superior effectiveness compared to IANB alone.

1 | Introduction

Symptomatic irreversible pulpitis (SIP) presents with intermittent or spontaneous pain that is exacerbated by cold stimuli or rapid temperature changes (Berman and Hargreaves 2020). Patients typically exhibit a characteristic triad of spontaneous pain, hyperalgesia, and allodynia (Hargreaves et al. 2012), necessitating endodontic intervention to remove the inflamed

tissue and alleviate discomfort. Managing pain during these procedures poses significant challenges, with patients experiencing an eightfold higher anaesthetic failure rate compared to those without pulpitis (Hargreaves and Keiser 2002). The prevalence of inadequate anaesthesia ranges from 43% to 83% in mandibular molars (Reisman et al. 1997; Nusstein et al. 1998, 2003; Lindemann et al. 2008; Fowler et al. 2016; Aggarwal et al. 2018).

This high failure rate is attributed to several mechanisms related to both peripheral and central sensitization caused by pulpal inflammation. Inflammatory mediators sensitise nociceptors, reduce anaesthetic penetration through tissue acidosis, and increase local vasodilation, while enhanced expression of tetrodotoxin-resistant sodium channels makes nerves less responsive to local anaesthetics (Hargreaves and Keiser 2002). Additionally, central sensitization amplifies pain signals, and psychological factors such as anxiety can further compromise anaesthetic efficacy (Hargreaves and Keiser 2002; Takeda et al. 2011; Dureja et al. 2017).

The inferior alveolar nerve block (IANB), despite being the most commonly used technique for mandibular molars, is associated with high failure rates in patients with SIP. To address this clinical challenge, two principal strategies have emerged: supplemental injections administered after IANB failure (SUPP) and combination techniques where supplemental injections are administered simultaneously with IANB as primary injections (COMB). Both approaches utilise established techniques including buccal infiltration (BI), lingual infiltration (LI), and intraligamentary injection (ILI) (Malamed 2019).

Systematic reviews and meta-analyses have consistently demonstrated that both SUPP and COMB strategies achieve superior anaesthetic efficacy compared to IANB alone (Dias-Junior et al. 2021; Gupta et al. 2021, 2022; Almadhoon et al. 2022). However, the comparative efficacy between SUPP and COMB remains unexamined in RCTs. This knowledge gap likely stems from practical feasibility and ethical considerations inherent in conducting direct comparative trials, where patients would be randomised to experience intentional IANB failure before receiving supplemental treatment. This absence of direct comparative evidence presents a significant methodological limitation for traditional meta-analyses, which require head-to-head RCT comparisons to establish relative treatment effects (Nagendrababu et al. 2022).

A network meta-analysis (NMA) can overcome this limitation with its inferential statistical power. As an extension of a traditional meta-analysis, NMA enables clinicians to analyse interventions using indirect evidence; with this technique, interventions can be compared with a common comparator, such as a control (IANB) (Lumley 2002). Several NMAs of local anaesthesia have been conducted for comprehensive analysis and multiple pairwise comparisons within a single study (Pulikkotil et al. 2018; Nagendrababu et al. 2019; Sivaramakrishnan et al. 2019; Zanjir et al. 2019; Larocca de Geus et al. 2020). In one study, details regarding various strategies for pain control in SIP, including supplemental techniques, increasing anaesthetic volumes, premedication, and type of anaesthetic agents, were comprehensively collected. These strategies were then ranked according to their anaesthetic efficacy. However, there was no distinction made between SUPP and COMB (Zanjir et al. 2019).

To date, no NMAs have specifically focused on indirect comparisons between supplemental and combination techniques. This study was therefore designed to perform an NMA that combines available direct and indirect evidence to evaluate the efficacy of supplemental injection techniques and combination techniques with IANB in mandibular molars diagnosed with SIP.

The aim of this study was to perform a systematic review and NMA to assess the anaesthetic efficacy among different IANB strategies, SUPP and COMB, used for mandibular molars with SIP.

2 | Method

This systematic review and NMA were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for NMAs (Hutton et al. 2015).

2.1 | Registration

The protocols were registered in the PROSPERO international database, with the registration ID: CRD42024579494.

2.2 | Data Sources and Search Strategy

An exhaustive search was performed in the following electronic databases: PubMed, Embase, CINAHL, Cochrane Library, and Scopus. Additional search attempts were made for both completed and ongoing trials in the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov trial registries. Unpublished and grey literature from ProQuest, OpenGrey and Google Scholar (the first 100 hits) was also explored for additional studies. The search was conducted until October 2024, without any restriction on language and date of publication.

The search strategy was constructed using a combination of the main keywords or medical subject heading terms related to SIP, hot tooth, local anaesthesia, supplemental injections, combination injections, and IANB (Table S1).

Additional data were manually obtained from Mahidol University's library; four major textbooks including Cohen's Pathway of the Pulp (Berman and Hargreaves 2020), Seltzer and Bender's Dental Pulp (Hargreaves et al. 2012), Handbook of Local Anaesthesia (Malamed 2019), and Ingle's Endodontics, 7th edition (Rotstein and Ingle 2019); and citations in the included studies.

2.3 | Study Selection and Outcome Measurement

Two authors (T.R. and S.O.) independently screened the titles and abstracts using a web-based systematic review application,

Rayyan (Ouzzani et al. 2016). Any discrepancies were resolved by consensus with a third author (K.C.). The final study selection process was described using a PRISMA flow diagram (Page et al. 2021).

2.4 | Inclusion Criteria

A PICOS strategy was used to formulate the inclusion criteria as follows:

1. Participants (P): patients with SIP in permanent mandibular molars referred for endodontic treatment.
2. Intervention (I): primary anaesthetic method administered by combining IANB with BI, LI, or ILI (COMB); or primary IANB technique supplemented with BI, LI, or ILI after IANB failure (SUPP).
3. Comparison (C): IANB.
4. Outcome measure (O): anaesthetic effectiveness determined by absence of pain on electric pulp test (EPT), cold test, visual analogue scale (VAS), and cavity testing.
5. Study Design (S): RCTs

2.5 | Exclusion Criteria

The following exclusion criteria were used:

1. Treatment and interventions performed in animals or in human primary dentition.
2. Sample size not provided.
3. Reported success rates not retrievable.
4. History of analgesic, sedative, anti-depressant, or anxiolytic use that could hamper or affect the pain evaluation.

2.6 | Outcome Measure

The primary outcome measure of this study was successful pulpal anaesthesia in permanent mandibular molars with SIP. The success of pulpal anaesthesia is determined by achieving lip numbness within 5–25 min or the absence of pain during EPT, cold test, and cavity test.

2.7 | Data Extraction

The following parameters were included: study characteristics, population characteristics (gender and age), details of interventions, and anaesthetic success (Table 1).

The authors contacted the corresponding author of any study with missing or incomplete outcome data via email. If the author did not reply within 2 weeks, the request was repeated, and if a response was not received after the second attempt, the data were reported to be not accessible and were excluded from the analysis.

2.8 | Assessment of Risk of Bias

Cochrane risk of bias tool 2 (RoB 2.0 tool) was independently used by two authors (T.R. and O.S.) to determine and assess the quality of the included studies in the following five domains: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results (Sterne et al. 2019).

Any disagreements were resolved through discussion and consensus or by consulting a third reviewer (K.C.). The quality assessment results were categorised into 'low risk', 'some concerns', and 'high risk' of bias.

2.9 | Quality of Evidence

The quality of evidence for the outcome was assessed using the Confidence in Network Meta-Analysis (CINeMA) approach, which is an adaptation of the GRADE framework for NMAs, developed by the Cochrane Comparing Multiple Interventions Methods Group (Nikolakopoulou et al. 2020). The following six domains were evaluated:

1. Within-study bias: The methodological limitations of individual studies were evaluated, focusing on their risk of bias assessment results.
2. Reporting bias: This evaluation determined whether the available evidence provided a comprehensive representation of the research landscape. Particular attention was paid to time lags and gaps between publication years, with comparisons receiving lower quality ratings if these temporal disparities were attributed to changes in treatment regimens or management protocols.
3. Indirectness: Studies were examined according to their adherence to the PICO framework, with 'major concerns' assigned to studies that showed greater divergence from the PICO framework.
4. Imprecision: The uncertainty level in treatment effect estimates was evaluated by examining the width of the confidence interval (CI) to determine the precision of network estimates (Figure S1).
5. Heterogeneity: This domain was assessed by determining whether the prediction intervals and CIs led to different conclusions about clinical significance (using the same zone of equivalence used for the imprecision domain) (Figure S1).
6. Incoherence: This evaluation assessed whether the NMA provided similar estimates when using direct evidence compared to when using indirect evidence.

Each domain was assigned one of three levels of concern (no concerns, some concerns, or major concerns), and the overall assessment resulted in four levels of evidence quality: 'high', 'moderate', 'low', or 'very low' (Nikolakopoulou et al. 2020). Any disagreements were resolved through consultation with a third reviewer (K.C.) until consensus was reached.

TABLE 1 | Characteristics of the included studies.

Study ID	Author and year	Type of intervention	Baseline information	Interventions given, anaesthetic used, volume (mL)	Success/sample size, success (%)	Diagnosis	Evaluation
1	Afkhami et al. (2021)	Combined injections	*Group 1* First molars Age: 31.05 ± 8.36 (18–51) Males: Females 5:15 *Group 2* First molars Age: 31.90 ± 8.00 (18–44) Males: Females 4:16 *Group 3* First molars Age: 30.10 ± 11.22 (18–51) Males: Females 8:12 *Group 4* Second molars Age: 31.05 ± 8.36 (18–51) Males: Females 5:15 *Group 5* Second molars Age: 31.90 ± 8.00 (18–44) Males: Females 4:16 *Group 6* Second molars Age: 30.10 ± 11.22 (18–51) Males: Females 8:12 *Group NMA (Control)* Mandibular molars *Group NMA (Intervention)* Mandibular molars	*Group 1*: *IANB (3.6 mL)* IANB: 4% articaine 1:100 000 epinephrine *Group 2*: *IANB + BI (1.8 + 1.8 mL)* IANB, BI: 4% articaine 1:100 000 epinephrine *Group 3*: *IANB + LI (1.8 + 1.8 mL)* IANB, LI: 4% articaine 1:100 000 epinephrine *Group 4*: *IANB (3.6 mL)* IANB: 4% articaine 1:100 000 epinephrine *Group 5*: *IANB + BI (1.8 + 1.8 mL)* IANB, BI: 4% articaine 1:100 000 epinephrine *Group 6*: *IANB + LI (1.8 + 1.8 mL)* IANB, LI: 4% articaine 1:100 000 epinephrine *Group NMA (Control)*: IANB (3.6 mL) IANB: 4% articaine 1:100 000 epinephrine *Group NMA (Intervention)*: IANB+BI (1.8 ± 1.8 mL) IANB, BI: 4% articaine 1:100 000 epinephrine IANB+LI (1.8 ± 1.8 mL) IANB, LI: 4% articaine 1:100 000 epinephrine	*Group 1* 5/10 (50%) *Group 2* 10/10 (100%) *Group 3* 5/10 (50%) *Group 4* 7/10 (70%) *Group 5* 8/10 (80%) *Group 6* 6/10 (60%) *Group NMA (Control)* 12/20 (60%) *Group NMA (Intervention)* 29/40 (72.5%)	Irreversible pulpitis *Tools*: Hx: mod-severe pain Cold: prolonged response (> 30 s)	HP-VAS Cavity test

(Continues)

TABLE 1 | (Continued)

Study ID	Author and year	Type of intervention	Baseline information	Interventions given, anaesthetic used, volume (mL)	Success/sample size, success (%)	Diagnosis	Evaluation
2	Aggarwal et al. (2009)	Combined injections	*Group 1* Age: 24–37 Males: 14 Females: 10 Mandibular molars *Group 2* Age: 23–36 Males: 16 Females: 14 Mandibular molars *Group 3* Age: 26–37 Males: 15 Females: 15 Mandibular molars *Group NMA* Mandibular molars	*Group 1*: IANB (1.8 mL) IANB: 2% lidocaine 1:200 000 epinephrine *Group 2*: IANB + BI + LI (1.8 + 1.8 + 1.8 mL) IANB, BI, LI: 2% lidocaine 1:200 000 epinephrine *Group 3*: IANB + BI + LI (1.8 + 1.7 + 1.7 mL) IANB: 2% lidocaine 1:200 000 epinephrine BI, LI: 2% articaine 1:200 000 epinephrine *Group NMA*: IANB+BI+LI (1.8 ± 1.8 ± 1.8 mL) IANB, BI, LI: 2% lidocaine 1:200 000 epinephrine IANB+BI+LI (1.8 ± 1.7 ± 1.7 mL) IANB: 2% lidocaine 1:200 000 epinephrine BI, LI: 2% articaine 1:200 000 epinephrine	*Group 1* 8/24 (33%) *Group 2* 14/30 (47%) *Group 3* 20/30 (67%) *Group NMA* 34/60 (56.66%)	Irreversible pulpitis *Tools*: Hx: active pain Cold: prolonged response EPT: responded	HP-VAS Cavity test
3	Aggarwal et al. (2011)	Combined injections	*Group 1* Age: 30 ± 4.00 (24–34) Males: 12 Females: 11 Mandibular molars *Group 2* Age: 31 ± 5.00 (26–35) Males: 11 Females: 13 Mandibular molars	*Group 1*: *IANB (1.8 mL)* IANB: 2% lidocaine 1:200 000 epinephrine *Group 2*: *IANB + BI (1.8 + 1.7 mL)* IANB: 2% lidocaine 1:200 000 epinephrine BI: 4% articaine 1:100 000 epinephrine	*Group 1* 9/23 (39%) *Group 2* 13/24 (54%)	Irreversible pulpitis *Tools*: Hx: active pain Cold: prolonged response EPT: responded	HP-VAS Cavity test

(Continues)

TABLE 1 | (Continued)

Study ID	Author and year	Type of intervention	Baseline information	Interventions given, anaesthetic used, volume (mL)	Success/sample size, success (%)	Diagnosis	Evaluation
4	Aggarwal et al. (2018)	Supplement after failure	*Group 1* Age: N/A Males: N/A Females: N/A Mandibular molars *Group 2* Age: 29 ± 7.00 (19–38) Males: 16 Females: 23 Mandibular molars *Group 3* Age: 30 ± 9.00 (21–43) Males: 23 Females: 15 Mandibular molars *Group NMA*	*Group 1: IANB (1.8 mL)* IANB: 2% lidocaine 1:80 000 epinephrine *Group 2: IANB + ILI (1.8 + 0.4 mL)* IANB, ILI: 2% lidocaine 1:80 000 epinephrine *Group 3: IANB + ILI (1.8 + 1.2 mL)* IANB, ILI: 2% lidocaine 1:80 000 epinephrine *Group NMA*: IANB+ILI (1.8 ± 0.4 mL) IANB+ILI (1.8 ± 1.2 mL) IANB, ILI: 2% lidocaine 1:80 000 epinephrine	*Group 1* 19/97 (19.6%) *Group 2* 25/39 (64.1%) *Group 3* 33/39 (84.6%) *Group NMA* 58/78 (74.5%)	Symptomatic irreversible pulpitis *Tools*: Cold: prolonged response EPT: responded	HP-VAS Cavity test
5	Aggarwal et al. (2019)	Supplement after failure	*Group 1* Age: N/A Males: N/A Females: N/A Mandibular molars *Group 2* Age: 34 ± 9.00 (21–43) Males: 24 Females: 17 Mandibular molars *Group 3* Age: 37 ± 8.00 (23–44) Males: 27 Females: 14 Mandibular molars *Group NMA* Mandibular molars	*Group 1: IANB (1.8 mL)* IANB: 2% lidocaine 1:80 000 epinephrine *Group 2: IANB + ILI (1.8 + 1.2 mL)* IANB, ILI: 2% lidocaine 1:80 000 epinephrine *Group 3: IANB + ILI (1.8 + 1.2 mL)* IANB: 2% lidocaine 1:80 000 epinephrine ILI: 4% articaine 1:100 000 epinephrine *Group NMA*: IANB+ILI (1.8 ± 1.2 mL) IANB, ILI: 2% lidocaine 1:80 000 epinephrine IANB+ILI (1.8 ± 1.2 mL) IANB: 2% lidocaine 1:80 000 epinephrine ILI: 4% articaine 1:100 000 epinephrine	*Group 1* 19/101 (18.8%) *Group 2* 32/41 (78.0%) *Group 3* 27/41 (66.0%) *Group NMA* 59/82 (71.9%)	Symptomatic irreversible pulpitis *Tools*: Carious exposure Hx: active pain Cold: prolonged response EPT: responded	HP-VAS Cavity test

(Continues)

TABLE 1 | (Continued)

Study ID	Author and year	Type of intervention	Baseline information	Interventions given, anaesthetic used, volume (mL)	Success/sample size, success (%)	Diagnosis	Evaluation
6	Aggarwal et al. (2020)	Supplement after failure	*Group 1* Age: N/A Males: N/A Females: N/A Mandibular molars *Group 2* Age: 39 ± 11.00 (25–52) Males: 28 Females: 16 Mandibular molars *Group 3* Age: 37 ± 9.00 (23–48) Males: 27 Females: 17 Mandibular molars *Group NMA* Mandibular molars	*Group 1*: *IANB (1.8 mL)* IANB: 2% lidocaine 1:80 000 epinephrine *Group 2*: *IANB + ILI (1.8 + 1.2 mL)* IANB, ILI: 2% lidocaine 1:80 000 epinephrine *Group 3*: *IANB + ILI (1.8 + 1.2 mL)* IANB: 2% lidocaine 1:80 000 epinephrine ILI: 2% lidocaine 1:200 000 epinephrine *Group NMA*: *IANB+ILI (1.8 ± 1.2 mL)* IANB, ILI: 2% lidocaine 1:80 000 epinephrine *IANB+ILI (1.8 ± 1.2 mL)* IANB: 2% lidocaine 1:80 000 epinephrine ILI: 2% lidocaine 1:200 000 epinephrine	*Group 1* 27/115 (23.5%) *Group 2* 36/44 (82.0%) *Group 3* 25/44 (57.0%) *Group NMA* 61/88 (69.3%)	Symptomatic irreversible pulpitis *Tools*: Carious exposure Hx: active pain Cold: positive and prolonged response	HP-VAS Cavity test

(Continues)

TABLE 1 | (Continued)

Study ID	Author and year	Type of intervention	Baseline information	Interventions given, anaesthetic used, volume (mL)	Success/sample size, success (%)	Diagnosis	Evaluation
7	Aggarwal et al. (2023)	Supplement after failure	*Group 1* Age: N/A Males: N/A Females: N/A Mandibular molars *Group 2* Age: 36.8 ± 8.20 (23–51) Males: 18 Females: 26 Mandibular molars *Group 3* Age: 33.8 ± 10.20 (26–48) Males: 23 Females: 21 Mandibular molars *Group NMA* Mandibular molars	*Group 1*: *IANB (1.8 mL)* IANB: 2% lidocaine 1:80 000 epinephrine *Group 2*: *IANB + ILI (1.8 + 1.2 mL) (4°C)* IANB: 2% lidocaine 1:80 000 epinephrine ILI: 2% lidocaine 1:200 000 epinephrine *Group 3*: *IANB + ILI (1.8 + 1.2 mL)* IANB: 2% lidocaine 1:80 000 epinephrine ILI: 2% lidocaine 1:200 000 epinephrine *Group NMA*: IANB+ILI (1.8 ± 1.2 mL) (4°C) IANB, ILI: 2% lidocaine 1:80 000 epinephrine IANB+ILI (1.8 ± 1.2 mL) IANB: 2% lidocaine 1:80 000 epinephrine ILI: 2% lidocaine 1:200 000 epinephrine	*Group 1* 50/138 (36.2%) *Group 2* 26/44 (59.1%) *Group 3* 23/44 (52.7%) *Group NMA* 49/88 (55.68%)	Symptomatic irreversible pulpitis *Tools*: Carious exposure Hx: active pain Cold: prolonged response EPT: responded	HP-VAS EPT Cavity test
8	Aggarwal, Singla, Gupta, Kumar, et al. (2024)	Supplement after failure	*Group 1* Age: N/A Males: N/A Females: N/A Mandibular molars *Group 2* Age: 28 ± 12.00 (18–59) Males: 21 Females: 14 Mandibular molars	*Group 1*: *IANB (1.8 mL)* IANB: 2% lidocaine 1:80 000 epinephrine *Group 2*: *IANB + ILI (1.8 + 1.2 mL)* IANB, ILI: 2% lidocaine 1:80 000 epinephrine	*Group 1* 48/153 (31.4%) *Group 2* 19/35 (54.0%)	Symptomatic irreversible pulpitis *Tools*: Carious exposure Hx: active pain Cold: prolonged response EPT: responded	HP-VAS EPT Cold test Cavity test

(Continues)

TABLE 1 | (Continued)

Study ID	Author and year	Type of intervention	Baseline information	Interventions given, anaesthetic used, volume (mL)	Success/sample size, success (%)	Diagnosis	Evaluation
9	Aggarwal, Singla, Gupta, Saatchi, et al. (2024)	Supplement after failure	*Group 1* Age: 34 ± 9 (21–50) Males: 25 Females: 15 Mandibular molars *Group 2* Age: 37 ± 11 (20–48) Males: 21 Females: 12 Mandibular molars	*Group 1*: *IANB (1.8 mL)* IANB: 2% lidocaine 1:80 000 epinephrine *Group 2*: *IANB + ILI (1.8 + 1.2 mL)* IANB, ILI: 2% lidocaine 1:80 000 epinephrine	*Group 1* 40/135 (29.6%) *Group 2* 33/47 (70.2%)	Symptomatic irreversible pulpitis *Tools*: Carious exposure Cold: extended response EPT: extended response	HP-VAS Cavity test
10	Ashraf et al. (2013)	Supplement after failure	*Group 1* Age: 40 ± 6.67 (20–60) Males: 47 Females: 55 Mandibular molars *Group 2* Age: 32.5 ± 8.70 Males: 24 Females: 27 Mandibular molars *Group 3* Age: 37.9 ± 10.00 Males: 23 Females: 28 Mandibular molars *Group NMA* Mandibular molars	*Group 1*: *IANB (1.8 mL)* IANB: 2% lidocaine 1:100 000 epinephrine IANB: 4% articaine 1:100 000 epinephrine *Group 2*: *IANB + BI (1.8 + 1.8 mL)* IANB, BI: 2% lidocaine 1:100 000 epinephrine *Group 3*: *IANB + BI (1.8 + 1.8 mL)* IANB, BI: 4% articaine 1:100 000 epinephrine *Group NMA*: IANB + BI (1.8 ± 1.8 mL) IANB, BI: 2% lidocaine 1:100 000 epinephrine IANB, BI: 4% articaine 1:100 000 epinephrine	*Group 1* 17/119 (14.3%) *Group 2* 17/51 (33.3%) *Group 3* 41/51 (80.4%) *Group NMA* 58/102 (56.9%)	Irreversible pulpitis *Tools*: Hx: active pain Cold: prolonged response	HP-VAS Cavity test

(Continues)

TABLE 1 | (Continued)

Study ID	Author and year	Type of intervention	Baseline information	Interventions given, anaesthetic used, volume (mL)	Success/sample size, success (%)	Diagnosis	Evaluation
11	Dianat et al. (2019)	Combined injections	*Group 1* Age: 32.9 ± 10.67 (18–65) Males: 16 Females: 14 Mandibular molars *Group 2* Age: 32.9 ± 10.67 (18–65) Males: 14 Females: 16 Mandibular molars	*Group 1*: *IANB (1.7 mL)* IANB: 2% lidocaine 1:100 000 epinephrine *Group 2*: *IANB + BI (1.7 + 1.7 mL)* IANB: 2% lidocaine 1:100 000 epinephrine BI: 4% articaine 1:100 000 epinephrine	*Group 1* 10/30 (33.3%) *Group 2* 20/30 (66.7%)	Symptomatic irreversible pulpitis *Tools*: Hx: spontaneous pain Cold: moderate to severe lingering pain EPT: responded	HP-VAS EPT Cavity test
12	Gandhi et al. (2021)	Combined injections	*Group 1* Age: 30 ± 8 Males: 16 Females: 14 Mandibular molars *Group 2* Age: 29 ± 8 Males: 15 Females: 15 Mandibular molars *Group 3* Age: 28 ± 7 Males: 17 Females: 13 Mandibular molars *Group NMA* Mandibular molars	*Group 1*: *IANB (1.8 mL)* IANB: 2% lidocaine 1:200 000 epinephrine *Group 2*: *IANB + BI (1.8 + 1.8 mL)* IANB, BI: 2% lidocaine 1:200 000 epinephrine *Group 3*: *IANB + BI (1.8 + 1.8 mL)* IANB: 2% lidocaine 1:200 000 epinephrine BI: 4% articaine 1:200 000 epinephrine *Group NMA*: IANB+BI (1.8 ± 1.8 mL) IANB, BI: 2% lidocaine 1:200 000 epinephrine IANB+BI (1.8 ± 1.8 mL) IANB: 2% lidocaine 1:200 000 epinephrine BI: 4% articaine 1:200 000 epinephrine	*Group 1* 9/30 (30.0%) *Group 2* 15/30 (50.0%) *Group 3* 21/30 (70.0%) *Group NMA* 36/60 (60.0%)	Irreversible pulpitis *Tools*: Hx: moderate to severe active pain Cold: prolonged response EPT: responded	HP-VAS Cavity test

(Continues)

TABLE 1 | (Continued)

Study ID	Author and year	Type of intervention	Baseline information	Interventions given, anaesthetic used, volume (mL)	Success/sample size, success (%)	Diagnosis	Evaluation
13	Gao and Meng (2020)	Supplement after failure	*Group 1* Age: N/A Males: N/A Females: N/A Mandibular molars *Group 2* Age: 39.2 ± 13.2 Males: 24 Females: 28 Mandibular molars *Group 3* Age: 40.1 ± 12.9 Males: 22 Females: 30 Mandibular molars *Group 4* Age: 39.6 ± 13 Males: 22 Females: 30 Mandibular molars *Group NMA* Mandibular molars	*Group 1*: *IANB (1.8 mL)* IANB: 2% lidocaine 1:100 000 epinephrine *Group 2*: *IANB + BI (1.8 + 0.9 mL)* IANB: 2% lidocaine 1:100 000 epinephrine BI: 4% articaine 1:100 000 epinephrine *Group 3*: *IANB + BI (1.8 + 0.9 mL)* IANB, BI: 2% lidocaine 1:100 000 epinephrine *Group 4*: *IANB + BI (1.8 + 0.9 mL)* IANB: 2% lidocaine 1:100 000 epinephrine BI: 2% mepivacaine 1:100 000 epinephrine *Group NMA*: IANB+BI (1.8 ± 0.9 mL) IANB: 2% lidocaine 1:100 000 epinephrine BI: 4% articaine 1:100 000 epinephrine IANB+BI (1.8 ± 0.9 mL) IANB, BI: 2% lidocaine 1:100 000 epinephrine IANB+BI (1.8 ± 0.9 mL) IANB: 2% lidocaine 1:100 000 epinephrine BI: 2% mepivacaine 1:100 000 epinephrine	*Group 1* 64/220 (29.0%) *Group 2* 36/43 (83.7%) *Group 3* 24/42 (57.1%) *Group 4* 26/43 (60.5%) *Group NMA* 86/128 (67.2%)	Irreversible pulpitis *Tools*: Cold: moderate to severe prolonged response EPT: responded	HP-VAS Cold test Cavity test

(Continues)

TABLE 1 | (Continued)

Study ID	Author and year	Type of intervention	Baseline information	Interventions given, anaesthetic used, volume (mL)	Success/sample size, success (%)	Diagnosis	Evaluation
14	Kanaa et al. (2012)	Supplement after failure	*Group 1* Age: 31.9 ± 10 (18–66) Males: 133 Females: 49 Mandibular molars *Group 2* Age: N/A Males: N/A Females: N/A Mandibular molars *Group 3* Age: N/A Males: N/A Females: N/A Mandibular molars *Group NMA* Mandibular molars	*Group 1*: *IANB (2.0 mL)* IANB: 2% lidocaine 1:80 000 epinephrine *Group 2*: *IANB + BI (2.0 + 2.0 mL)* IANB: 2% lidocaine 1:80 000 epinephrine BI: 4% articaine 1:100 000 epinephrine *Group 3*: *IANB + ILI (2.0 + 0.36 mL)* IANB, ILI: 2% lidocaine 1:80 000 epinephrine *Group NMA*: IANB+BI (2.0 ± 2.0 mL) IANB: 2% lidocaine 1:80 000 epinephrine BI: 4% articaine 1:100 000 epinephrine IANB+ILI (2.0 ± 0.36 mL) IANB, ILI: 2% lidocaine 1:80 000 epinephrine	*Group 1* 110/162 (67.9%) *Group 2* 21/25 (84.0%) *Group 3* 9/21 (42.9%) *Group NMA* 30/46 (65.2%)	Symptomatic irreversible pulpitis *Tools*: Already diagnosed (not specified) EPT: responded	Patient's feedback EPT every 2 min Cavity test
15	Monteiro et al. (2015)	Supplement after failure	*Group 1* Age: 33.5 ± 16.5 Males: 4 Females: 16 Mandibular molars *Group 2* Age: 33.5 ± 16.5 Males: 4 Females: 16 Mandibular molars	*Group 1*: *IANB (1.8 mL)* IANB: 2% lidocaine 1:80 000 epinephrine *Group 2*: *IANB + BI (1.8 + 1.7 mL)* IANB: 2% lidocaine 1:80 000 epinephrine BI: 4% articaine 1:100 000 epinephrine	*Group 1* 2/20 (10.0%) *Group 2* 14/18 (77.8%)	Irreversible pulpitis *Tools*: Hx: spontaneous pain Cold: long-lasting moderate to severe pain	HP-VAS EPT Cavity test

(Continues)

TABLE 1 | (Continued)

Study ID	Author and year	Type of intervention	Baseline information	Interventions given, anaesthetic used, volume (mL)	Success/sample size, success (%)	Diagnosis	Evaluation
16	Parirokh et al. (2010)	Combined injections	*Group 1* Age: 26 ± 6.9 Males: 10 Females: 17 Mandibular molars *Group 2* Age: 27.7 ± 7.9 Males: 7 Females: 20 Mandibular molars	*Group 1*: *IANB (1.8 mL)* IANB: 2% lidocaine 1:80 000 epinephrine *Group 2*: *IANB + BI (1.8 + 1.8 mL)* IANB, BI: 2% lidocaine 1:80 000 epinephrine	*Group 1* 4/27 (14.8%) *Group 2* 17/26 (65.4%)	Irreversible pulpitis *Tools*: Hx: spontaneous pain Cold: moderate to severe pain with prolonged response EPT: responded	HP-VAS Cold test Cavity test
17	Parirokh et al. (2014)	Combined injections	*Group 1* Age: 18–52 Males: 15 Females: 21 Mandibular molars *Group 2* Age: 18–52 Males: 16 Females: 17 Mandibular molars	*Group 1*: *IANB (3.6 mL)* IANB: 2% lidocaine 1:80 000 epinephrine *Group 2*: *IANB + BI + ILI (1.8 + 1.8 + 0.5 mL)* IANB, BI, ILI: 2% lidocaine 1:80 000 epinephrine	*Group 1* 8/36 (22.2%) *Group 2* 19/33 (57.6%)	Asymptomatic irreversible pulpitis *Tools*: Cold: prolonged response with moderate to severe pain EPT: responded	HP-VAS Cold test Cavity test

(Continues)

TABLE 1 | (Continued)

Study ID	Author and year	Type of intervention	Baseline information	Interventions given, anaesthetic used, volume (mL)	Success/sample size, success (%)	Diagnosis	Evaluation
18	Rogers et al. (2014)	Supplement after failure	*Group 1* Age: 38 ± 14 Males: 43 Females: 57 Mandibular molars *Group 2* Age: 36 ± 14 Males: 17 Females: 22 Mandibular molars *Group 3* Age: 36 ± 12 Males: 12 Females: 23 Mandibular molars *Group NMA* Mandibular molars	*Group 1*: *IANB (1.7 mL)* IANB: 4% articaine 1:100 000 epinephrine *Group 2*: *IANB + BI (1.7 + 1.7 mL)* IANB, BI: 4% articaine 1:100 000 epinephrine *Group 3*: *IANB + BI (1.7 + 1.8 mL)* IANB: 4% articaine 1:100 000 epinephrine BI: 2% lidocaine 1:100 000 epinephrine *Group NMA*: IANB+BI (1.7 ± 1.7 mL) IANB, BI: 4% articaine 1:100 000 epinephrine IANB+BI (1.7 ± 1.8 mL) IANB: 4% articaine 1:100 000 epinephrine BI: 2% lidocaine 1:100 000 epinephrine	*Group 1* 26/100 (26.0%) *Group 2* 24/39 (62.0%) *Group 3* 13/35 (37.0%) *Group NMA* 37/74 (50.0%)	Symptomatic irreversible pulpitis *Tools*: Hx: moderate to severe spontaneous pain Cold: prolonged response EPT: responded	HP-VAS Cold test Cavity test
19	Saber et al. (2022)	Combined injections	*Group 1* Age: 29 ± 9.1 Males: 15 Females: 25 Mandibular molars *Group 2* Age: 33 ± 5.5 Males: 14 Females: 26 Mandibular molars *Group 3* Age: 29 ± 8.2 Males: 17 Females: 23 Mandibular molars *Group NMA* Mandibular molars	*Group 1*: *IANB (3.6 mL)* IANB: 4% articaine 1:100 000 epinephrine *Group 2*: *IANB + ILI (1.8 + 1.8 mL)* IANB, ILI: 4% articaine 1:100 000 epinephrine *Group 3*: *IANB + BI (1.8 + 1.8 mL)* IANB, BI: 4% articaine 1:100 000 epinephrine *Group NMA*: IANB+ILI (1.8 ± 1.8 mL) IANB, ILI: 4% articaine 1:100 000 epinephrine IANB+BI (1.8 ± 1.8 mL) IANB, BI: 4% articaine 1:100 000 epinephrine	*Group 1* 16/40 (40.0%) *Group 2* 29/40 (72.5%) *Group 3* 26/40 (65.0%) *Group NMA* 55/80 (68.7%)	Symptomatic irreversible pulpitis *Tools*: Hx: spontaneous pain Cold: moderate to severe painful response	VRS Cold test EPT Cavity test

(Continues)

TABLE 1 | (Continued)

Study ID	Author and year	Type of intervention	Baseline information	Interventions given, anaesthetic used, volume (mL)	Success/sample size, success (%)	Diagnosis	Evaluation
20	Shahi et al. (2018)	Combined injections	*Group 1* Age: 18–65 Males: 14 Females: 18 Mandibular molars *Group 2* Age: 18–65 Males: 14 Females: 18 Mandibular molars *Group 3* Age: 18–65 Males: 14 Females: 18 Mandibular molars *Group NMA*: Mandibular molars	*Group 1*: *IANB (1.8 mL)* IANB: 4% articaine 1:100 000 epinephrine *Group 2*: *IANB + BI (1.8 + 0.5 mL)* IANB, BI: 4% articaine 1:100 000 epinephrine *Group 3*: *IANB + ILI (1.8 + 0.4 mL)* IANB, ILI: 4% articaine 1:100 000 epinephrine *Group NMA*: IANB+BI (1.8 ± 0.5 mL) IANB, BI: 4% articaine 1:100 000 epinephrine IANB+ILI (1.8 ± 0.4 mL) IANB, ILI: 4% articaine 1:100 000 epinephrine	*Group 1* 9/32 (28.1%) *Group 2* 21/32 (65.6%) *Group 3* 24/32 (75.0%) *Group NMA* 45/64 (70.3%)	Symptomatic irreversible pulpitis *Tools*: Hx: moderate to severe spontaneous pain Cold: prolonged response	HP-VAS Cavity test
21	Shapiro et al. (2018)	Supplement after failure	*Group 1* Age: 39 ± 15.0 Males: 54[a] Females: 45[a] Mandibular molars *Group 2* Age: 39 ± 14.5 Males: 24[a] Females: 14[a] Mandibular molars *Group 3* Age: 37.5 ± 14.0 Males: 20[a] Females: 17[a] Mandibular molars *Group NMA* Mandibular molars [a]Male–female ratio obtained by subtracting form Rogers 2014	*Group 1*: *IANB (1.7 mL)* IANB: 4% articaine 1:100 000 epinephrine *Group 2*: *IANB + BI (1.7 + 1.7 mL)* IANB, BI: 4% articaine 1:100 000 epinephrine *Group 3*: *IANB + BI (1.7 + 1.7 mL)* IANB: 4% articaine 1:100 000 epinephrine BI: 2% lidocaine 1:100 000 epinephrine *Group NMA*: IANB+BI (1.7 ± 1.7 mL) IANB, BI: 4% articaine 1:100 000 epinephrine IANB+BI (1.7 ± 1.7 mL) IANB: 4% articaine 1:100 000 epinephrine BI: 2% lidocaine 1:100 000 epinephrine	*Group 1* 24/99 (24.2%) *Group 2* 21/38 (55.3%) *Group 3* 23/37 (62.2%) *Group NMA* 44/75 (58.7%)	Symptomatic irreversible pulpitis *Tools*: Hx: moderate to severe pain Cold: lingering sensitivity	HP-VAS Cold test Cavity test

(Continues)

TABLE 1 | (Continued)

Study ID	Author and year	Type of intervention	Baseline information	Interventions given, anaesthetic used, volume (mL)	Success/sample size, success (%)	Diagnosis	Evaluation
22	Silva et al. (2019)	Supplement after failure	*Group 1* Age: 30.8 ± 8.3 Males: 18 Females: 27 Mandibular molars *Group 2* Age: 31.1 ± 8.2 Males: 19 Females: 26 Mandibular molars *Group 3* Age: N/A Males: N/A Females: N/A Mandibular molars *Group 4* Age: N/A Males: N/A Females: N/A Mandibular molars *Group NMA (Control)* Age: 30.9 ± 8.2 Males: 37 Females: 53 Mandibular molars *Group NMA (Intervention)* Mandibular molars	*Group 1*: *IANB (1.8 mL)* IANB: 4% articaine 1:100 000 epinephrine *Group 2*: *IANB (3.6 mL)* IANB: 4% articaine 1:100 000 epinephrine *Group 3*: *IANB + ILI (1.8 + 1.8 mL)* IANB, LI: 4% articaine 1:100 000 epinephrine *Group 4*: *IANB + ILI (3.6 + 1.8 mL)* IANB: 4% articaine 1:100 000 epinephrine *Group NMA (Control)*: IANB (1.8 mL) IANB: 4% articaine 1:100 000 epinephrine IANB (3.6 mL) IANB: 4% articaine 1:100 000 epinephrine *Group NMA (Intervention)*: IANB+ILI (1.8 ± 1.8 mL) IANB, ILI: 4% articaine 1:100 000 epinephrine IANB+ILI (3.6 ± 1.8 mL) IANB, ILI: 4% articaine 1:100 000 epinephrine	*Group 1* 12/45 (27.0%) *Group 2* 19/45 (42.0%) *Group 3* 12/16 (75.0%) *Group 4* 5/12 (42.0%) *Group NMA (Control)* 31/90 (34.4%) *Group NMA (Intervention)* 17/28 (60.7%)	Irreversible pulpitis *Tools*: Hx: moderate to severe spontaneous pain Cold: prolonged response EPT: responded	HP-VAS EPT Cavity test

(Continues)

TABLE 1 | (Continued)

Study ID	Author and year	Type of intervention	Baseline information	Interventions given, anaesthetic used, volume (mL)	Success/sample size, success (%)	Diagnosis	Evaluation
23	Singhal et al. (2022)	Supplement after failure	*Group 1* Age: 18–50 Mandibular molars *Group 2* Mandibular molars *Group 3* Mandibular molars *Group 4* Mandibular molars *Group 5* Mandibular molars *Group NMA* Mandibular molars	*Group 1*: *IANB (1.8 mL)* IANB: 2% lidocaine 1:80 000 epinephrine *Group 2*: *IANB + BI (1.8 + ? mL)* IANB: 2% lidocaine 1:80 000 epinephrine BI: 4% articaine 1:100 000 epinephrine *Group 3*: *IANB + ILI (1.8 + ? mL)* IANB: 2% lidocaine 1:80 000 epinephrine ILI: 4% articaine 1:100 000 epinephrine *Group 4*: *IANB + BI (1.8 + ? mL)* IANB: 2% lidocaine 1:80 000 epinephrine BI: 2% mepivacaine 1:100 000 epinephrine *Group 5*: *IANB + ILI (1.8 + ? mL)* IANB: 2% lidocaine 1:80 000 epinephrine ILI: 2% mepivacaine 1:100 000 epinephrine *Group NMA*: IANB+BI (1.8 + ? mL) IANB: 2% lidocaine 1:80 000 epinephrine BI: 4% articaine 1:100 000 epinephrine IANB: 2% lidocaine 1:80 000 epinephrine BI: 2% mepivacaine 1:100 000 epinephrine IANB+ILI (1.8 + ? mL) IANB: 2% lidocaine 1:80 000 epinephrine BI: 4% articaine 1:100 000 epinephrine IANB: 2% lidocaine 1:80 000 epinephrine ILI: 2% mepivacaine 1:100 000 epinephrine	*Group 1* 146/266 (54.9%) *Group 2* 27/30 (90.0%) *Group 3* 20/30 (66.7%) *Group 4* 21/30 (70.0%) *Group 5* 15/30 (50.0%) *Group NMA* 83/120 (69.2%)	Irreversible pulpitis *Tools*: Hx: cariously exposed with pain prior to treatment EPT: responded and prolonged response	HP-VAS EPT Cavity test

(Continues)

TABLE 1 | (Continued)

Study ID	Author and year	Type of intervention	Baseline information	Interventions given, anaesthetic used, volume (mL)	Success/sample size, success (%)	Diagnosis	Evaluation
24	Singla et al. (2015)	Supplement after failure	*Group 1* Age: N/A Males: N/A Females: N/A Mandibular molars *Group 2* Age: 38 ± 5.2 Males: 37 Females: 36 Mandibular molars *Group 3* Age: 32 ± 4.4 Males: 35 Females: 39 Mandibular molars *Group NMA* Mandibular molars	*Group 1*: *IANB (1.8 mL)* IANB: 4% articaine 1:100 000 epinephrine *Group 2*: *IANB + BI (1.8 + 1.8 mL)* IANB, BI: 4% articaine 1:100 000 epinephrine *Group 3*: *IANB + BI (1.8 + 3.6 mL)* IANB, BI: 4% articaine 1:100 000 epinephrine *Group NMA*: IANB+BI (1.8 ± 1.8 mL) IANB, BI: 4% articaine 1:100 000 epinephrine IANB+BI (1.8 ± 3.6 mL) IANB, BI: 4% articaine 1:100 000 epinephrine	*Group 1* 87/234 (37.2%) *Group 2* 45/73 (61.6%) *Group 3* 47/74 (63.5%) *Group NMA* 92/147 (62.6%)	Symptomatic irreversible pulpitis *Tools*: Hx: active pain Cold: prolonged response EPT: responded	HP-VAS Cavity test
25	Vatankhah et al. (2023)	Combined injections	*Group 1* Age: 37.53 ± 2.22 Males: 21 Females: 15 Mandibular molars *Group 2* Age: 39.81 ± 2.45 Males: 17 Females: 19 Mandibular molars	*Group 1*: *IANB (1.8 mL)* IANB: 2% lidocaine 1:80 000 epinephrine *Group 2*: *IANB + BI (1.8 + 1.7 mL)* IANB: 2% lidocaine 1:80 000 epinephrine BI: 4% articaine 1:100 000 epinephrine	*Group 1* 18/36 (50.0%) *Group 2* 34/36 (94.4%)	Symptomatic irreversible pulpitis *Tools*: Cold: lingering with moderate to severe pain response EPT: responded	HP-VAS EPT Cold test Cavity test
26	Zarei et al. (2012)	Supplement after failure	*Group 1* Age: 18–50 Mandibular molars *Group 2* Age: 27.2 Mandibular molars	*Group 1*: *IANB (1.8 mL)* IANB: 2% lidocaine 1:100 000 epinephrine *Group 2*: *IANB + ILI (1.8 + 1.8 mL)* IANB, ILI: 2% lidocaine 1:100 000 epinephrine	*Group 1* 7/47 (14.9%) *Group 2* 14/20 (70.0%)	Irreversible pulpitis *Tools*: Hx: spontaneous or diffuse pain Cold: severe sensitivity Heat: severe sensitivity	HP-VAS EPT Cold test Cavity test

(Continues)

TABLE 1 | (Continued)

Study ID	Author and year	Type of intervention	Baseline information	Interventions given, anaesthetic used, volume (mL)	Success/sample size, success (%)	Diagnosis	Evaluation
27	Zargar et al. (2021)	Supplement after failure	*Group 1* Mandibular molars *Group 2* Mandibular molars *Group 3* Age: 33.3 ± 11.98 Males: 16 Females: 16 Mandibular molars *Group 4* Age: 33.3 ± 11.98 Males: 16 Females: 16 Mandibular molars *Group NMA (Control)* Mandibular molars *Group NMA (Intervention)* Age: 33.3 ± 11.98 Males: 32 Females: 32 Mandibular molars	*Group 1*: *IANB (1.8 mL)* IANB: 2% lidocaine 1:80 000 epinephrine *Group 2*: *IANB (1.8 mL)* IANB: 4% articaine 1:100 000 epinephrine *Group 3*: *IANB + ILI (1.8 + 0.4 mL)* IANB, ILI: 2% lidocaine 1:80 000 epinephrine *Group 4*: *IANB + ILI (1.8 + 0.4 mL)* IANB, ILI: 4% articaine 1:100 000 epinephrine *Group NMA (Control)*: IANB (1.8 mL) IANB: 2% lidocaine 1:80 000 epinephrine IANB: 4% articaine 1:100 000 epinephrine *Group NMA (Intervention)*: IANB+ILI (1.8 ± 0.4 mL) IANB, ILI: 2% lidocaine 1:80 000 epinephrine IANB+ILI (1.8 ± 0.4 mL) IANB, ILI: 4% articaine 1:100 000 epinephrine	*Group 1* 4/38 (10.5%) *Group 2* 6/38 (15.7%) *Group 3* 23/32 (71.9%) *Group 4* 25/32 (78.1%) *Group NMA (Control)* 10/76 (13.2%) *Group NMA (Intervention)* 48/64 (75%)	Irreversible pulpitis *Tools*: Cold: moderate to severe prolonged pain EPT: responded	HP-VAS EPT Cold test Cavity test

(Continues)

TABLE 1 | (Continued)

Study ID	Author and year	Type of intervention	Baseline information	Interventions given, anaesthetic used, volume (mL)	Success/sample size, success (%)	Diagnosis	Evaluation
28	Zargar et al. (2022)	Supplement after failure	*Group 1* Age: 18–60 Mandibular molars *Group 2* Age: 34.6 ± 9.8 Males: 26 Females: 24 Mandibular molars *Group 3* Age: 34.3 ± 9.7 Males: 23 Females: 27 Mandibular molars *Group NMA* Mandibular molars	*Group 1*: *IANB (1.7 mL)* IANB: 2% lidocaine 1:100 000 epinephrine *Group 2*: *IANB + BI (1.7 + 1.7 mL)* IANB: 2% lidocaine 1:100 000 epinephrine BI: 4% articaine 1:100 000 epinephrine *Group 3*: *IANB + ILI (1.7 + 0.4 mL)* IANB: 2% lidocaine 1:100 000 epinephrine ILI: 4% articaine 1:100 000 epinephrine *Group NMA*: IANB+BI (1.7 ± 1.7 mL) IANB: 2% lidocaine 1:100 000 epinephrine BI: 4% articaine 1:100 000 epinephrine IANB+ILI (1.7 ± 0.4 mL) IANB: 2% lidocaine 1:100 000 epinephrine ILI: 4% articaine 1:100 000 epinephrine	Group 1 37/137 (27.0%) *Group 2* 37/50 (74.0%) *Group 3* 40/50 (80.0%) *Group NMA* 77/100 (77.0%)	Irreversible pulpitis *Tools*: Cold: moderate to severe or lingering pain	HP-VAS EPT Cold test Cavity test

Note: Group NMA was created for the NMA by pooling data from either the intervention or control groups. Cavity test, Initiation of endodontic treatment.
Abbreviations: ?, unspecified information; BI, buccal infiltration; Cold, cold test; EPT, electric pulp test; HP-VAS, Heft-Parker visual analogue scale; Hx, history; IANB, inferior alveolar nerve block; ILI, intraligamentary injection; LI, lingual infiltration; VRS, verbal rating scale.

2.10 | Data Synthesis and Analysis

Data were analysed using STATA version 18 (Stata Corp, College Station, TX, USA). Summary statistics were calculated as risk ratios (RRs) with corresponding 95% CIs. Direct comparisons between COMB and IANB were performed by pairwise meta-analysis with a random-effects model using the restricted maximum likelihood method to account for between-study heterogeneity. For SUPP versus IANB comparisons, we employed conditional probability to accommodate the sequential clinical pathway whereby SUPP was administered to participants with IANB failure. The overall success rate was calculated as: P(Overall success) = P(IANB success) + P(IANB failure) × P(SUPP success|IANB failure). Risk ratios were derived by comparing this sequential success rate with IANB-only rates while accounting for the inherent dependency structure between treatment stages. Heterogeneity among studies was assessed using the I^2 statistic and Cochrane's Q test. An I^2 value greater than 50% indicated significant heterogeneity, and for Cochrane's Q test, a p-value less than 0.05 was considered indicative of heterogeneity.

To combine direct and indirect evidence, we conducted a random-effects NMA using a frequentist approach. In the context of an NMA, inconsistency refers to the statistical disagreement between direct and indirect evidence within the network, which may suggest a lack of transitivity (Veroniki et al. 2013). For inconsistency testing, a forced loop was used to compare direct estimates from the pairwise meta-analysis with indirect estimates from the NMA.

Interventions were ranked based on their efficacy using the surface under the cumulative ranking (SUCRA) curve, with higher SUCRA values indicating greater efficacy (Salanti et al. 2011). For each outcome, league tables were created to present the estimated treatment effects and to rank all included treatments according to their mean ranks and SUCRA values.

For the direct comparisons of COMB versus IANB and SUPP versus IANB, publication bias was evaluated using multiple approaches. We generated comparison-adjusted funnel plots to assess asymmetry in the distribution of study results and applied Egger's regression test to quantitatively evaluate small-study effects. The trim-and-fill method was implemented to estimate the potential impact of missing studies and adjust for publication bias by imputing hypothetically missing studies. For the NMA, we employed both comparison-adjusted and contour-enhanced funnel plots to comprehensively assess publication bias across the network. The contour-enhanced funnel plots were particularly useful in distinguishing publication bias from other sources of funnel plot asymmetry by incorporating statistical significance contours.

2.11 | Sensitivity and Subgroup Analyses

Two sensitivity analysis were performed: one excluding only high-risk studies, and another excluding both high-risk and some-concerns studies. Additional subgroup analysis was performed to examine effects across different effect modifiers: anaesthetic agents for IANB (lidocaine and articaine) and anaesthetic agents for BI and ILI (lidocaine and articaine).

3 | Results

3.1 | Search Results

The comprehensive literature search identified 1159 potentially relevant records (828 from electronic databases, 331 from additional sources). After deduplication, 462 studies remained for title and abstract screening, resulting in 80 studies for full-text assessment. After applying the exclusion criteria as detailed in the PRISMA flowchart (Figure 1), 36 studies were excluded (Table S2). The final analysis included 28 studies that met all eligibility criteria for the NMA.

3.2 | Study Characteristics

3.2.1 | Populations

This NMA synthesised data from 28 RCTs encompassing 3211 participants, divided into combined injections with IANB (COMB; $n = 10$ RCTs) and supplemental injection following IANB failure (SUPP; $n = 18$ RCTs). Detailed characteristics of the included studies are presented in Table 1.

Participants ranged from 18 to 66 years, with mean ages predominantly in the early to mid-30s. Gender distribution was balanced in most trials. Diagnostic methodology varied, with the most common approach integrating patient history, cold testing, and EPT (12 trials), while others used dual methodology or single diagnostic approaches.

3.2.2 | Interventions

Primary IANB used 2% lidocaine or 4% articaine with epinephrine, administered in volumes of 1.7–3.6 mL. Five supplemental techniques were identified: buccal infiltration (BI), lingual infiltration (LI), intraligamentary injection (ILI), and combinations of BI+LI or BI+ILI. Buccal infiltration was the predominant supplemental technique, followed by ILI.

3.2.3 | Outcome Assessment

All studies employed standardised protocols confirming initial IANB success through lip numbness, followed by pulpal anaesthesia verification using EPT, cold testing, or both methods. Successful EPT was defined as achieving maximum readings. Definitive anaesthetic success was evaluated through cavity testing (initiation of access preparation) in all studies. Pain assessment predominantly used the Heft-Parker VAS, with two methodological variations: one study employed the Verbal Rating Scale and another used direct patient verbal feedback. Any reported pain resulted in immediate treatment cessation and classification as anaesthetic failure.

3.3 | Quality of the Included Studies

According to Cochrane Risk of Bias tool 2.0, two studies were identified as having a high risk of bias. One study (Kanaa

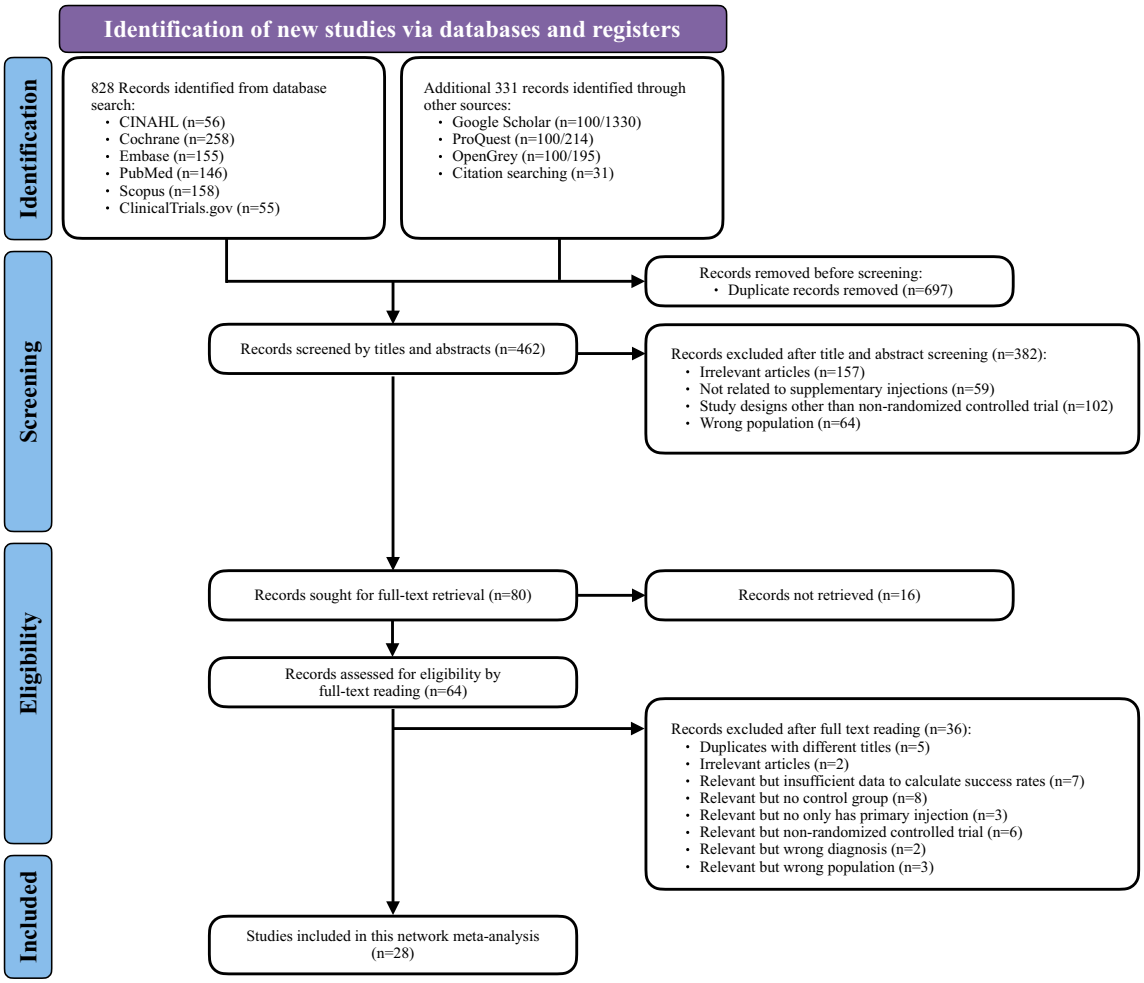

FIGURE 1 | PRISMA flow diagram. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

et al. 2012) exhibited bias due to deviations from the intended interventions, and another study (Monteiro et al. 2015) showed bias in the measurement of outcomes. Among the remaining studies, seven were evaluated as having some concerns—mainly related to the randomization process and selection of reported outcome domains (Zarei et al. 2012; Shapiro et al. 2018; Dianat et al. 2019; Silva et al. 2019; Afkhami et al. 2021; Zargar et al. 2022; Vatankhah et al. 2023). The other 17 studies were assessed as having a low risk of bias (Figure 2).

3.4 | Pairwise Meta-Analysis

The direct pairwise meta-analysis revealed that both SUPP and COMB interventions were significantly more effective in achieving successful pulpal anaesthesia than IANB alone. The comparison between IANB and SUPP revealed an RR of 2.20 ($p < 0.001$; 95% CI, 1.73–2.81; $I^2 = 9.65\%$), indicating a statistically significant advantage of SUPP (Figure S2A). Similarly, the comparison between IANB and COMB yielded an RR of 1.82 ($p < 0.001$; 95% CI, 1.54–2.16; $I^2 = 7.72\%$), favouring COMB over IANB alone (Figure S2B).

Sensitivity analyses were also performed by excluding studies with a high risk of bias (Kanaa et al. 2012; Monteiro et al. 2015) and studies with some concerns (Zarei et al. 2012; Shapiro et al. 2018; Dianat et al. 2019; Silva et al. 2019; Afkhami et al. 2021; Zargar et al. 2022; Vatankhah et al. 2023) to high risk of bias. The results of the sensitivity analyses remained in a similar trend with low heterogeneity (Figure S3).

Publication bias was evaluated using funnel plots for both the COMB versus IANB and SUPP versus IANB comparisons, with Egger's regression test quantifying the degree of asymmetry (Figure S4A,B). While both comparisons exhibited asymmetry in their funnel plots and $p < 0.1$ in Egger's regression test, subsequent analysis using the trim-and-fill method demonstrated the robustness of our findings, as the adjusted RRs and 95% CIs maintained their direction of effect favouring both interventions over IANB alone (Figure S4C,D).

3.5 | Network Map

To indirectly compare the effect estimates between COMB and SUPP interventions, all included studies were categorised into three groups (Figure 3): IANB alone, COMB and SUPP. Two direct comparisons were identified within this network—IANB versus COMB and IANB versus SUPP—with IANB serving as the common comparator. After pooling the data, 18 trials compared IANB and SUPP, while 10 trials examined IANB and COMB.

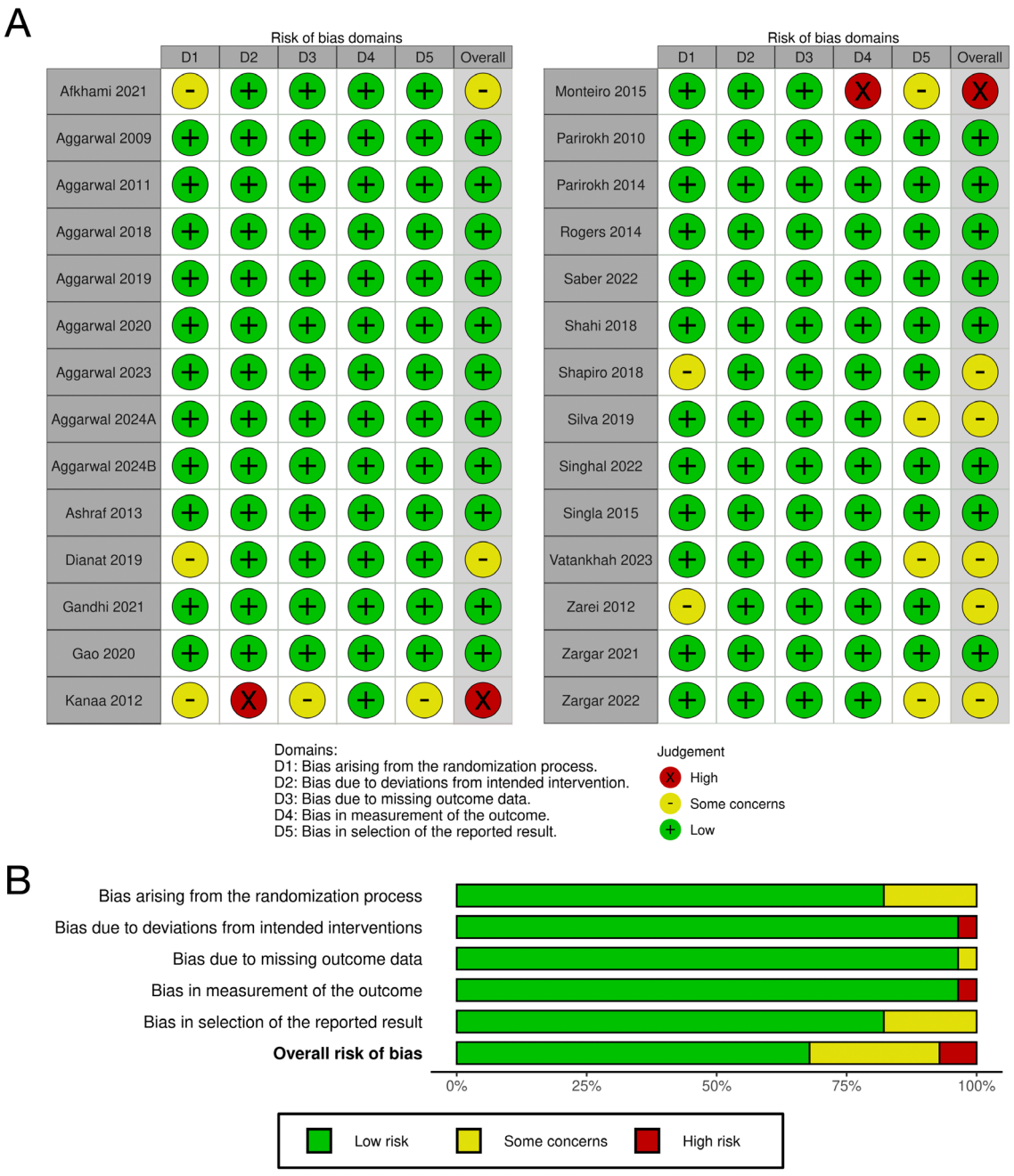

FIGURE 2 | (A) Summary of the risk of bias in the included studies. (B) Distribution of the risk of bias across the domains.

Due to the open-loop nature of the network map—where there is no direct comparison between COMB and SUPP—a consistency model was fitted for the analysis. This approach assumes that the indirect evidence is consistent and allows for the estimation of the effect size between COMB and SUPP through their common comparator (IANB).

3.6 | NMA and Ranking Probabilities

The head-to-head comparison results of the RRs for anaesthetic success for each intervention administered to teeth with SIP are shown in the league table (Table 2). The highest-ranking clinical intervention for anaesthetic success was SUPP (RR = 2.02; 95% CI, 1.55–2.65), followed by COMB (RR = 1.86; 95% CI, 1.50–2.30). The ranking probabilities and SUCRA for anaesthetic success were 85.1% for SUPP and 64.9% for COMB. However, the RRs between COMB and SUPP were not significant since 95% CIs included the value '1' (RR = 1.09; 95% CI, 0.78–1.51).

3.7 | Sensitivity and Subgroup Analyses

Sensitivity analyses were conducted to evaluate the robustness of our NMA findings by excluding studies with high risk of bias and studies with some concerns to high risk of bias. Both sensitivity analyses revealed that the RRs in the SUPP versus COMB comparison did not achieve statistical significance, as evidenced by the 95% CIs consistently including the no-effect value.

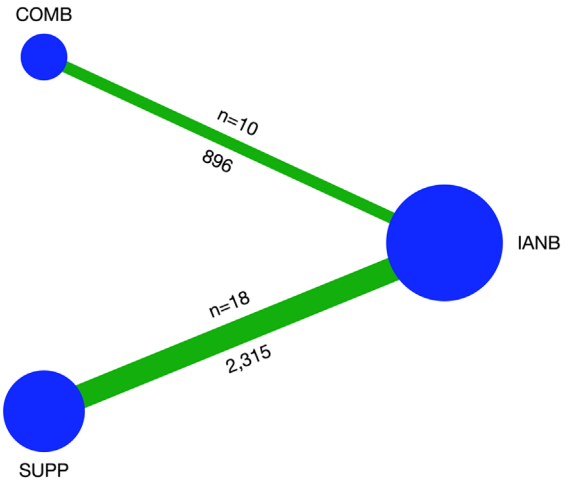

FIGURE 3 | Network map illustrating the two direct comparisons, COMB versus IANB and SUPP versus IANB, with IANB serving as the common comparator. The size of each node is proportional to the total number of participants receiving that intervention. The width of each connecting line reflects the number of trials comparing each pair in the direct comparisons. Numbers above the lines indicate the number of trials for each comparison, while numbers below the lines represent the total number of participants involved. The colour of the lines denotes the average risk of bias for each comparison, with green lines indicating a low risk of bias on average. COMB, combined injections with IANB; IANB, inferior alveolar nerve block alone; SUPP, supplement injections after IANB failure.

TABLE 2 | League table of anaesthetic success.

SUPP	—	—
1.09 (0.78, 1.51)	COMB	—
2.02 (1.55, 2.65)[a]	1.86 (1.50, 2.30)[a]	IANB

Note: NMA results are expressed in risk ratios (RR) and 95% confidence intervals (95% CI). A comparison should be read from left to right, and the estimate should be located at the intersection of the column- and row-defining interventions. An RR value higher than 1 suggests that the column group has a higher anaesthetic success tendency than the row group. When RR value is > 1, the column-intervention is favoured over the row-intervention.
Abbreviations: COMB, combined injections with IANB; IANB, inferior alveolar nerve block alone; SUPP, supplement injections after IANB failure.
[a]Statistical significance.

In the initial sensitivity analysis (Table 3) excluding studies with high risk of bias (Matthews et al. 2009; Kanaa et al. 2012), the hierarchical effectiveness demonstrated in the primary analysis was maintained, with SUPP emerging as the higher ranking intervention (RR = 2.18; 95% CI, 1.68–2.83), followed by COMB (RR = 1.82; 95% CI, 1.50–2.30). A subsequent analysis, excluding both high-risk studies and those with some concerns (Zarei et al. 2012; Shapiro et al. 2018; Dianat et al. 2019; Silva et al. 2019; Afkhami et al. 2021; Zargar et al. 2022; Vatankhah et al. 2023), yielded concordant results (SUPP: RR = 2.10; 95% CI, 1.57–2.80; COMB: RR = 1.98; 95% CI, 1.59–2.47).

Subgroup analyses were performed based on anaesthetic agents (lidocaine and articaine) and anaesthetic techniques. The findings of the analyses examining IANB with articaine and infiltration with articaine were consistent with the primary NMA findings, and the RRs and 95% CIs in the SUPP versus COMB comparison remained statistically non-significant.

In this analysis, SUPP maintained its ranking as the higher-ranking intervention followed by COMB. However, distinctive patterns emerged in subgroups utilising lidocaine with IANB, lidocaine infiltration, and articaine ILI, in which COMB ranked higher than SUPP. However, despite these variations in ranking, the RRs between COMB and SUPP within these subgroups did not achieve statistical significance (Table 3).

3.8 | Test for Inconsistency

Due to the open-loop structure of our network, where interventions were connected only through the common IANB comparator, global consistency testing could not be performed. As described by Lumley (2002), inconsistency assessment requires closed loops where both direct and indirect evidence can be compared (Lumley 2002). Given this network configuration, we modified our approach to assess inconsistency by examining comparisons with available direct evidence (COMB vs. IANB and SUPP vs. IANB) by modifying the node-splitting test proposed by Dias et al. (2010) (Dias et al. 2010). Comparison between the direct estimates from pairwise meta-analysis and mixed evidence from NMA revealed no significant differences in their respective 95% CIs, indicating consistent evidence across these comparisons (Nikolakopoulou et al. 2020; Papakonstantinou et al. 2020).

3.9 | Publication Bias in NMA

In this NMA, publication bias was evaluated using two complementary approaches. First, examination of the comparison-adjusted funnel plot (Figure S5A) revealed asymmetry characterised by the absence of small studies with high standard errors and unfavourable effect estimates. This pattern suggests potential publication bias, as smaller studies with non-significant or negative findings may be underrepresented in the literature.

Further analysis using a contour-enhanced funnel plot (Figure S5B) demonstrated that potentially missing studies would likely fall within the non-significant region ($p > 0.1$ or 10%). This observation suggests the presence of small-study effects, where smaller studies with non-significant results are less frequently published or more difficult to identify and include in systematic reviews and meta-analyses. However, as these potentially missing studies would be characterised by small sample sizes and non-significant effects, their inclusion would likely not substantially alter our effect estimates.

3.10 | CINeMA Summary of Evidence

The quality of evidence was assessed using the CINeMA tool, which evaluates six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence. Across all comparisons (Figure 4), there were no serious concerns regarding within-study bias, reporting bias, or indirectness.

TABLE 3 | Treatment effects of all interventions compared with those of inferior alveolar nerve block (IANB) expressed in risk ratios with 95% confidence interval and SUCRA.

	SUPP		COMB	
Results	**Risk ratio (95% CI)**	**SUCRA (%)**	**Risk ratio (95% CI)**	**SUCRA (%)**
Primary analysis of the NMA	**2.02 (1.55–2.30)**	**85.1**	1.86 (1.50–2.30)	64.9
Sensitivity				
Exclude high RoB	**2.18 (1.68–2.83)**	**94.2**	1.82 (1.53–2.15)	55.8
Exclude some concerns to high RoB	**2.10 (1.57–2.80)**	**81.1**	1.98 (1.59–2.47)	68.9
Subgroup				
IANB with lidocaine	1.94 (1.37–2.74)	72.8	**2.00 (1.52–2.62)**	**77.2**
IANB with articaine	**1.89 (1.12–3.18)**	**83.3**	1.64 (1.18–2.27)	66.2
Infiltrate with lidocaine	1.79 (1.28–2.52)	70.0	**1.95 (1.17–3.26)**	**79.7**
Infiltrate with articaine	**2.09 (1.70–2.57)**	**91.6**	1.77 (1.38–2.27)	58.4
ILI with articaine	1.80 (0.99–3.30)	68.2	**2.07 (0.93–4.60)**	**78.2**

Note: Bold text indicates the superior intervention in each analysis.
Abbreviations: COMB, combined injections with IANB; IANB, inferior alveolar nerve block alone; ILI, intraligamentary injections; NMA, network meta-analysis; RoB, risk of bias; SUCRA, surface under the cumulative ranking; SUPP, supplement injections after IANB failure.

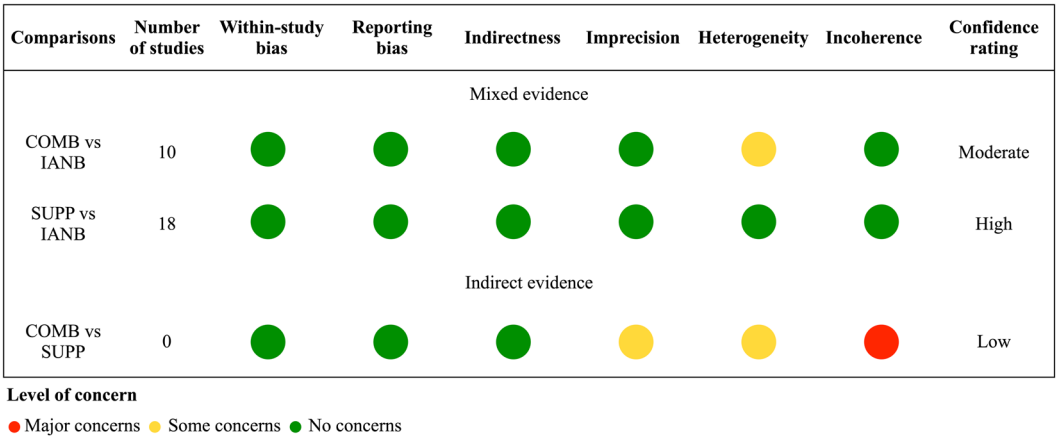

FIGURE 4 | CINeMA summary of evidence. Final output of CINeMA for the network of SUPP, COMB, and IANB alone. The table shows the level of concern in each of the six domains for each comparison. CINeMA, confidence in network meta-analysis; COMB, combined injections with IANB; IANB, inferior alveolar nerve block alone; SUPP, supplement injections after IANB failure.

However, major concerns were identified in specific domains for certain comparisons. In the case of imprecision, the COMB versus IANB and SUPP versus IANB comparisons revealed no issues, whereas the COMB versus SUPP comparison showed major concerns. In terms of heterogeneity, significant concerns were noted in the COMB versus IANB comparison, while the other comparisons did not reveal heterogeneity based on prediction intervals. Regarding incoherence, major concerns arose solely in the indirect comparison between COMB and SUPP, which was attributed to the open-loop nature of our network.

The overall confidence in the evidence was rated as high for the SUPP versus IANB comparison and low for both the COMB versus IANB and COMB versus SUPP comparisons (Figure 4).

4 | Discussion

4.1 | Efficacy of SUPP and COMB Over IANB

The results of our NMA confirmed that both SUPP and COMB significantly outperform IANB alone in achieving successful anaesthesia in SIP. This finding is consistent with those of previous studies, which have demonstrated the superior efficacy of SUPP over IANB alone, with supplemental injections following IANB failure achieving success rates as high as 90% when using BI with articaine (Singhal et al. 2022) or 84% when using ILI with lidocaine (Aggarwal et al. 2018). Similarly, COMB, such as BI or ILI administered alongside IANB, consistently yielded superior outcomes to those of IANB alone (Afkhami et al. 2021; Vatankhah et al. 2023). Our pairwise meta-analysis further reinforced the superiority of both SUPP and COMB over

IANB alone, which was in agreement with the findings of previous pairwise meta-analyses (Dias-Junior et al. 2021; Gupta et al. 2021). However, our study included and comprehensively assessed more combinations, such as ILI plus IANB or BI plus ILI plus IANB, which were not evaluated in these prior analyses (Tupyota et al. 2018; Dias-Junior et al. 2021; Gupta et al. 2021; Gupta et al. 2022) (Table S3).

4.2 | Comparable Efficacy of SUPP and COMB

The evaluation of relative efficacy between SUPP and COMB has been limited by the absence of direct comparative RCTs, possibly due to ethical concerns regarding the methodology of intentionally allowing IANB failure before supplementing with additional injections. Our NMA methodology circumvented this limitation through indirect comparisons. The findings of this NMA not only contribute substantively to the existing evidence base but also potentially eliminate the necessity for additional comparative RCTs between these techniques (Lumley 2002).

The observed similarity in anaesthetic efficacy between SUPP and COMB interventions can be attributed to several factors. Both therapeutic approaches effectively address the anatomical challenges associated with IANB failure, including accessory innervations and anatomical variations (Malamed 2011). The evidence from our analysis demonstrates that supplemental injections, despite being administered sequentially after IANB failure, possess sufficient anaesthetic potency to overcome both peripheral and central sensitisation mechanisms characteristic of SIP. The similar level of effectiveness manifests in comparable success rates between SUPP and COMB approaches, irrespective of their different administration routes or types of anaesthetic solutions. This finding suggests that the pain experienced during endodontic treatment following IANB failure does not significantly compromise the effectiveness of subsequent supplemental anaesthetic injections. The robustness of these findings is further validated by their consistency across various subgroup analyses and subsequent sensitivity analyses.

4.3 | Clinical Applications

Given the comparable anaesthetic efficacy of SUPP and COMB, clinicians should consider other factors when choosing between these two strategies. While both approaches offer similar efficacy in managing SIP, patient comfort, anxiety levels, and overall treatment experience should be considered when selecting an anaesthetic technique. Successful anaesthesia significantly influences both patient comfort and psychological well-being, with failed anaesthesia potentially triggering a vicious cycle in which unexpected pain heightens anxiety, which in turn lowers pain thresholds and increases pain perception (Lautch 1971; Weisenberg et al. 1984; van Wijk and Makkes 2008). This relationship is particularly significant given the well-documented correlation between anxiety levels and perceived pain during dental procedures (Sanikop et al. 2011), suggesting that the selection of anaesthetic technique should incorporate considerations of patient comfort, anxiety levels, and overall treatment experience alongside technical efficacy.

Careful evaluation of the distinct clinical characteristics and implementation approaches between SUPP and COMB is required in order to choose between the two techniques. The COMB technique offers immediate and comprehensive anaesthesia through its initial delivery of higher anaesthetic volumes, aligning with contemporary goals of painless dentistry through rapid and profound pain control. This approach may be particularly advantageous in urgent clinical scenarios, potentially expediting treatment by reducing chair time compared to that with SUPP. In contrast, the SUPP strategy, which employs a more conservative approach by first verifying IANB failure before administering additional anaesthetic agents, potentially optimises total anaesthetic volume while maintaining comparable effectiveness. This selective method proves particularly valuable in cases in which IANB alone achieves successful pulpal anaesthesia, despite its generally low success rates. Both techniques present unique advantages: COMB's immediate profound anaesthetic effects benefit anxious patients, while SUPP's measured approach may better serve those requiring minimal anaesthetic exposure. When choosing between these techniques, clinicians must carefully weigh the benefits of COMB's immediate pain control against SUPP's conservative volume administration, while considering individual patient factors, such as anxiety levels, previous dental experiences, and overall treatment comfort preferences.

The choice between these techniques should be guided by a comprehensive evaluation of individual patient factors. COMB's immediate profound anaesthetic effect may be better for anxious patients or urgent clinical situations, while SUPP's measured approach might be preferable for patients requiring minimal anaesthetic exposure. Clinicians must consider multiple factors, including medical history, body weight, anxiety levels, previous dental experiences, and the urgency of the clinical situation, to ensure both safety and efficacy while maintaining alignment with contemporary standards of painless dentistry.

The practical value of these findings is strengthened by our focus on readily available supplemental techniques. BI, LI, and ILI can be performed with standard dental syringes and needles found in every dental office. Unlike intraosseous injections that require specialised equipment or intrapulpal injections that need prior cavity preparation, these three techniques are immediately accessible to all practitioners. The approach is particularly valuable in diverse clinical settings, from private practices to community health centres, ensuring that evidence-based pain management for SIP is available regardless of resource limitations.

4.4 | Strengths

The main strength of this study lies in its comprehensive search strategy, strict adherence to the PICO framework, and careful evaluation of diagnostic criteria. We prioritised sensitivity in our NMA by extensively using the Boolean operator 'OR' across multiple keywords within each PICO component (Methley et al. 2014), thereby enhancing the likelihood of capturing all

relevant studies while minimising the risk of missing pertinent research. Consequently, 28 RCTs were identified and included in our analyses. To ensure clinical transitivity, a fundamental assumption in NMA, we applied strict inclusion criteria, focusing on RCTs that specifically compared IANB alone versus SUPP or IANB alone versus COMB in human permanent mandibular molars with SIP. This methodological decision ensured that the treatment effects observed were theoretically comparable across different trials, thereby validating the indirect comparison between SUPP and COMB and strengthening the reliability of our findings. Additionally, we carefully evaluated diagnostic methods during study selection, including studies that used different terms (Aggarwal et al. 2009, 2011; Parirokh et al. 2010, 2014; Zarei et al. 2012; Ashraf et al. 2013; Monteiro et al. 2015; Silva et al. 2019; Gao and Meng 2020; Afkhami et al. 2021; Gandhi et al. 2021; Zargar et al. 2021, 2022; Singhal et al. 2022) but diagnostic protocols consistent with key indicators of SIP, such as a history of active or spontaneous pain and prolonged or lingering response to cold tests. This approach ensured comprehensive data inclusion while maintaining methodological integrity.

4.5 | Limitations

Despite the strengths of our study, some limitations need to be acknowledged. The primary limitation stems from the open-loop network structure of our NMA, which lacks direct comparisons between the SUPP and COMB strategies. Consequently, we were unable to globally test for inconsistency (referred to as incoherence in CINeMA) within the network (Salanti et al. 2014). According to the CINeMA framework, the absence of direct head-to-head evidence automatically downgrades the quality of evidence, as indirect estimates are generally less robust than direct comparisons (Nikolakopoulou et al. 2020). Therefore, the confidence in the effects between COMB and SUPP was rated as low by CINeMA, largely due to the incoherence resulting from the open-loop nature of our study. While concerns about imprecision were minimal, the presence of heterogeneity in the COMB versus IANB and COMB versus SUPP comparisons may have affected conclusions about clinical significance. Overall, the confidence ratings assigned by CINeMA were high for the SUPP versus IANB comparison, moderate for the COMB versus IANB comparison, and low for the COMB versus SUPP comparison.

Several potential confounding factors may have influenced our observed results and merit careful consideration. The heterogeneity of anaesthetic agents and volumes across included studies represents a primary concern, with studies employing varying concentrations of lidocaine and articaine at different volumes for both IANB and supplemental techniques. Clinical and methodological heterogeneity introduced additional confounding potential through variations in diagnostic criteria for SIP, assessment timing, and outcome measurement approaches. Patient-related factors including age distribution, gender balance, and baseline anxiety levels may have also influenced pain perception and anaesthetic requirements.

However, our study's PICOS framework specifically focused on comparing anaesthetic strategies (SUPP vs. COMB) rather than individual agent types or volumes as primary interventions. Although these factors represent potential confounders that could influence absolute success rates, our research objective was to compare the relative effectiveness of treatment strategies rather than optimise specific anaesthetic formulations.

Our NMA approach provided several methodological controls against confounding bias through careful restriction to homogeneous populations, consistent primary outcomes, and sensitivity analyses excluding studies with methodological concerns. These analyses demonstrated robust findings with treatment rankings remaining consistent across analytical approaches, supporting the clinical validity of our comparative effectiveness estimates between SUPP and COMB strategies. Another key limitation involves potential violations of the transitivity assumption when comparing SUPP and COMB strategies through indirect comparisons. The transitivity assumption requires similar patient populations across studies to enable valid NMA. However, fundamental differences exist in patient selection between these approaches. SUPP studies analyse outcomes in patients who failed initial IANB, representing a subset with demonstrated anaesthetic failure that may indicate more challenging clinical conditions, anatomical variations, or heightened inflammatory states. In contrast, COMB studies evaluate outcomes across the entire patient population, including both those who would succeed with IANB alone and those requiring additional intervention. This creates distinct clinical contexts where SUPP effectiveness is measured in patients who experienced IANB failure while COMB effectiveness reflects outcomes across a more heterogeneous population. These population differences may confound indirect comparisons between strategies, as treatment effect estimates derive from fundamentally different patient contexts, potentially introducing bias into our NMA results.

4.6 | Future Directions

While our NMA provides valuable insights into the comparative efficacy of SUPP and combined COMB injection techniques for managing SIP in mandibular molars, several promising research directions warrant further investigation. Future studies should expand the scope of research beyond anaesthetic success rates to explore patient-centred outcomes, particularly focusing on the relationship between preoperative anxiety levels and patient response to different anaesthetic techniques. This approach could facilitate the development of more personalised treatment protocols based on individual patient characteristics. Given the well-established lower anaesthetic efficacy of IANB alone for ensuring pulpal anaesthesia than that of COMB or SUPP, future studies should use these more advanced techniques as their baseline for comparison. For instance, researchers could use IANB plus BI in a control group for testing different anaesthetic techniques or different anaesthetic solutions. This research direction would build upon our current findings and help develop better, more personalised anaesthetic approaches for treating SIP in mandibular molars.

5 | Conclusions

Our NMA, with low confidence in the quality of evidence, demonstrates comparable anaesthetic efficacy between SUPP and COMB for treating SIP in mandibular molars. This finding

suggests that the choice between these two approaches should be guided by patient-specific factors, particularly anxiety levels and psychological well-being. Importantly, both SUPP and COMB strategies showed significantly superior effectiveness compared to IANB alone. These results support the routine implementation of either SUPP or COMB techniques to enhance anaesthetic success in endodontic treatments for mandibular molars affected by SIP, as they provide a clear advantage over traditional IANB-only approaches.

Author Contributions

Thanatpong Rujirawan: data curation (equal), formal analysis (supporting) investigation (equal), methodology (equal), project administration (equal), validation (equal), visualisation (equal), writing – original draft preparation (equal), writing – review and editing (equal). Sittichoke Osiri: conceptualization (lead), data curation (equal), formal analysis (lead), investigation (equal), methodology (equal), project administration (equal), resources (equal), supervision (equal), validation (equal), visualisation (equal), writing – original draft preparation (equal), writing – review and editing (equal). Kanet Chotvorrarak: investigation (supporting), methodology (equal), project administration (equal), supervision (equal), validation (equal), visualisation (equal), writing – original draft preparation (equal), writing – review and editing (equal).

Disclosure

Relevant reporting guidelines paperwork: This study used the PRISMA for NMA checklist, which is the reporting guideline for network meta-analyses.

Registration: This study was registered in the PROSPERO database (CRD42024579494).

Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data supporting the findings of this study are available within the article and its Supporting Information. The supporting raw data are available from the corresponding author.

References

Afkhami, F., S. Pirmoazen, A. Ardestani, and M. J. K. Fard. 2021. "Comparative Evaluation of Anesthetic Efficacy of Inferior Alveolar Nerve Block and Inferior Alveolar Nerve Block Plus Buccal or Lingual Infiltration Using Articaine in Mandibular Molars With Irreversible Pulpitis: A Preliminary Prospective Randomized Single-Blind Clinical Trial." *Quintessence International* 52: 820–826.

Aggarwal, V., A. Jain, and D. Kabi. 2009. "Anesthetic Efficacy of Supplemental Buccal and Lingual Infiltrations of Articaine and Lidocaine After an Inferior Alveolar Nerve Block in Patients With Irreversible Pulpitis." *Journal of Endodontics* 35: 925–929.

Aggarwal, V., M. Singla, A. Gupta, U. Kumar, and M. Saatchi. 2024. "Effect of Intraligamentary Tramadol Hydrochloride on Anesthetic Success During Endodontic Management of Mandibular Molars: A Randomized Clinical Controlled Trial." *European Endodontic Journal* 9: 99–105.

Aggarwal, V., M. Singla, A. Gupta, et al. 2024. "Effect of Back-Pressure Anesthesia on Postoperative Pain After the Endodontic Treatment in Patients With Symptomatic Irreversible Pulpitis: Randomized Double-Blind Clinical Trial." *Journal of Endodontics* 50: 1037–1043.

Aggarwal, V., M. Singla, S. Miglani, and S. Kohli. 2019. "Efficacy of Articaine Versus Lidocaine Administered as Supplementary Intraligamentary Injection After a Failed Inferior Alveolar Nerve Block: A Randomized Double-Blind Study." *Journal of Endodontics* 45: 1–5.

Aggarwal, V., M. Singla, S. Miglani, S. Kohli, V. Sharma, and S. S. Bhasin. 2018. "Does the Volume of Supplemental Intraligamentary Injections Affect the Anaesthetic Success Rate After a Failed Primary Inferior Alveolar Nerve Block? A Randomized-Double Blind Clinical Trial." *International Endodontic Journal* 51: 5–11.

Aggarwal, V., M. Singla, A. Rizvi, and S. Miglani. 2011. "Comparative Evaluation of Local Infiltration of Articaine, Articaine Plus Ketorolac, and Dexamethasone on Anesthetic Efficacy of Inferior Alveolar Nerve Block With Lidocaine in Patients With Irreversible Pulpitis." *Journal of Endodontics* 37: 445–449.

Aggarwal, V., M. Singla, M. Saatchi, A. Gupta, M. Hasija, and B. Meena. 2023. "Effect of Cooling of Lidocaine With Epinephrine on the Anesthetic Success of Supplementary Intraligamentary Injection After a Failed Primary Inferior Alveolar Nerve Block: A Randomized Controlled Trial." *European Endodontic Journal* 8: 239–245.

Aggarwal, V., M. Singla, M. Saatchi, and M. Hasija. 2020. "Anaesthetic Efficacy of 2% Lidocaine With Different Concentrations of Epinephrine (1:80,000 and 1:200,000) in Intraligamentary Injection After a Failed Primary Inferior Alveolar Nerve Block: A Randomized Double-Blind Study." *Acta Odontologica Scandinavica* 78: 275–280.

Almadhoon, H. W., R. W. Abuiriban, H. Almassri, and F. S. Al-Hamed. 2022. "Efficacy of 4% Articaine Buccal Infiltration Versus Inferior Alveolar Nerve Block for Mandibular Molars With Symptomatic Irreversible Pulpitis: A Systematic Review and Meta-Analysis." *Journal of Evidence-Based Dental Practice* 22: 101712.

Ashraf, H., M. Kazem, O. Dianat, and F. Noghrehkar. 2013. "Efficacy of Articaine Versus Lidocaine in Block and Infiltration Anesthesia Administered in Teeth With Irreversible Pulpitis: A Prospective, Randomized, Double-Blind Study." *Journal of Endodontics* 39: 6–10.

Berman, L. H., and K. M. Hargreaves. 2020. *Cohen's Pathways of the Pulp: Cohen's Pathways of the Pulp*. Elsevier Health Sciences.

Dianat, O., M. A. Mozayeni, M. K. Layeghnejad, and S. Shojaeian. 2019. "The Efficacy of Supplemental Intraseptal and Buccal Infiltration Anesthesia in Mandibular Molars of Patients With Symptomatic Irreversible Pulpitis." *Clinical Oral Investigations* 24: 1281–1286.

Dias, S., N. J. Welton, D. M. Caldwell, and A. E. Ades. 2010. "Checking Consistency in Mixed Treatment Comparison Meta-Analysis." *Statistics in Medicine* 29: 932–944.

Dias-Junior, L., A. Bezerra, D. Schuldt, et al. 2021. "Effectiveness of Different Anesthetic Methods for Mandibular Posterior Teeth With Symptomatic Irreversible Pulpitis: A Systematic Review and Meta-Analysis." *Clinical Oral Investigations* 25: 6477–6500.

Dureja, G. P., R. N. Iyer, G. Das, J. Ahdal, and P. Narang. 2017. "Evidence and Consensus Recommendations for the Pharmacological Management of Pain in India." *Journal of Pain Research* 10: 709–736.

Fowler, S., M. Drum, A. Reader, and M. Beck. 2016. "Anesthetic Success of an Inferior Alveolar Nerve Block and Supplemental Articaine Buccal Infiltration for Molars and Premolars in Patients With Symptomatic Irreversible Pulpitis." *Journal of Endodontics* 42: 390–392.

Gandhi, S. A., S. Das, A. Das, Y. Agnihotri, R. V. Mohan, and V. R. Dasu Subramanian. 2021. "Anaesthetic Efficacy of Lidocaine and Articaine

in Inferior Alveolar Nerve Block Combined With Buccal Infiltration in Patients With Irreversible Pulpitis." *Journal of Pharmacy & Bioallied Sciences* 13: S731–s734.

Gao, X., and K. Meng. 2020. "Comparison of Articaine, Lidocaine and Mepivacaine for Buccal Infiltration After Inferior Alveolar Nerve Block in Mandibular Posterior Teeth With Irreversible Pulpitis." *British Dental Journal* 228: 605–608.

Gupta, A., A. Sahai, V. Aggarwal, et al. 2021. "Anesthetic Efficacy of Primary and Supplemental Buccal/Lingual Infiltration in Patients With Irreversible Pulpitis in Human Mandibular Molars: A Systematic Review and Meta-Analysis." *Journal of Dental Anesthesia and Pain Medicine* 21: 283–309.

Gupta, A., J. Wadhwa, V. Aggarwal, et al. 2022. "Anesthetic Efficacy of Supplemental Intraligamentary Injection in Human Mandibular Teeth With Irreversible Pulpitis: A Systematic Review and Meta-Analysis." *Journal of Dental Anesthesia and Pain Medicine* 22: 1–10.

Hargreaves, K., and K. Keiser. 2002. "Local Anesthetic Failure in Endodontics: Mechanisms and Management." *Endodontic Topics* 1: 26–39.

Hargreaves, K. M., H. E. Goodis, and F. R. Tay. 2012. *Seltzer and Bender's Dental Pulp*. Quintessence Pub.

Hutton, B., G. Salanti, D. M. Caldwell, et al. 2015. "The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analyses of Health Care Interventions: Checklist and Explanations." *Annals of Internal Medicine* 162: 777–784.

Kanaa, M. D., J. M. Whitworth, and J. G. Meechan. 2012. "A Prospective Randomized Trial of Different Supplementary Local Anesthetic Techniques After Failure of Inferior Alveolar Nerve Block in Patients With Irreversible Pulpitis in Mandibular Teeth." *Journal of Endodontics* 38: 421–425.

Larocca de Geus, J., J. K. Nogueira da Costa, L. M. Wambier, B. M. Maran, A. D. Loguercio, and A. Reis. 2020. "Different Anesthetics on the Efficacy of Inferior Alveolar Nerve Block in Patients With Irreversible Pulpitis: A Network Systematic Review and Meta-Analysis." *Journal of the American Dental Association* 151: 87–97.e84.

Lautch, H. 1971. "Dental Phobia." *British Journal of Psychiatry* 119: 151–158.

Lindemann, M., A. Reader, J. Nusstein, M. Drum, and M. Beck. 2008. "Effect of Sublingual Triazolam on the Success of Inferior Alveolar Nerve Block in Patients With Irreversible Pulpitis." *Journal of Endodontics* 34: 1167–1170.

Lumley, T. 2002. "Network Meta-Analysis for Indirect Treatment Comparisons." *Statistics in Medicine* 21: 2313–2324.

Malamed, S. F. 2011. "Is the Mandibular Nerve Block Passé?" *Journal of the American Dental Association* 142, no. Suppl 3: 3s–7s.

Malamed, S. F. 2019. *Handbook of Local Anesthesia*. 7th ed. Elsevier Inc.

Matthews, R., M. Drum, A. Reader, J. Nusstein, and M. Beck. 2009. "Articaine for Supplemental Buccal Mandibular Infiltration Anesthesia in Patients With Irreversible Pulpitis When the Inferior Alveolar Nerve Block Fails." *Journal of Endodontics* 35: 343–346.

Methley, A. M., S. Campbell, C. Chew-Graham, R. McNally, and S. Cheraghi-Sohi. 2014. "PICO, PICOS and SPIDER: A Comparison Study of Specificity and Sensitivity in Three Search Tools for Qualitative Systematic Reviews." *BMC Health Services Research* 14: 579.

Monteiro, M. R., F. C. Groppo, F. Haiter-Neto, M. C. Volpato, and J. F. Almeida. 2015. "4% Articaine Buccal Infiltration Versus 2% Lidocaine Inferior Alveolar Nerve Block for Emergency Root Canal Treatment in Mandibular Molars With Irreversible Pulpits: A Randomized Clinical Study." *International Endodontic Journal* 48: 145–152.

Nagendrababu, V., C. M. Faggion Jr., S. J. Pulikkotil, A. Alatta, and P. M. Dummer. 2022. "Methodological Assessment and Overall Confidence in the Results of Systematic Reviews With Network Meta-Analyses in Endodontics." *International Endodontic Journal* 55: 393–404.

Nagendrababu, V., S. J. Pulikkotil, A. Suresh, S. K. Veettil, S. Bhatia, and F. C. Setzer. 2019. "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." *International Endodontic Journal* 52: 779–789.

Nikolakopoulou, A., J. P. T. Higgins, T. Papakonstantinou, et al. 2020. "CINeMA: An Approach for Assessing Confidence in the Results of a Network Meta-Analysis." *PLoS Medicine* 17: e1003082.

Nusstein, J., S. Kennedy, A. Reader, M. Beck, and J. Weaver. 2003. "Anesthetic Efficacy of the Supplemental X-Tip Intraosseous Injection in Patients With Irreversible Pulpitis." *Journal of Endodontics* 29: 724–728.

Nusstein, J., A. Reader, R. Nist, M. Beck, and W. J. Meyers. 1998. "Anesthetic Efficacy of the Supplemental Intraosseous Injection of 2% Lidocaine With 1:100,000 Epinephrine in Irreversible Pulpitis." *Journal of Endodontics* 24: 487–491.

Ouzzani, M., H. Hammady, Z. Fedorowicz, and A. Elmagarmid. 2016. "Rayyan—A Web and Mobile App for Systematic Reviews." *Systematic Reviews* 5: 1–10.

Page, M. J., D. Moher, P. M. Bossuyt, et al. 2021. "PRISMA 2020 Explanation and Elaboration: Updated Guidance and Exemplars for Reporting Systematic Reviews." *BMJ* 372: n160.

Papakonstantinou, T., A. Nikolakopoulou, J. P. T. Higgins, M. Egger, and G. Salanti. 2020. "CINeMA: Software for Semiautomated Assessment of the Confidence in the Results of Network Meta-Analysis." *Campbell Systematic Reviews* 16: e1080.

Parirokh, M., S. Sadr, N. Nakhaee, P. V. Abbott, and S. Askarifard. 2014. "Efficacy of Supplementary Buccal Infiltrations and Intraligamentary Injections to Inferior Alveolar Nerve Blocks in Mandibular First Molars With Asymptomatic Irreversible Pulpitis: A Randomized Controlled Trial." *International Endodontic Journal* 47: 926–933.

Parirokh, M., S. A. Satvati, R. Sharifi, et al. 2010. "Efficacy of Combining a Buccal Infiltration With an Inferior Alveolar Nerve Block for Mandibular Molars With Irreversible Pulpitis." *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* 109: 468–473.

Pulikkotil, S. J., V. Nagendrababu, S. K. Veettil, P. Jinatongthai, and F. C. Setzer. 2018. "Effect of Oral Premedication on the Anaesthetic Efficacy of Inferior Alveolar Nerve Block in Patients With Irreversible Pulpitis - A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials." *International Endodontic Journal* 51: 989–1004.

Reisman, D., A. Reader, R. Nist, M. Beck, and J. Weaver. 1997. "Anesthetic Efficacy of the Supplemental Intraosseous Injection of 3% Mepivacaine in Irreversible Pulpitis." *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* 84: 676–682.

Rogers, B. S., T. M. Botero, N. J. McDonald, R. J. Gardner, and M. C. Peters. 2014. "Efficacy of Articaine Versus Lidocaine as a Supplemental Buccal Infiltration in Mandibular Molars With Irreversible Pulpitis: A Prospective, Randomized, Double-Blind Study." *Journal of Endodontics* 40: 753–758.

Rotstein, I., and J. I. Ingle. 2019. *Ingle's Endodontics 7, 50th Anniversary Edition*. PMPH USA.

Saber, S. M., A. A. Hashem, D. M. Khalil, C. Pirani, and R. Ordinola-Zapata. 2022. "Efficacy of Four Local Anaesthesia Protocols for Mandibular First Molars With Symptomatic Irreversible Pulpitis: A Randomized Clinical Trial." *International Endodontic Journal* 55: 219–230.

Salanti, G., A. E. Ades, and J. P. Ioannidis. 2011. "Graphical Methods and Numerical Summaries for Presenting Results From Multiple-Treatment Meta-Analysis: An Overview and Tutorial." *Journal of Clinical Epidemiology* 64: 163–171.

Salanti, G., C. Del Giovane, A. Chaimani, D. M. Caldwell, and J. P. Higgins. 2014. "Evaluating the Quality of Evidence From a Network Meta-Analysis." *PLoS One* 9: e99682.

Sanikop, S., P. Agrawal, and S. Patil. 2011. "Relationship Between Dental Anxiety and Pain Perception During Scaling." *Journal of Oral Science* 53: 341–348.

Shahi, S., S. Rahimi, H. R. Yavari, N. Ghasemi, and F. Ahmadi. 2018. "Success Rate of 3 Injection Methods With Articaine for Mandibular First Molars With Symptomatic Irreversible Pulpitis: A Consort Randomized Double-Blind Clinical Trial." *Journal of Endodontics* 44: 1462–1466.

Shapiro, M. R., N. J. McDonald, R. J. Gardner, M. C. Peters, and T. M. Botero. 2018. "Efficacy of Articaine Versus Lidocaine in Supplemental Infiltration for Mandibular First Versus Second Molars With Irreversible Pulpitis: A Prospective, Randomized, Double-Blind Clinical Trial." *Journal of Endodontics* 44: 523–528.

Silva, S. A., A. Horliana, C. M. Pannuti, et al. 2019. "Comparative Evaluation of Anesthetic Efficacy of 1.8 mL and 3.6 mL of Articaine in Irreversible Pulpitis of the Mandibular Molar: A Randomized Clinical Trial." *PLoS One* 14: e0219536.

Singhal, N., A. Vats, A. Khetarpal, M. Ahlawat, V. K. R. Vijayran, and Harshita. 2022. "Efficacy of Articaine Versus Mepivacaine Administered as Different Supplementary Local Anesthetic Techniques After a Failed Inferior Alveolar Nerve Block With Lidocaine in Patients With Irreversible Pulpitis: An In Vivo Study." *Journal of Conservative Dentistry* 25: 654–660.

Singla, M., A. Subbiya, V. Aggarwal, et al. 2015. "Comparison of the Anaesthetic Efficacy of Different Volumes of 4% Articaine (1.8 and 3.6 mL) as Supplemental Buccal Infiltration After Failed Inferior Alveolar Nerve Block." *International Endodontic Journal* 48: 103–108.

Sivaramakrishnan, G., M. Alsobaiei, and K. Sridharan. 2019. "Interventions for Anesthetic Success in Symptomatic Irreversible Pulpitis: A Network Meta-Analysis of Randomized Controlled Trials." *Journal of Dental Anesthesia and Pain Medicine* 19: 323–341.

Sterne, J. A., J. Savović, M. J. Page, et al. 2019. "RoB 2: A Revised Tool for Assessing Risk of Bias in Randomised Trials." *BMJ (Clinical Research Ed.)* 366: l4898.

Takeda, M., S. Matsumoto, B. J. Sessle, M. Shinoda, and K. Iwata. 2011. "Peripheral and Central Mechanisms of Trigeminal Neuropathic and Inflammatory Pain." *Journal of Oral Biosciences* 53: 318–329.

Tupyota, P., P. Chailertvanitkul, M. Laopaiboon, C. Ngamjarus, P. V. Abbott, and S. Krisanaprakornkit. 2018. "Supplementary Techniques for Pain Control During Root Canal Treatment of Lower Posterior Teeth With Irreversible Pulpitis: A Systematic Review and Meta-Analysis." *Australian Endodontic Journal* 44: 14–25.

van Wijk, A. J., and P. C. Makkes. 2008. "Highly Anxious Dental Patients Report More Pain During Dental Injections." *British Dental Journal* 205: E7; discussion 143.

Vatankhah, M., N. Zargar, M. Naseri, et al. 2023. "Primary and Supplementary Anesthetic Efficacy of a Modified Two-Step Buccal Infiltration of 4% Articaine in Mandibular Molars With Symptomatic Irreversible Pulpitis: A Randomized Clinical Trial." *Clinical Oral Investigations* 28: 33.

Veroniki, A. A., H. S. Vasiliadis, J. P. Higgins, and G. Salanti. 2013. "Evaluation of Inconsistency in Networks of Interventions." *International Journal of Epidemiology* 42: 332–345.

Weisenberg, M., O. Aviram, Y. Wolf, and N. Raphaeli. 1984. "Relevant and Irrelevant Anxiety in the Reaction to Pain." *Pain* 20: 371–383.

Zanjir, M., N. L. Lighvan, C. Yarascavitch, J. Beyene, P. S. Shah, and A. Azarpazhooh. 2019. "Efficacy and Safety of Pulpal Anesthesia Strategies During Endodontic Treatment of Permanent Mandibular Molars With Symptomatic Irreversible Pulpitis: A Systematic Review and Network Meta-Analysis." *Journal of Endodontics* 45: 1435–1464.

Zarei, M., J. Ghoddusi, E. Sharifi, M. Forghani, F. Afkhami, and P. Marouzi. 2012. "Comparison of the Anaesthetic Efficacy of and Heart Rate Changes After Periodontal Ligament or Intraosseous X-Tip Injection in Mandibular Molars: A Randomized Controlled Clinical Trial." *International Endodontic Journal* 45: 921–926.

Zargar, N., S. Shojaeian, M. Vatankhah, et al. 2022. "Anesthetic Efficacy of Supplemental Buccal Infiltration Versus Intraligamentary Injection in Mandibular First and Second Molars With Irreversible Pulpitis: A Prospective Randomized Clinical Trial." *Journal of Dental Anesthesia and Pain Medicine* 22: 339–348.

Zargar, N., E. Shooshtari, L. Pourmusavi, A. Akbarzadeh Baghban, H. Ashraf, and A. Parhizkar. 2021. "Anaesthetic Efficacy of 4% Articaine in Comparison With 2% Lidocaine as Intraligamentary Injections After an Ineffective Inferior Alveolar Nerve Block in Mandibular Molars With Irreversible Pulpitis: A Prospective Randomised Triple-Blind Clinical Trial." *Pain Research & Management* 2021: 6668738.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** iej70007-sup-0001-Supinfo01.docx.