

Comparing the anaesthetic efficacy of 1.8 mL and 3.6 mL of anaesthetic solution for inferior alveolar nerve blocks for teeth with irreversible pulpitis: a systematic review and meta-analysis with trial sequential analysis

V Nagendrababu ¹, PV Abbott², SJ Pulikkotil ¹, SK Veettil³, PMH Dummer⁴

¹ Division of Clinical Dentistry, School of Dentistry, International Medical University, Kuala Lumpur, Malaysia; ²UWA Dental School, University of Western Australia, Australia; ³School of Pharmacy, International Medical University, Kuala Lumpur, Malaysia; and ⁴School of Dentistry, College of Biomedical and Life Sciences, Cardiff University, Cardiff, UK.

Corresponding author

V Nagendrababu BDS, MFDS RCPS (Glasg), MDS, PhD.

Division of Clinical Dentistry,

School of Dentistry, International Medical University

Bukit Jalil – 57000, Kuala Lumpur, Malaysia.

E mail: venkateshbabu@imu.edu.my, hivenkateshbabu@yahoo.com

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Abstract

Background: The scientific literature is contradictory in relation to selecting the appropriate volume of local anaesthetic solution for inferior alveolar nerve blocks (IANB) when attempting to anaesthetize mandibular teeth with irreversible pulpitis.

Objectives: To compare the efficacy of 1.8 mL and 3.6 mL of the same anaesthetic solution for IANBs when treating mandibular teeth with irreversible pulpitis.

Methods: A literature search was performed in PubMed, Scopus and EBSCOhost databases until May 2020. Randomized clinical trials published in English, comparing 1.8 mL with 3.6 mL of the same anaesthetic solution for IANBs in permanent mandibular teeth with irreversible pulpitis were included. The risk of bias of the included trials was appraised using the revised Cochrane risk of bias tool. A meta-analysis was performed using the random-effects model. The effect of random errors on the results of the meta-analysis was evaluated by trial sequential analysis and the quality of evidence was appraised using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

Results: Four clinical trials involving 280 teeth from patients with ages ranging from 18 to 65 years were included. Among the four trials, three were categorized as having a “low” risk of bias and one was categorised as having “some concerns”. The primary meta-analysis revealed that 3.6 mL of anaesthetic solution when administered for IANBs was associated with significantly greater success rates compared with 1.8 mL (RR = 1.94; 95% CI, 1.07,3.52; I² = 77%). Similarly, the results of the sensitivity analysis (restricting trials only to those that used the Heft-Parker visual analogue pain scale) revealed that the use of 3.6 mL significantly increased the success of IANBs compared with 1.8 mL. The trial sequential analysis confirmed the evidence for the beneficial effect of 3.6 mL to achieve success for IANBs was “conclusive”. The quality of evidence was graded as “high”.

Conclusion: Increasing the volume of anaesthetic solution from 1.8 mL to 3.6 mL improved the success rate for IANBs in mandibular molars with irreversible pulpitis. The quality of the

evidence was “high”. Future high-quality clinical trials are required with different types of anaesthetic solutions and other types of teeth.

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Introduction

Performing pain-free root canal treatment is a major challenge for clinicians (Parirokh & Abbott 2014). The inferior alveolar nerve block (IANB) is the most common technique used to achieve anaesthesia in mandibular teeth; however, the failure rate of IANBs in teeth diagnosed with irreversible pulpitis has been reported to be between 43% and 83% (Lindemann *et al.* 2008, Poorni *et al.* 2011, Fowler *et al.* 2016, Aggarwal *et al.* 2017), with the high failure being attributed primarily to inflammation within the pulp (Henry & Hargreaves 2007). Various strategies have been used to increase the success rate of IANBs in these situations, such as changing the type of local anaesthetic solution (Visconti *et al.* 2016, Nagendrababu *et al.* 2020), prescribing an oral premedication of corticosteroids or NSAIDs (Parirokh *et al.* 2010, Noguera-Gonzalez *et al.* 2013, Shahi *et al.* 2013), and the administration of supplementary buccal and lingual infiltrations and/or intra-osseous and intra-pulpal injections (Hargreaves *et al.* 2008, Aggarwal *et al.* 2009, Poorni *et al.* 2011, Zanjir *et al.* 2019).

Another strategy used to improve the success rate of IANBs is to simply increase the volume of anaesthetic solution deposited during the injection (Aggarwal *et al.* 2012, Abazarpoor *et al.* 2015). Two randomized clinical trials concluded that using larger volumes of local anaesthetic solution increased the success rate of IANBs when treating mandibular molars with irreversible pulpitis (Aggarwal *et al.* 2012, Abazarpoor *et al.* 2015). Conversely, one randomized clinical trial (Silva *et al.* 2018) and one retrospective study (Fowler & Reader 2013) reported no significant difference in success rates of IANBs when the volume of local anaesthetic solution was increased while treating teeth with irreversible pulpitis. Two systematic reviews concluded that increasing the volume of local anaesthetic solution increased the success rate of IANBs when treating mandibular molars with irreversible pulpitis (Tupyota *et al.* 2018, Milani *et al.* 2018), whereas one systematic review concluded there was no significant difference (Corbella *et al.* 2017). In summary, the current literature and available evidence is contradictory, making it impossible to know the appropriate volume of local anaesthetic solution for IANBs when performing root canal treatment in mandibular teeth with irreversible pulpitis.

The validity of the results from a meta-analysis can be affected by random errors, especially when small numbers of randomized controlled trials are included or when they have inadequate sample sizes. This can lead to the detection of spurious positive outcomes (Wetterslev *et al.* 2008, Brok *et al.* 2009). Trial sequential analysis evaluates the risk due to random errors and determines the sample size required to assess whether the evidence in a meta-analysis is conclusive. The “optimal information size” estimated by a trial sequential analysis is similar to a sample size calculation for a large study and, when used, it ensures there is adequate power for the results to be considered reliable (Wetterslev *et al.* 2008, Thorlund *et al.* 2017). GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) is a systematic and transparent approach that provides guidance to grade the quality of evidence and the strength of recommendations in healthcare (Guyatt *et al.* 2008, Brozek *et al.* 2009). The published systematic reviews and meta-analyses did not evaluate the risk of random errors, and did not grade the quality of evidence using the GRADE approach to assess the reliability of the individual studies they included. In order to address these deficiencies, the aim of the current systematic review with meta-analysis and trial sequential analysis was to compare the efficacy of 1.8 mL and 3.6 mL of the same anaesthetic solution for IANBs when treating mandibular teeth with irreversible pulpitis.

Methods

The current systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher *et al.* 2009) and the protocol was registered *a priori* in the PROSPERO database (CRD42020189172).

Research question

The research question for the current review was framed based on the PICOS format: Is 3.6 mL (C) of a local anaesthetic solution more effective compared to 1.8 mL (I) of the same solution in achieving anaesthesia (O) in permanent mandibular teeth with irreversible pulpitis (P) following an IANB when assessed during randomized clinical trials (S)?

Study selection

A literature search was performed using the following search strategy: (((volume) OR (1.8 mL)) OR (3.6 mL)) AND ("inferior alveolar nerve block") OR (IANB) in PubMed, Scopus and EBSCOhost (Dentistry & Oral Sciences Source) databases until June 2020. Additional searches were performed in the clinical trial registry (www.clinicaltrials.gov) and the reference lists of included studies, published reviews and textbooks. Two independent reviewers (V.N., S.P.) screened the titles and abstracts followed by a full text assessment. Disagreements were resolved by a third reviewer (P.D.).

Selection criteria

Trials were included if they satisfied the following criteria:

- Randomized clinical trials comparing 1.8 mL of anaesthetic solution with 3.6 mL of the same anaesthetic solution for IANBs in adult patients;
- Anaesthetic efficacy assessed in any permanent mandibular teeth with irreversible pulpitis. The outcome of interest was the success rate of IANBs anaesthesia defined as “no” or “weak/mild” pain according to patient-reported pain scores during access cavity preparation and root canal instrumentation;
- Randomized clinical trials published in English.

Case reports, case series, observational studies and reviews were excluded.

Data extraction and quality assessment

Data extraction and quality assessment was performed by two independent reviewers (V.N., S.P.). Disagreements were resolved mutually or referred to a third reviewer (P.D.) for arbitration. Missing information was obtained by contacting the corresponding authors of the included studies. A data extraction form was created, which consisted of name and country of the first author, year of publication, age and gender of the patients, interventions, number of individuals randomized, success rate and adverse effects (if any). The Cochrane risk of bias tool for randomized trials (RoB 2.0) (Higgins *et al.* 2016) was used to assess the

quality of studies. The studies were categorized as having 'low', 'some concerns' or 'high risk' of bias based on the following domains: randomization, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result and overall quality. A clinical trial is rated as "low risk" for bias when all the key bias domains are scored as "low risk". If at least one bias domain is scored as "some concerns", the trial is rated as having "some concerns". The scoring of at least one bias domain as having "high risk" will render the trial as being rated as "high risk".

Statistical analysis

A meta-analysis to calculate the pooled risk ratio (RR) with 95% confidence interval was performed by the random effects model due to the presence of within and in-between heterogeneity of the selected studies. Significant heterogeneity was present if the I^2 statistic was more than 50%. In any meta-analysis, with 10 or more trials, publication bias would be assessed visually by funnel plots (Sterne *et al.* 2000). The meta-analysis was conducted using STATA 14.1 (StataCorp, College Station, TX, USA). Trial sequential analysis was performed by using the software available at <http://www.ctu.dk>. Control event rate and an anticipated intervention effect from the meta-analysis were used to perform the trial sequential analysis.

Evidence grading

The quality of evidence obtained by the meta-analysis was evaluated by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach (GRADEpro GDT: GRADEpro Guideline Development Tool [software], McMaster University, 2015 [developed by Evidence Prime Inc.]) (Guyatt *et al.* 2008, Brozek *et al.* 2009) into "very low", "low", "moderate" or "high" quality.

Results

Study selection

The PRISMA flow chart (Figure 1) describes the randomized clinical trial selection process for the current review. The initial literature search resulted in the identification of 1551 studies, of these 390 were removed as duplicates. The number of studies identified for title and abstract screening was 1161, among which four studies were selected for full text

retrieval. After full text reading, four randomized clinical trials (Parirokh *et al.* 2010, Aggarwal *et al.* 2012, Abazarpour *et al.* 2015, Silva *et al.* 2019) were included for qualitative and quantitative synthesis.

Characteristics and quality of the included trials

The characteristics of the included randomized clinical trials are shown in Table 1. The total number of teeth randomized in the trials was 280 from both male and female patients with ages ranging from 18 to 65 years. Three trials used the Heft-Parker visual analogue pain scale for outcome assessment (Parirokh *et al.* 2010, Aggarwal *et al.* 2012, Abazarpour *et al.* 2015), whereas one used a verbal analogue scale (Silva *et al.* 2019). Among the four trials, two were conducted in Iran (Parirokh *et al.* 2010, Abazarpour *et al.* 2015), one in India (Aggarwal *et al.* 2012) and another in Brazil (Silva *et al.* 2019). All trials were published between 2010 to 2019 and all included only mandibular molars. Two trials explicitly mentioned that no adverse effects were observed (Abazarpour *et al.* 2015, Silva *et al.* 2019). The assessment of risk of bias of the included trials is shown in Table 2. Among the four trials, three were of “low” risk of bias (Parirokh *et al.* 2010, Abazarpour *et al.* 2015, Silva *et al.* 2019), whereas one was categorised as having “some concerns” in regard to risk of bias (Aggarwal *et al.* 2012) because of bias in the randomization process.

Meta-analyses

The results of the primary meta-analysis (Figure 2) (trials including both Heft-Parker visual analogue pain scale and verbal analogue scale) from the four clinical trials revealed that the use of 3.6 mL of solution significantly increased the anaesthetic success of IANBs compared with 1.8 mL (RR = 1.94; 95% CI, 1.07,3.52; I² = 77%). Similarly, the results of the sensitivity analysis (Figure 3) from three clinical trials (restricting trials only to those that used the Heft-Parker visual analogue pain scale) revealed that the use of 3.6 mL of solution significantly increased the anaesthetic success of IANBs compared with 1.8 mL (RR = 2.55; 95% CI, 1.72,3.78; I² = 0%). The use of 3.6 mL of local anaesthesia had a 36% higher success rate compared to 1.8 mL. The primary analysis revealed 77% heterogeneity, whereas the sensitivity analysis had 0% heterogeneity.

Publication bias

Due to the small number of studies, publication bias was not assessed.

Trial sequential analysis

Trial sequential analysis comparing the 1.8 mL and 3.6 mL volumes of anaesthetic solutions for the success for IANBs from three clinical trials (Parirokh *et al.* 2010, Aggarwal *et al.* 2012, Abazarpour *et al.* 2015) was undertaken with type 1 error of 5% and type II error of 20% using a random effects model. The information size (n=59) was calculated using an anticipated intervention effect of RR=2.55 (the intervention effect obtained from the sensitivity analysis as shown in Figure 3) and control event proportion of 23.4%. The cumulative Z-curve (blue) crossed the alpha-spending boundary (red-dotted line) indicating a significant benefit of the intervention (i.e. 3.6 mL) as demonstrated in the meta-analysis (Figure 3). The number of patients included in the meta-analysis (n=190) exceeded the required information size. Hence the evidence obtained from the meta-analysis of three trials can be considered as 'conclusive'.

Quality of evidence

The quality of evidence assessed using the GRADE approach is shown in Table 3. The GRADE approach substantiated the evidence for assessing the anaesthetic efficacy of IANBs when comparing two volumes of the same solution. The GRADE evaluation confirmed that the evidence was of "high" quality.

Discussion

Selecting the appropriate volume of anaesthetic solution for IANBs is important for clinicians while performing root canal treatment in teeth with irreversible pulpitis and the decision should be evidence-based. Based on the outcomes of individual randomized clinical trials, several systematic reviews and meta-analyses have not been able to demonstrate the superiority of one or other of the two most commonly used volumes of anaesthetic solution, 1.8 mL or 3.6 mL. By conducting a meta-analysis followed by a trial sequential analysis, the aim of the present review was to compare the efficacy of 1.8 mL and 3.6 mL of the same anaesthetic solution for IANBs when treating mandibular teeth with irreversible pulpitis. A

summary efficacy measure comparing the effectiveness of treatments can be derived from a meta-analysis of the pooled outcome measures (Haidich 2010). The meta-analysis also evaluates the statistical heterogeneity on account of pooling the data (Haidich 2010).

The results of the primary and sensitivity meta-analyses demonstrated that 3.6 mL of local anaesthetic solution for IANBs was associated overall with greater success rates compared to 1.8 mL when treating mandibular molars with irreversible pulpitis. The results of the current review are in agreement with the conclusions of two systematic reviews (Tupyota *et al.* 2018, Milani *et al.* 2018), but contrary to another (Corbella *et al.* 2017). The probable reasons for the disagreement is likely due to the number of studies included. The systematic review by Corbella *et al.* 2017 included only two trials (Parirokh *et al.* 2010, Aggarwal *et al.* 2012), whereas the present review included four trials (Parirokh *et al.* 2010, Aggarwal *et al.* 2012, Abazarpour *et al.* 2015, Silva *et al.* 2019) in the primary meta-analysis and three trials (Parirokh *et al.* 2010, Aggarwal *et al.* 2012, Abazarpour *et al.* 2015) in the sensitivity analysis.

Several potential reasons for the larger volume of anaesthetic solution increasing the success of pulp anaesthesia significantly have been suggested. These include:

- i) a certain length of nerve needs to be bathed in the anaesthetic solution in order to effectively block conduction; De Jong (1974) suggested that this length should be at least 10 mm;
- ii) according to Potoćnik & Bajrović (1999), a sufficient volume of the anaesthetic solution must be applied to three inter-nodal lengths of the largest nerve fibre and, since the longest intermodal span in the inferior alveolar nerve is 1.8 mm, at least 6 mm of the nerve needs to be exposed to the anaesthetic for it to be effective; as a consequence, the larger volume of anaesthetic injected is more likely to come into contact with this length of nerve;
- iii) Kohler *et al.* (2008) recommended filling the pterygomandibular space with the anaesthetic solution so that the maximum length of the inferior alveolar nerve was exposed to the solution;

- iv) by injecting a larger volume (such as two cartridges) of anaesthetic solution into the pterygomandibular space, a greater amount will be available to act on the inferior alveolar nerve (Franz & Perry 1974, Aggarwal *et al.* 2012, Fowler & Reader 2013);
- v) administration of two cartridges of anaesthetic agent in separate injections improves the chances of depositing the solutions nearer the inferior alveolar nerve compared to giving only one injection (Abazarpour *et al.* 2015);
- vi) giving two separate injections reduces the chances of missing the inferior alveolar nerve compared to a single injection (Fowler *et al.* 2015).

In the current review, two meta-analyses were performed: the primary analysis was conducted using four clinical trials (Parirokh *et al.* 2010, Aggarwal *et al.* 2012, Abazarpour *et al.* 2015, Silva *et al.* 2019) that used the Heft-Parker visual analogue pain scale (VAS) or a verbal analogue scale as outcome measures. The primary meta-analysis, revealed significant heterogeneity of 77%. The presence of heterogeneity affects the extent to which generalizable conclusions can be formed (Higgins *et al.* 2019). The inconsistency among the studies that were included (significant heterogeneity more than 75%) revealed by the meta-analysis reduces confidence in the recommendations for the intervention/treatment (Schünemann *et al.* 2013, Higgins *et al.* 2019). However, the predictive value of I2 statistics should be considered with caution as there is possibility of heterogeneity not detected by the I2 measure (Melsen *et al.* 2014). All the trials were included in the primary meta-analysis because the outcomes described in each were based on dichotomous data (success/failure) and were reported as the proportion of patients where the IANB was successful irrespective of the pain scale used. However, using different pain scales can be a source of heterogeneity. Therefore, the second analysis was a sensitivity analysis conducted on three trials (Parirokh *et al.* 2010, Aggarwal *et al.* 2012, Abazarpour *et al.* 2015) that used only the Heft-Parker visual analogue pain scale (VAS). The use of different pain scales as outcome measures can lead to variations in the results that are reflected as statistical heterogeneity in the meta-analysis. The sensitivity analysis, which excluded the study of Silva *et al.* (2019) that used the verbal analogue scale, revealed no heterogeneity (0 %), proving that the inclusion of

studies using the two scales was the reason for the heterogeneity noted in the primary analysis. To ensure the results were more precise and robust, the current review performed a trial sequential analysis and GRADE analysis using the data from the three studies included in the sensitivity analysis (Parirokh *et al.* 2010, Aggarwal *et al.* 2012, Abazarpour *et al.* 2015).

Determining the adequacy of the sample sizes pooled from the individual clinical trials is essential in order for the results of the meta-analysis to be considered as conclusive. This can be done using trial sequential analysis (Wetterslev *et al.* 2008, Brok *et al.* 2009, Thorlund *et al.* 2017). In the current review, the trial sequential analysis revealed that the result of the meta-analysis was conclusive because the pooled sample size exceeded the required information size, which is interpreted as the sample size required. In the current review, 36% as the minimum desired effect was used based on the results of the meta-analysis. The results of a trial sequential analysis may vary depending on the anticipated intervention effect.

The GRADE approach is an objective way to assess the quality of evidence from systematic reviews and meta-analyses. The assessment of the quality of evidence is important as it has implications in the development of recommendations and guidelines for clinical practice (Guyatt *et al.* 2008, Brozek *et al.* 2009). The evidence from the present review was therefore evaluated objectively using the GRADE approach, which revealed that overall the evidence was of “high quality” based on the quality of the studies included, the consistency and precision of the results, and directness of the evidence (Table 3). In one trial, there were “some concerns” in the domain of randomization when assessing the risk of bias because the method of allocation concealment of the study subjects was not reported (Aggarwal *et al.* 2012). The sensitivity meta-analysis revealed no heterogeneity (0%). Taken together with the conclusive evidence from the trial sequential analysis, the current review provides valid and reliable evidence of high quality.

Strength

The following parameters were considered as the strengths of the current review:

1. Only randomized clinical trials were included; systematic reviews of randomized clinical trials are considered as the highest quality of evidence;

2. The *a priori* registration of the study protocol, which provided transparency in the conduct of the review;
3. The review process (e.g. identifying relevant trials, data extraction, quality assessment) was performed by two independent examiners and disagreements were addressed by a third reviewer. In addition, the literature search was conducted in three electronic databases;
4. A sensitivity analysis was performed by restricting the trials to those that used a visual analogue scale, which provided a robust conclusion;
5. The meta-analysis was supplemented with a trial sequential analysis, which confirmed the results of the meta-analysis;
6. The clinical trials that were included assessed the success of anaesthesia when pain was recorded during access cavity preparation and root canal instrumentation. Achieving lip anaesthesia and pulp anaesthesia when assessed only by an electric pulp tester is not a reliable indicator for the determination of clinical analgesia while performing root canal treatment in teeth with irreversible pulpitis (Sampaio *et al.* 2012, Allegretti *et al.* 2016). Recording the pain experienced by patients during access cavity preparation and root canal instrumentation provides a much more valid assessment of the efficacy of anaesthesia (Poorni *et al.* 2011).

Limitations

Due to the small number of studies, the current systematic review did not conduct a separate analysis to evaluate the influence of different types of anaesthetic solutions (e.g. articaine vs lidocaine) or the quantity of vasoconstrictors. Additionally, the aim of the current review was to include all types of teeth (e.g. incisors, canine, premolars, molars); however, the literature search only located studies that assessed mandibular molars. Hence, only mandibular molars were included. Among the four trials, only one (Abazarpour *et al.* 2015) was conducted in teeth with symptomatic irreversible pulpitis, whereas the other three studies (Parirokh *et al.* 2010, Aggarwal *et al.* 2012, Silva *et al.* 2019) included teeth with a diagnosis of irreversible pulpitis without mentioning whether there were symptoms or not. Due to small number of studies, a separate analysis for the teeth with irreversible pulpitis (excluding the trial with cases diagnosed as symptomatic irreversible pulpitis) was not performed. Unfortunately, the terminology used in some studies and classifications of pulp

conditions is somewhat misleading and this may be a reason why some studies have not stated a specific diagnosis. The use of the terms “symptomatic” and “asymptomatic” rather than “acute” and “chronic” has been shown to be problematic as the former terms were associated with dentist being less inclined to provide treatment than when the latter were used (Bestall *et al.* 2020). This suggests that dentists make treatment decisions based on the presence/absence of symptoms rather than on the nature of the disease or condition that is present. In addition, because of the nature of irreversible pulpitis (being a severe inflammatory condition), it is highly unlikely that it would ever be entirely “asymptomatic”. It is most likely that there have been symptoms – either at the time of presentation or previously – and therefore the use of the terms “acute” for current and severe symptoms, and “chronic” for long-standing, occasional symptoms is more appropriate. If such appropriate terminology was standardised in all studies, then more valid comparisons between studies would be possible.

Future clinical trials are required with different types of anaesthetic solutions and other types of teeth. There is also a need to study the effects of the volume of anaesthetic solution used during other anaesthetic techniques such as the Gow-Gates, Vazirani-Akinosi mandibular nerve blocks, and mental and incisive nerve blocks. Additionally, future clinical trials must mention explicitly the exact nature of irreversible pulpitis (acute or chronic rather than symptomatic/asymptomatic). [Additionally, more clinical trials should be conducted using a verbal analogue scale as the outcome measure. This will lead to exclusive trial sequential analysis with data from the trials.](#)

Conclusion

Based on high quality evidence, larger volumes of local anaesthetic solutions significantly increase the success rate of IANBs when treating mandibular molars with irreversible pulpitis. However, 100% anaesthetic success was still not achieved. Hence, supplemental techniques are recommended to achieve pulp anaesthesia when failure of IANBs occurs in teeth with irreversible pulpitis

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Legends

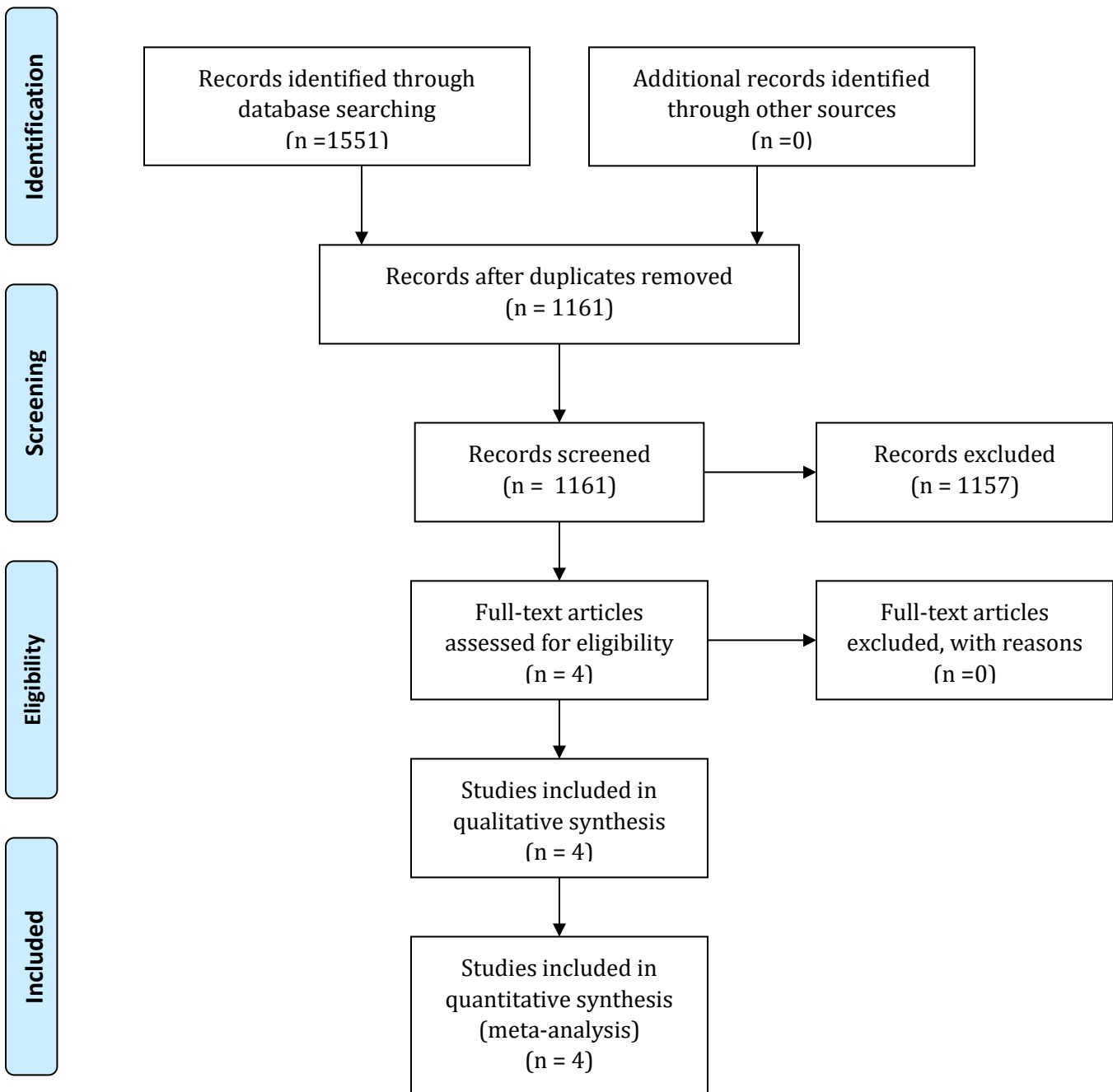
Figure 1: Literature search process

Figure 2: Primary meta-analysis comparing the anaesthetic efficacy of 1.8 mL and 3.6 mL volume of anaesthetic solution for Inferior Alveolar Nerve Blocks.

Figure 3: Sensitivity meta-analysis comparing anaesthetic efficacy of 1.8 mL and 3.6 mL volume of solution for Inferior Alveolar Nerve Blocks.

Figure 4: Trial sequential analysis assessing the anaesthetic efficacy of 1.8 mL and 3.6 mL volumes of solution for Inferior Alveolar Nerve Blocks. The cumulative Z-curve (blue) crosses the alpha-spending boundary (red-dotted line), which confirms the conclusive evidence for a beneficial effect of 3.6 mL volume of anaesthetic solution on the success of Inferior Alveolar Nerve Blocks.

Figure 1: Literature search process



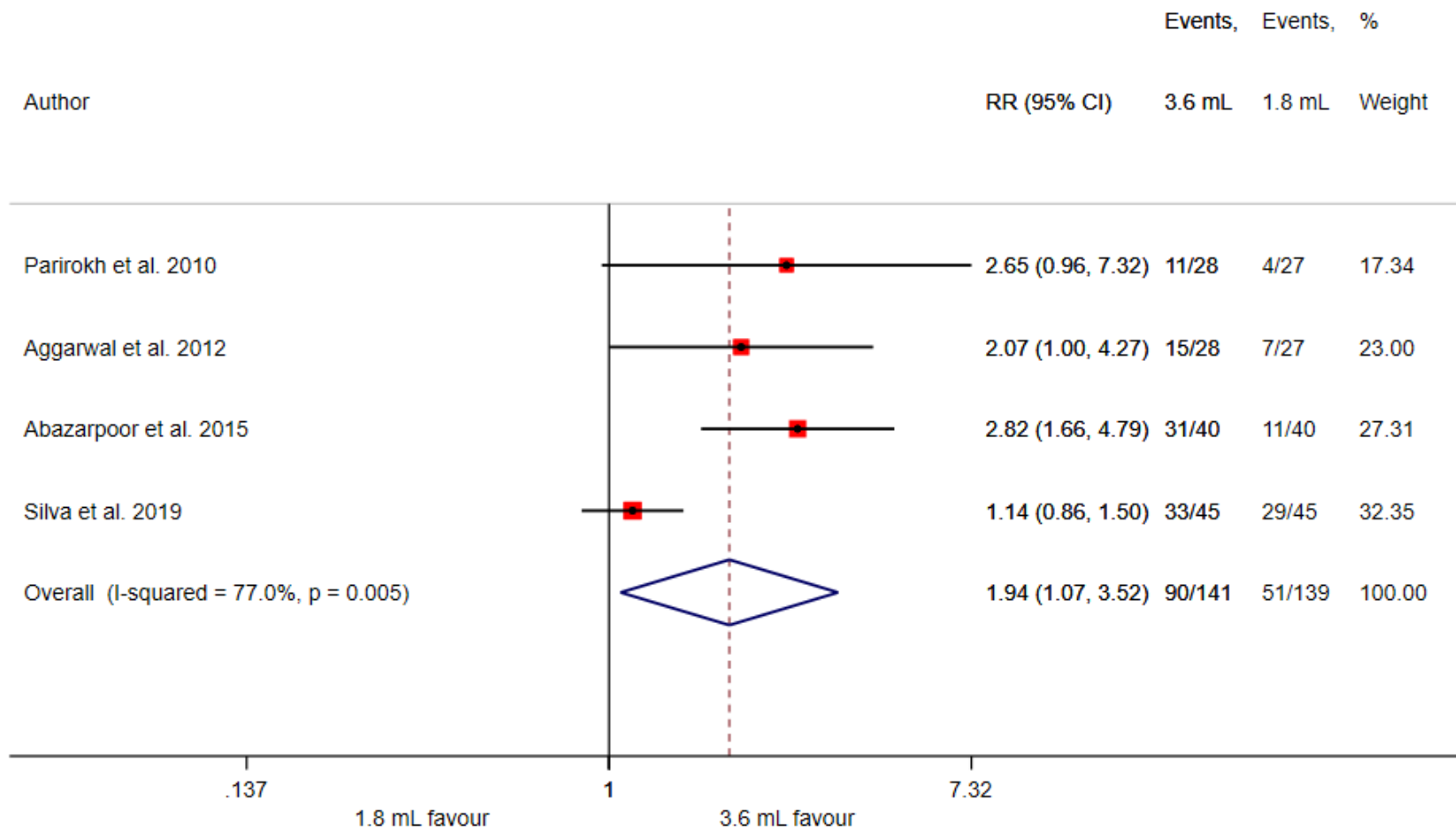


Figure 2: Primary meta-analysis comparing the anaesthetic efficacy of 1.8 mL and 3.6 mL volume of anaesthetic solution for Inferior Alveolar Nerve Blocks.

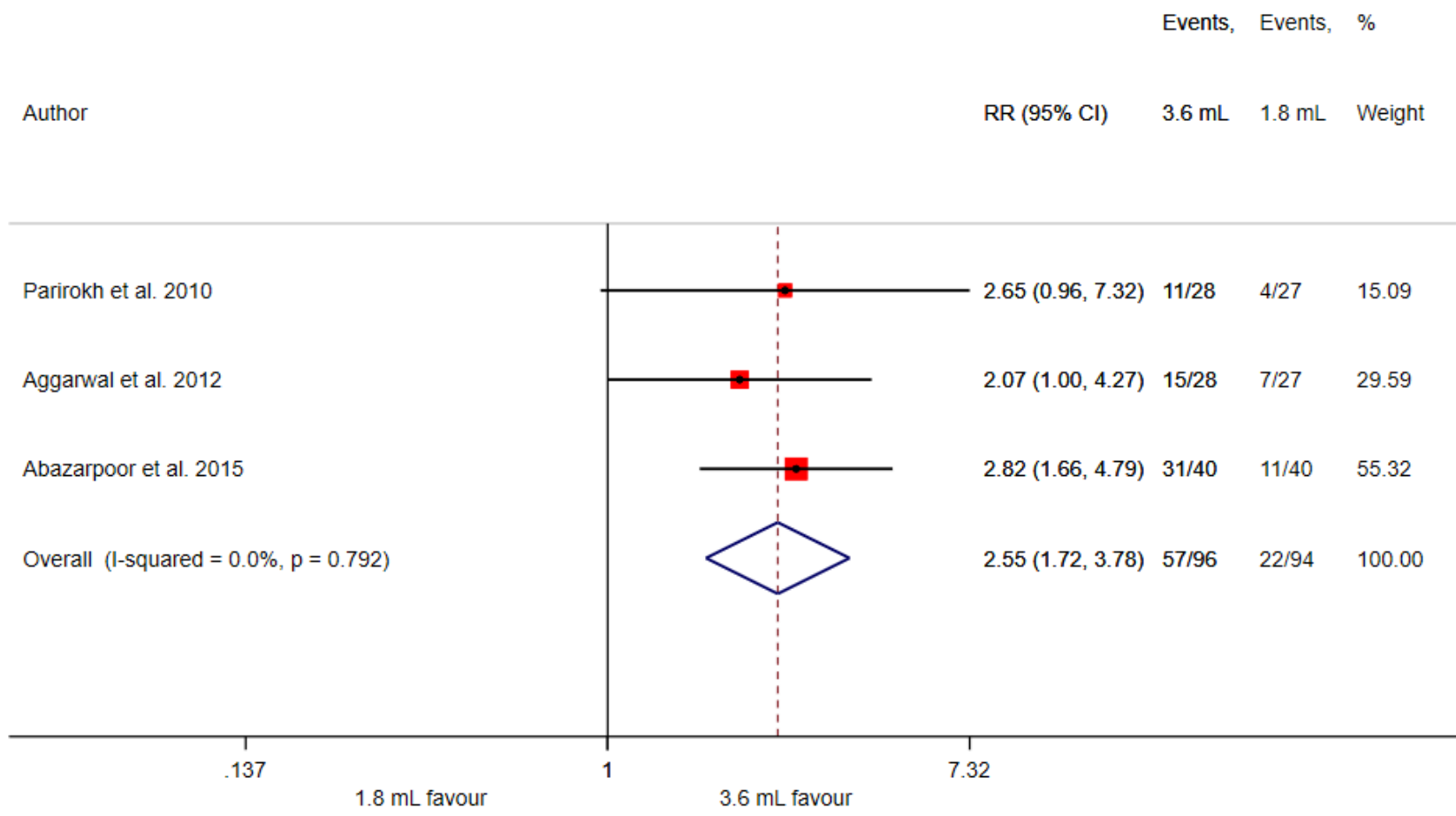


Figure 3: Sensitivity meta-analysis comparing anaesthetic efficacy of 1.8 mL and 3.6 mL volume of solution for Inferior Alveolar Nerve Blocks.

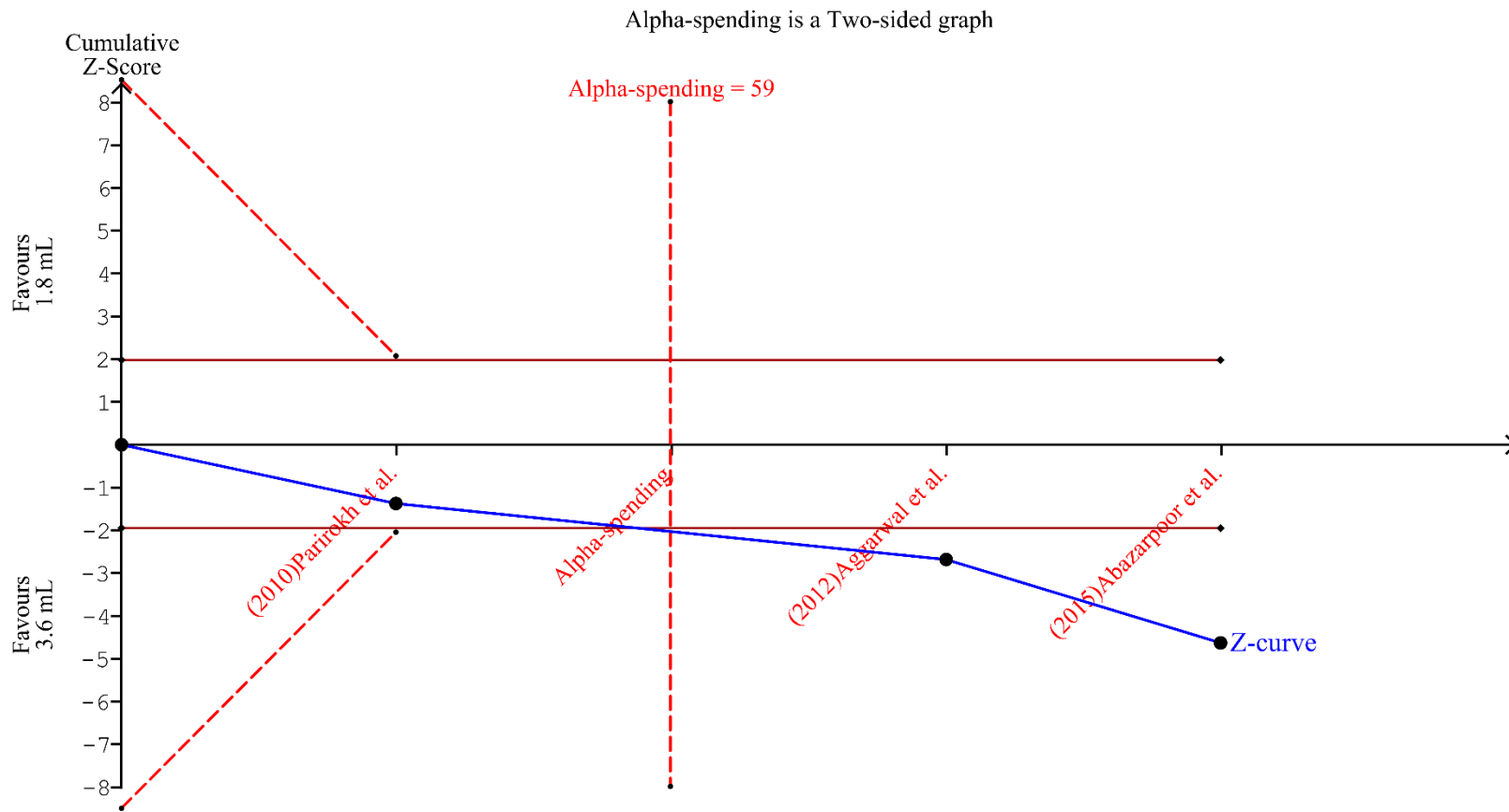


Figure 4: Trial sequential analysis assessing the anaesthetic efficacy of 1.8 mL and 3.6 mL volumes of solution for Inferior Alveolar Nerve Blocks. The cumulative Z-curve (blue) crosses the alpha-spending boundary (red-dotted line), which confirms the conclusive evidence for a beneficial effect of 3.6 mL volume of anaesthetic solution on the success of Inferior Alveolar Nerve Blocks.

Table 1: Characteristic of the include studies.

S No	Author, year	Country	Age (Range) yrs	Tooth type	Local anesthetic agent	Interventions (groups)	Age (mean \pm SD) yrs	Gender (n) (M/F)	Total number of samples (n)	Success (n)
1	Parirokh <i>et al.</i> 2010	Iran	Older than 18 years	Mandibular molars	2% lidocaine with 1/80,000 epinephrine	1.8 mL	26.0 \pm 6.9	10/17	27	4
						3.6 mL	28.4 \pm 8.1	8/20	28	11
2	Aggarwal <i>et al.</i> 2012	India	23-35	Mandibular molars	2% lidocaine with 1:200,000 epinephrine	1.8 mL	30 \pm 9	10/17	27	7
			25-37			3.6 mL	31 \pm 8	14/14	28	15
3	Abazarpour <i>et al.</i> 2015	Iran	18-65	Mandibular molars	4% articaine with 1:100,000 epinephrine	1.8 mL	NR	NR	40	11
						3.6 mL	NR	NR	40	31
4	Silva <i>et al.</i> 2019	Brazil	18 - 50	Mandibular molars	4 % articaine with 1:100,000 epinephrine	1.8 mL	30.8 \pm 8.3	18/27	45	29
						3.6 mL	31.1 \pm 8.2	19/26	45	33

Table 2: Risk of bias assessment for the included studies

Author, year	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall bias
Parirokh <i>et al.</i> 2010	+	+	+	+	+	+
Aggarwal <i>et al.</i> 2012	?	+	+	+	+	?
Abazarpour <i>et al.</i> 2015	+	+	-	+	+	+
Silva <i>et al.</i> 2019	+	+	+	+	+	+

+symbol/green colour means 'low risk of bias'; ?symbol/yellow colour means 'some concerns'

Table 3: Quality of evidence using GRADE approach.

Certainty assessment							No of patients		Effect		Certainty
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3.6 mL	1.8 mL	Relative (95% CI)	Absolute (95% CI)	
3	randomized trials	not serious	not serious	not serious	not serious	none	57/96 (59.4%)	22/94 (23.4%)	RR 2.55 (1.72 to 3.78)	363 more per 1,000 (from 169 more to 651 more)	⊕⊕⊕⊕ HIGH

CI: Confidence interval; RR: Risk ratio