Review Article

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Anesthetic efficacy of supplemental intraligamentary injection in human mandibular teeth with irreversible pulpitis: a systematic review and meta-analysis

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Background: Inferior alveolar nerve block (IANB) is known to have a lower success rate for anesthesia in patients with irreversible pulpitis. This calls for supplementary techniques to effectively anesthetize such patients. This systematic review aimed to evaluate the published literature for determining the success rate of anesthesia induction using post-IANB intraligamentary (IL) injection in the mandibular teeth of patients with symptomatic irreversible pulpitis. The review question was, "What is the success rate of IL injection in the mandibular teeth of patients with irreversible pulpitis as a supplementary technique for endodontic treatment?"
Methods: A thorough search of electronic databases and manual searches were performed. The protocol of the review was framed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and was registered in the International Prospective Register of Ongoing Systematic Reviews (PROSPERO) with a proper criterion for inclusion and exclusion of studies. The included studies were analyzed using the Cochrane Collaboration "Risk of Bias" tool. A meta-analysis that included a comparison of primary nerve block and supplemental IL injection was performed. The success rate was evaluated using the combined risk ratio (RR) with a random risk model. A funnel plot was created to measure publication bias.
Results: After all analyses, four studies were included. In the forest plot representation, RRs were 3.56 (95% CI: 2.86, 4.44), which were in favor of the supplemental IL injections. Statistical heterogeneity was found to be 0%. These values suggest that supplemental IL injections provide better success rates for anesthesia.
Conclusion: According to the pooled qualitative and quantitative analyses, supplemental IL injections increased anesthetic efficacy.

Keywords: Intraligamentary Injection; Irreversible Pulpitis; Local Anesthesia; Mandible; Tooth.

INTRODUCTION

The most common method of anesthetizing the mandibular teeth is inferior alveolar nerve block (IANB) [1]; however, the failure rate is high [2,3]. According to previous studies, IANB has a success rate of < 30% in cases of symptomatic irreversible pulpitis [4,5]. This may be due to the inflammation-related activation of certain receptors, such as tetrodotoxin-resistant receptors and capsaicin-sensitive transient receptor potential vanilloid type 1. These receptors resist local anesthetic agents and reduce their efficacy [6-8]. Various studies have suggested alternative methods to reduce the pain and

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discomfort experienced during root canal treatment, including the application of supplemental injections such as periodontal ligament (PDL) or IL, intraosseous (IO), and intrapulpal injections as well as buccal infiltrations (BIs) [9,10]. Additionally, evidence suggests that the administration of pre-medications, such as non-steroidal anti-inflammatory drugs, potentiates pre-treatment analgesia [11]. Furthermore, BI with 4% articaine shows an improved but inconsistent success rate [12-15]. It was also found that BI successfully anesthetized maxillary teeth subjected to dental treatment; however, its efficacy was hindered by the thickness of the buccal cortical bone [16].

Intrapulpal injections have a reportedly high success rate and are often regarded as the final option for inducing anesthesia. These injections have an immediate onset but short duration of action. For proper deposition of the anesthetic solution, the pulpal space must be properly and adequately exposed [9]. On the other hand, IL and IO injections are also common supplemental anesthetic techniques [8,9,14,17-20]. The solution is injected directly into the bone around the tooth. IO injections have a good success rate as a supplemental injection [18]; however, special equipment may be needed, which could lead to adverse effects [9,17].

According to an investigative survey by members of the American Association of Endodontists, patients with symptomatic irreversible pulpitis require supplemental anesthetic injections. In such cases, an IL injection is frequently administered [10]. This technique involves forcefully injecting the agent into the bone adjacent to the affected tooth root and periodontal ligament [10,17]. In 1982, Malamed recommended IL as an alternative to IANB. In endodontics, IL injections have been studied as both primary and supplemental injections [20,21]. Supplemental IL injections have a success rate of 50-96% for painless endodontic treatment [18, 22-27].

The efficacy of supplemental injections may be influenced by the volume of the solution. However, evidence regarding its required volume for administration remains scarce. Various studies report a volume range of 0.2 to 0.9 mL per root [17,22,24,26,28]; injecting 0.2 mL of the solution into the PDL space was advised by Malamed [17]. However, successful IL injections have no clearly defined volume. Another factor that may affect its efficacy is the mode of delivery. The IL technique can be applied using standardized, specialized mechanical, or computer-operated syringes [21,22,24]. Following a failed nerve block in mandibular teeth with irreversible pulpitis, a computerized local anesthetic delivery system was used for its delivery, with a success rate of approximately 56% [22].

Many investigations have attempted to determine the most optimal local anesthetic agent in association with the IL technique. By comparing 4% articaine with 1:100,000 epinephrine and 2% lidocaine with 1:100,000 epinephrine, no significant difference in pain elimination during anesthetic induction was observed [10]. Therefore, there is ambiguity regarding the type of solution used for IL injection.

As a result, the present review focuses on the success rate of IL injection as a supplementary technique in symptomatic irreversible pulpitis in human mandibular teeth; conflicting variables such as volume, type, and mode of delivery were excluded.

METHODS

1. Registration

The review protocol was prepared following the established Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and was registered on International Prospective Register of Ongoing Systematic Reviews (PROSPERO) under the number, CRD42020201534 [28].

2. Eligibility criteria

The PICO framework was applied to frame the question as, “What is the success rate of IL injection in the mandibular teeth of patients with irreversible pulpitis as a supplementary technique for endodontic treatment?”

Table 1. Lists of combination of keywords for electronic database search strategy

Database	Search strategy (2020)	n (search results as on Dec 2020)
PubMed	("Intraligamentary Injection" [All fields] OR "Periodontal Ligament Injection" [All fields] AND "Irreversible Pulipitis" [All fields] OR "Symptomatic Irreversible Pulpitis" [All fields] OR "Asymptomatic Irreversible Pulpitis" [All fields] AND "Systematic Review" [All fields])	38
SCOPUS	("Intraligamentary Injection" [All fields] OR "Periodontal Ligament Injection" [All fields] AND "Irreversible Pulipitis" [All fields] OR "Symptomatic Irreversible Pulpitis" [All fields] OR "Asymptomatic Irreversible Pulpitis" [All fields] AND "Systematic Review" [All fields])	132
EbscoHost	("Intraligamentary Injection" [All fields] OR "Periodontal Ligament Injection" [All fields] AND "Irreversible Pulipitis" [All fields] OR "Symptomatic Irreversible Pulpitis" [All fields] OR "Asymptomatic Irreversible Pulpitis" [All fields] AND "Systematic Review" [All fields])	27

The framework included:

P: Human mandibular teeth with irreversible pulpits

I: Anesthesia with IANB

C: Anesthesia with IANB + supplementary intraligamentary injection

O: Successful anesthesia and painless root canal treatment procedure

3. Search strategy

A thorough manual search was carried out in electronic databases (PubMed, Scopus, and Ebsco). A combination of keywords was prepared using the Boolean operators "AND" and "OR" for a systematic search for studies published until December 2020 (Table 1). Duplicates were identified and excluded.

4. Inclusion criteria

The following inclusion criteria were established and used for screening:

- Clinical studies published in English between 1960 and December 2020
- Studies with adult human patients planned for root canal treatment
- Studies of symptomatic irreversible pulpitis in mandibular teeth
- Studies with supplemental IL techniques after failed primary IANB injections
- Studies reporting the success of IL injection either in percentages or numbers
- Performed access preparation and pulp extirpation to check for pulpal anesthesia
- Patients able to understand pain scales

5. Exclusion criteria

The following exclusion criteria were established and used for screening:

- Studies evaluating other techniques such as infiltration, IO, and any pre-medication;
- Patients with systemic diseases
- Patients who received analgesics on the same day as the treatment
- Case reports and case series
- Studies evaluating the influence of any medication on the success of an anesthetic technique
- Studies in pediatric patients
- Patients with a known allergic response to local anesthesia

6. Data extraction

All articles were manually searched along with a

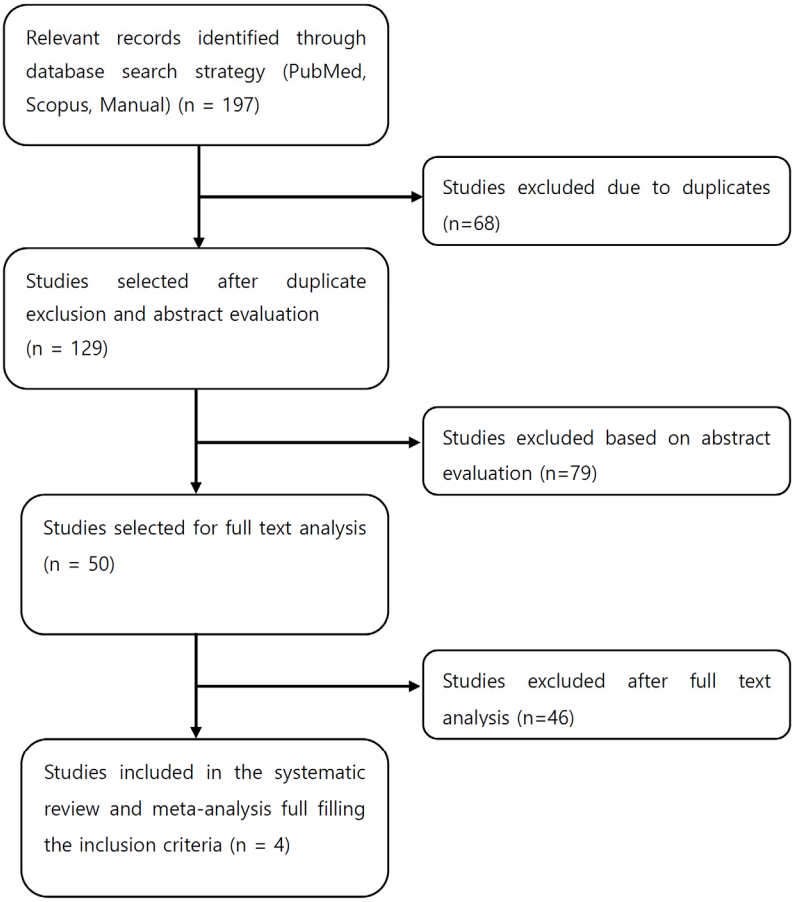

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart

thorough analysis of their bibliography to extract relevant data, which was then framed as a PRISMA flowchart (Fig. 1). Each study was examined according to multiple parameters, such as authors, language of publication, sample size, and information of participants as well as their evaluation of pain presented as scales and success rates with statistical values.

RESULTS

After thorough evaluation, 197 articles were found to be relevant; 129 abstracts were screened. Proper inclusion and exclusion criteria were followed to include only four articles in the final analysis.

1. Study characteristics

Four articles studied the effect of IL injection as a supplemental technique after a failed nerve block in irreversible pulpitis in mandibular teeth [24,26,27,29]. Individual study characteristics are presented in Table 2.

2. Outcomes

Successful anesthesia was assessed in each study. Absent or mild pain reported via scores on a scale, such as the Heft Parker Visual Analog (HP VAS) [30] and Visual Analog Scales (VAS), during root canal treatment steps (access cavity preparation and instrumentation) was considered a successful anesthetic effect.

3. Risk of bias assessment

The Cochrane Collaboration ‘‘Risk of Bias’’ tool was used to analyze the quality of the studies [31]. This was performed using the RevMan 5.3 software. Various domains were assessed; final judgments were indicated as low, high, or unclear risk. The meta-analysis of the

Table 2. Summary of the included studies

Author/ Country	Year & journal of publication (language)	Tooth type, number of subjects and group wise division	Primary or supplemental injection type	Case/ study type	Pain evaluation	Success rate with statistical result
Aggarwal, et al./ India [27]	2019, J Endod (English)	Mandibular 1st & 2nd molars Total patients: 82 in the age group 21-44years Group 1= 24 males and 17 females 1st Molars-30 2nd Molars-11 Group 2= 24 males and 14 females 1st Molars-34, 2nd Molars-7	1°-IANB 1.8 ml of 2% lidocaine with 1:100000 epinephrine Supplemental Group 1 IL – 0.6 ml of 4% articaine with 1 : 100000 epinephrine Group 2 IL - 2% Lidocaine with 1 : 80000 epinephrine	Symptomatic irreversible pulpitis Randomised double blind study	Heft parker VAS	Group 1 = 66% Group 2 = 78% (No significant difference among groups)
Aggarwal, et al./ India [26]	2018, Int End J (English)	Mandibular Molars Total patients= 78 Group 1 - Age group 19-35 years 16 males and 23 females Group 2 - Age group 21-43 years 24 males and 15 females	1°– IANB Supplemental Group 1 - IL - 0.2 ml of 2% Lidocaine with 1 : 80000 epinephrine Group 2 IL - 0.6 ml of 2% Lidocaine with 1 : 80000 epinephrine	Symptomatic irreversible pulpitis Randomised double blind study	Heft parker VAS	group 1= 64% group 2= 84% sig diff
Zarei, et al./ Iran [24]	2012 Int End J (English)	Mandibular Molars & Premolars Total patients = 40 in the age group of 18-50 years 18 males and 22 females	1° – IANB Supplemental Group 1 - IO with X tip Group 2 IL - 1,8 ml of 2% Lidocaine with 1 : 100000 epinephrine	Symptomatic irreversible pulpitis Randomised Controlled clinical single blind study	VAS	Group 1 = 100% Group 2 = 70% (No significant difference)
Aggarwal et al./ India [29]	2020 Act Odont Scand (English)	Mandibular Molars Total patients = 118 Group 1 - Age group 25-52 years 16 females and 28 males Group 2 - Age group 23-48 years 17 females and 27 males	1° – IANB 2% lidocaine with 1:80,000 epinephrine Supplemental: Group 1: 2% lidocaine with 1:80,000 epinephrine. Group 2: 2% lidocaine with 1:200,000 epinephrine.	Symptomatic irreversible pulpitis Randomised double blind study	Heft Parker VAS	Group 1: 82% Group 2: 57% No significant difference

IANB, inferior alveolar nerve block; IL, intraligamentary; IO, intraosseous; VAS, visaul analog scale.

included studies was based on a comparison of primary IANB versus supplementary IL injection.

4. Interpretation of studies

Aggarwal et al. (2019) [27] carried out a randomized trial to evaluate the anesthetic effect of 4% articaine and 2% lidocaine administered as a supplemental IL technique after unsuccessful anesthesia by primary nerve block injection. Interpretation of the success or failure of anesthesia was determined by mild or absent pain during access opening. If the patient reported minimal pain during treatment (HP VAS score < 55), it was regarded as successful anesthesia. Patients with primary IANB failure received supplementary IL injections of 2% lidocaine (1:80,000 epinephrine) or 4% articaine (1:100,000 epinephrine). Success rates of 66% and 78% was observed with 4% articaine (27 out of 41 patients) and 2% lidocaine injections (32 out of 41 patients), respectively. However, no significant difference was observed (P = 0.2).

In a randomized double-blind study, Aggarwal et al. (2018) [26] investigated the anesthetic efficiency of 2%

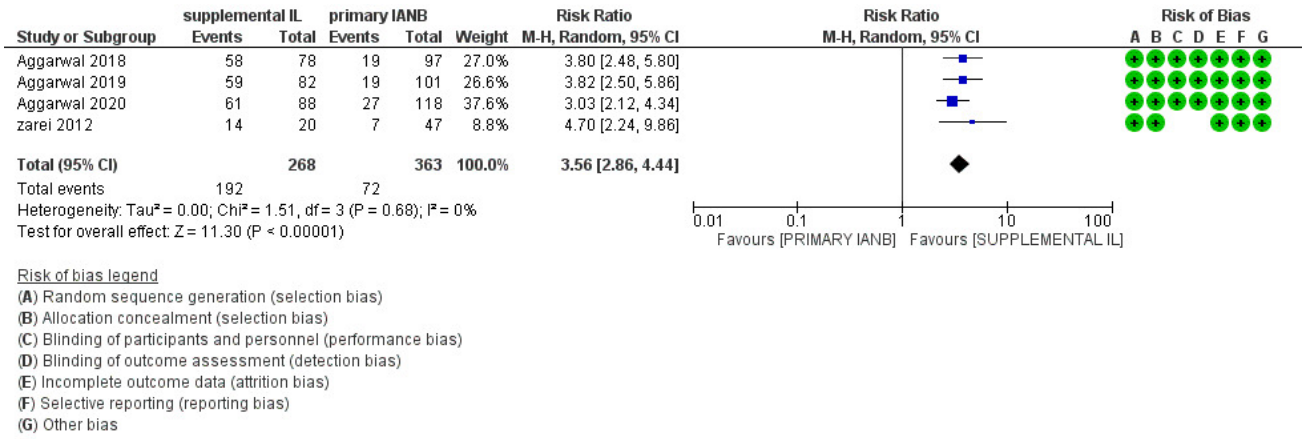

Fig. 2. Forest plot representation. CI, confidence interval; M-H, Mantel-Haenszel test; IANB, inferior alveolar nerve block; IL, intraligamentary.

lidocaine with 1:80 000 epinephrine in two volumes, that is 0.2 mL vs. 0.6 mL, injected as a supplementary IL injection after the failure of primary IANB. As a result, 97 patients were injected with an IANB followed by the initiation of root canal treatment. Furthermore, 78 patients randomly received an IL injection using either of the two volumes after unsuccessful anesthesia. An HP VAS score $\leq$ 54 during the initial steps of treatment was considered as successful anesthesia. In this study, volumes of 0.2 mL and 0.6 mL of the solution was found to be successful in 64% and 84% of cases with failed primary IANB (P = 0.03), respectively.

In a single-blind randomized trial, Zarei et al. (2012) [24] compared the efficiency of supplemental anesthesia using PDL and IO injected using the X-Tip system concerning measured heart rate and pain level reported by the patient. Forty patients diagnosed with irreversible pulpitis who had reported pain after IANB using 2% lidocaine with 1:100,000 epinephrine were selected and divided randomly into two groups. One group of patients received IO injection using the X-tip system, whereas the other group received PDL injection. Pain was scored using the VAS. Patients reported a 100% success rate with X-Tip system injections and a 70% success rate with PDL injections. However, these differences were not significant (P = 0.02).

Aggarwal et al. (2020) [29] investigated the effect of supplemental IL injections administered after failed primary IANB using 2% lidocaine with two epinephrine concentrations. In total, 118 patients received primary IANB injections before endodontic treatment. Pain was assessed using the HP VAS. As a result, 88 patients reported pain during treatment and were allocated to two groups according to the concentration of epinephrine in the supplemental IL injection. The group that received 2% lidocaine and 1:80,000 epinephrine showed a success rate of 82%, while the other group that received 2% lidocaine with 1:200,000 epinephrine showed a success rate of 57%. However, the differences were not significant (P=0.011).

5. Quality assessment

Three studies had a low risk of bias in most domains [26,27,29]. One study had unclear blinding of participants and results [24]. Evidence level grading was determined according to the National Services Scotland Guidelines [32]. Three studies had an evidence level of 1++; one study [24] had an evidence level of 1+ [26,27,29].

6. Meta-analysis

1) Forest plot calculations

RevMan 5.3 software was used for the quantitative analysis. The meta-analysis of the included studies was based on the comparison of a primary nerve block injection versus a supplementary IL injection

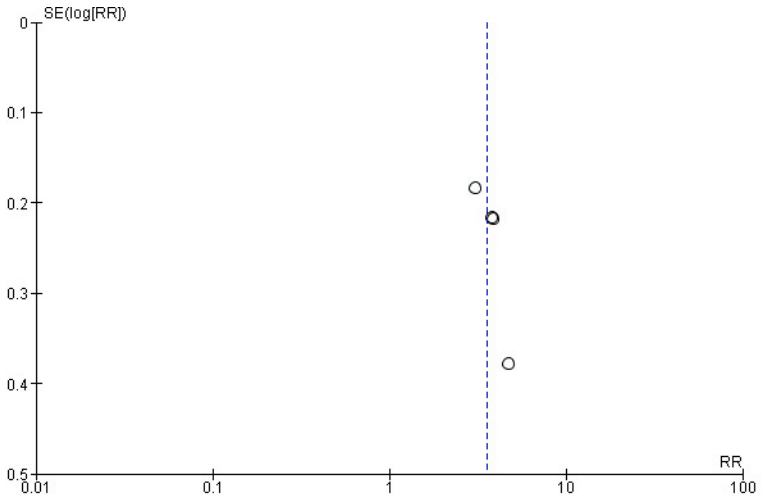

Fig. 3. Funnel plot representation. RR, relative risk; SE, standard error.

administered after a failed IANB [24,26,27,29]. The random-effects meta-analysis is shown in the forest plot (Fig. 2). The combined risk ratios (RRs) were 3.56 (95% CI: 2.86, 4.44), favoring the supplemental injection. The statistical heterogeneity was set at 0%. The results proved that supplementary IL injection increases anesthetic efficacy in cases of failure to achieve adequate anesthesia through primary nerve block injections.

2) Funnel plots

Funnel plots were drawn to analyze the extent of bias for each publication; studies evaluating supplemental IL injections showed lower publication bias (Fig. 3).

DISCUSSION

In cases of irreversible pulpitis, IANB injections may not always be satisfactory [1,3]; both 2% lidocaine and 4% articaine solutions were associated with poor success rates [28]. Both IL and IO injections administer the anesthetic agent directly into the bone [3,9,10,14,17-20]. IO injections directly inject the solution as it perforates the buccal cortical plate [10]. On the other hand, IL injections administer the solution into the periodontal space under pressure; thus, the solution diffuses towards adjacent bony areas through natural perforations in the alveolar bone [9,10,17].

In this review, we have summarized the anesthetic efficacy of supplemental IL injections in cases of irreversible pulpitis, particularly in mandibular teeth. This is a viable and less invasive injection technique [9]. However, these techniques have adverse effects that include suboptimal anesthetic intervals and postoperative discomfort [3,22,33]. Moreover, it is a highly sensitive technique; detecting the “back-pressure” that ensures if the needle is within the PDL remains a challenge [21].

In endodontics, the IL technique has been studied as both a primary and a supplemental injection. Various clinical studies have focused on the effects of supplemental IL injections. Studies showing its anesthetic efficacy as a supplemental injection in symptomatic irreversible pulpitis showed a higher success rate of 85% [18,24,26,27,29].

A similar systematic review reported that pulpal anesthetic strategies showed the efficacy of all forms of supplemental techniques for symptomatic irreversible pulpitis in lower molars [34], including three studies for IL injection [18,24,26]. The present review reports on the efficacy of IL supplemental technique in mandibular teeth with symptomatic irreversible pulpitis, with two additional studies included in the final review [27,28].

The study by Kanaa et al. (2012) [18] was excluded from the current review because its success was evaluated via electric pulp testing and not through pain scales, as in the other four included studies. Furthermore, two other studies were excluded from the review because access preparation and pulp extirpation were not performed to assess pulpal anesthesia [35,36]. Another study by Nusstein (2005) [22] was also not included in the current review because it did not mention primary IANB failure, and the supplemental IL injection was administered to all included patients.

The limiting factor of the current review is the limited number of included studies; more reliable clinical trials are required. However, the cumulative risk of bias in every domain was low for all studies. A meta-analysis was performed to quantify the qualitative results of the review. The success rate was evaluated by the combined RR using a random risk model. According to the forest plot representation, the RRs were found to be 3.56 (95% CI: 2.86, 4.44), favoring supplemental IL injections. The statistical heterogeneity was set at 0%. These values indicated that supplemental IL injections improved anesthetic success rates. The results suggested better success rates of supplemental IL injections given after failure of the primary nerve block. The qualitative and quantitative results suggest the inclusion of supplemental IL injection after an ineffective primary IANB injection for a more optimal induction of anesthesia.

In conclusion, in this review, we focused on the important role of supplemental IL injections in clinical practice. The use of supplemental injections after a primary IANB failure is clinically relevant.

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