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ORIGINAL ARTICLE

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

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ABSTRACT

Objective: The purpose of this prospective, randomized clinical trial was to evaluate the effect of cooling a 2% lidocaine solution with 1:200,000 epinephrine, administered as a supplementary intraligamentary injection to overcome a failed primary inferior alveolar nerve block (IANB).

Methods: The study was preceded by a pilot study to evaluate the anesthetic efficacy of plain lidocaine solutions given as intraligamentary injections. In the subsequent randomized clinical trial, one hundred and thirty-eight patients received IANB with 2% lidocaine with 1:80,000 epinephrine for endodontic management of a mandibular molar with symptomatic irreversible pulpitis. Eighty-eight patients reported pain greater than 54 mm on a visual analog scale (Heft-Parker VAS) were categorized as unsuccessful anesthesia. These patients received either of the following intraligamentary injections: 2% lidocaine with 1:200,000 epinephrine at room temperature; or 2% lidocaine with 1:200,000 epinephrine at 4°C. Anesthetic success was again evaluated after re-initiation of the endodontic treatment. The heart rates of the patients were measured using a finger pulse oximeter. The categorical success rates were statistically analyzed with the Pearson chi-square test at 5% significance levels. The heart rate measurements were analyzed using a t-test.

Results: The intraligamentary injections with anesthetic solutions at room temperature presented a success rate of 59.1%, while the injections with a solution at 4°C gave a success rate of 52.27%. There were no significant differences between the success rates of the groups (χ^2=0.41, p=0.52). Regarding the heart rates, there were no differences between the two solutions at baseline (T=1.2, p=0.2) or after injections (T=0.64, p=0.52).

Conclusion: Reducing the temperature of 2% lidocaine with 1:200,000 epinephrine to 4°C does not affect the anesthetic efficacy of supplemental intraligamentary injections, given after a failed primary IANB.

Keywords: Cooling, epinephrine, irreversible pulpitis, lidocaine, mandibular anesthesia

HIGHLIGHTS

- The symptomatic mandibular molars present a high anesthetic failure rate of a single primary inferior alveolar nerve block injection during endodontic treatment.
- A supplementary intraligamentary injection with 2% lidocaine with epinephrine can help to manage more than half of the failed cases.
- Cooling the anesthetic solution does not improve its efficacy when administered as a supplementary intraligamentary injection.

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INTRODUCTION

The mandibular molars with symptomatic irreversible pulpitis are difficult to anesthetize (1, 2). The endodontic treatment of such teeth usually involves the administration of supplemental anesthesia after a primary inferior alveolar nerve block (IANB) has failed (3–6). The roots of the mandibular teeth are surrounded by a thick cortical bone that impedes the flow of anesthetic solution (deposited as infiltration) to the root apex via cancellous bone (7, 8). To deposit a local anesthetic solution near the root apex, alternative methods such as intraosseous and intraligamentary injections can be used (5, 6, 9, 10). The Intraligamentary injection technique uses high pressure to administer the anesthetic solution into the periodontal space (4, 11, 12). The pressure forces the solution into the cancellous bone surrounding the root apex of the involved tooth (4). Thus, without perforating the cortical bone, unlike intraosseous anesthesia, the clinician can cross the bony barrier.

The anesthetic efficacy of the intraligamentary injections given after a failed IANB can be affected by different variables. Aggarwal et al. (13) reported that administration of 1.2 mL of 2% lidocaine with 1:80,000 epinephrine (0.6 mL per root) as supplementary intraligamentary injections gave better anesthetic success rates (84% vs. 64%) compared to 0.4 mL injections. Interestingly, Nusstein et al. (10) reported success rates of 54% using 1.4 mL of 2% lidocaine with 1:100,000 epinephrine injected with a computer-controlled local anesthetic delivery system. In other studies, the choice of local anesthetic solution did not affect the anesthesia. Using 4% articaine or 2% lidocaine with epinephrine had statistically similar results in different clinical experiments (9, 14, 15). Perhaps, the most significant variable affecting intraligamentary anesthesia is the amount of epinephrine in the anesthetic solution. Kaufman et al. (16) compared 2% lidocaine solutions with different amounts of epinephrine (plain vs 1:50,000) given as intraligamentary injections. It was reported that lidocaine with epinephrine had an anesthetic duration of 27 minutes compared to 1 minute with a plain solution. A study evaluating two different concentrations of epinephrine (1:80,000 vs 1:200,000) in 2% lidocaine given as an intraligamentary injection after a failed primary IANB reported significantly higher success rates in solutions with high epinephrine dosage (17).

The aim of adding epinephrine in the local anesthetic solution is to decrease the uptake via absorption in the blood. The epinephrine causes local vasoconstriction, thus decreasing the absorption of the local anesthetic solution. In the past, some concerns have been raised about the rapid uptake and safety of intraligamentary injections (18–20). It would be useful to find out a way to reduce the uptake of local anesthetic solutions without increasing the amount of epinephrine. A simple way is to decrease the temperature of the anesthetic solution. Cooling has been shown to cause vasoconstriction in cutaneous arteries via α1-adrenoceptor and α2C-adrenoceptors (21). Moreover, cooling the solution can lead to a reversible block of the compound action potential of rat sciatic nerves (22). Butterworth et al. (23) reported that ice cooling the lidocaine solution caused greater inhibition of sensory nerve action potential compared to room temperature solutions. Dabarakis et al. (24) evaluated 3% plain mepivacaine solution at different temperatures (4°C vs. 20°C) and reported that solutions at 4°C had a significantly longer duration of action. The evaluation of cooling of the anesthetic solution has not been researched extensively. To the best of our knowledge, no study has evaluated the effect of cooling the anesthetic solution for intraligamentary injections.

The present study aimed to evaluate and compare the anesthetic efficacy of 2% lidocaine with 1:200,00 epinephrine at different temperatures (4°C vs room temperature) when administered as supplementary intraligamentary injections after a failed primary IANB. The study was designed as a prospective, randomized, double-blind clinical trial. The study also evaluated heart rates as secondary outcomes. The null hypothesis was that anesthetic solutions at different temperatures do not affect the anesthetic success or the heart rates.

MATERIALS AND METHODS

The study was preceded by a pilot study to evaluate the anesthetic efficacy of plain lidocaine solutions for intraligamentary injections. A relevant ethical clearance was taken for the pilot and the subsequent trial (No: 24/5/330/XXX/IEC/5/2020). A total of eighteen patients were included in the pilot study. The patient required a restoration in a mandibular first or second molar. Teeth with irreversible pulpitis, necrotic pulps, and poor periodontal status were excluded. Intraligamentary injections of 0.6 mL (per root, total 1.2 mL) and 2% lidocaine without epinephrine (kept at 4°C using an ice bath) were given using a pressure-type syringe. An electric pulp tester (EPT) was used to check the response at a 60-second interval immediately after the injections. A complete absence of any response to the maximum current output was considered an anesthetic success. The duration of anesthesia was measured. It was found that 5 patients (28%) did not achieve any pulpal anesthesia. The mean duration of the anesthesia in the remaining patients was only 1.7±0.8 minutes. Considering the low success rates of plain solutions, it was decided to test solutions with a minimal amount of epinephrine i.e. 2% lidocaine with 1:200,000 epinephrine.

The clinical trial was a 6-month long study using a prospective, randomized design. Patients requiring endodontic treatment of a single symptomatic mandibular molar with irreversible pulpitis were enrolled in the study. Ethical clearance was obtained for the study (IEC/FOD/XXX/06/2020) and all participants gave informed written consent. The study was conducted in accordance with the Declaration of Helsinki. A combined visual analog scale, the Heft-Parker scale (HP VAS), was used to categorize/ quantify the pain during the treatment (25). The HP VAS has six categorical limits (faint, weak, mild, moderate, severe, and intense) on a 170 mm line. The ends of the line are labeled as 'no pain' and 'unbearable pain'. To use the scale, the patient was instructed to mark the pain line corresponding to his/her pain, with cues from the different categorical points (6, 10). The line marked from no pain to mild pain (corresponding to 0 to 54 mm) was considered a cut-off for assessing the success of the anesthesia. The injection was categorized as successful if i) there was a negative response anesthetic to the post-injection EPT, and ii) the

ability of clinician to perform canal instrumentation with no or mild pain (up to 54 mm on HP VAS). The anesthetic success was categorized as the primary outcome of the study and sample size calculations were performed.

Based on the data of a previous study (17), and keeping the type 1 error and type 2 error at 5% and 0.2 respectively, it was calculated that at least 39 patients should be recruited to determine a difference of 25% in the primary outcome. The sample size calculations for the secondary outcome (pre-and post-injection heart rates) revealed that including 19 patients per group would allow the detection of a difference of 10 beats (resting heart rate at 80±11). The preoperative data for this calculation was based on a previous study (26). Accordingly, 44 patients were recruited per group, considering a dropout rate of 10% during the treatment. Since it was a single-appointment study, the dropout rate was used to take into account any patient that would have refused to participate during the treatment.

To include a patient in the study, the following criteria were followed: carious exposed mandibular first or second molar with symptomatic irreversible pulpitis (confirmed with a positive and prolonged response to thermal and electric pulp sensibility tests and a vital pulp upon access opening), and American Society of Anesthesiologists class I or II medical history. The included patients were able to understand and use the pain scales. The specific exclusion criteria were: contraindication to any component of the local anesthetic solution, and patients taking any opioid drug affecting pain perception, which was determined by a written questionnaire and verbal question/answer. Furthermore, pregnant or breastfeeding patients, and patients with active pain in more than one tooth were excluded. Teeth with anatomical variations, such as fused or extra roots, were also excluded. The diagnosis and the recruitment were performed by a clinician not involved in the clinical experiment to reduce recruitment bias. A total of one hundred and thirty-eight patients were initially included in the study.

All included patients received a single IANB injection of 1.8 mL of 2% lidocaine with 1:80,000 epinephrine. Direct mandibular nerve block, also known as the Halsted technique was used to give the injections (27). The technique has been described in previous reports (13, 14, 17). Briefly, after the application of topical anesthesia, the anesthetic injection was given 2 mm above the occlusal plane, on an imaginary line drawn from the coronoid notch to the pterygomandibular raphae. The syringe was placed between the opposite mandibular premolars. When the target area was achieved, aspiration was performed. The solution was slowly deposited for two minutes. After ten minutes of the initial IANB, subjective symptoms of lip numbness were evaluated. The absence of a profound lip numbness indicated a missed block and the patients were excluded from the study. The patients were profound lip numbness received conventional endodontic access opening under a rubber dam. If patients experienced any pain, they were instructed to raise their hands and mark their pain on the HP VAS. Of the initial 138 patients, 88 patients presented with anesthetic failure (pain scores more than 54 on HP VAS. The patients with a failed initial IANB were assigned an alpha-numeric code and were randomly allocated to one of the two treatment groups (n=44) with the help of an online random generator, using permuted block stratified randomization protocol (sealedenvelope.com). A clinician from another institute prepared the patient allocation sequence. The sequence was enclosed in an opaque sealed envelope. The envelope was opened just before the injections. To prepare the anesthetic cartridges with 2% lidocaine with 1:200,000 epinephrine, standard anesthetic cartridges were emptied, washed, autoclaved, and filled with 2% lidocaine with 1:200,000 epinephrine using a 5 mL syringe. The solution was taken from commercially available 30 mL dental local anesthetic solutions (Lidayn, Dentaids, Gautam Buddha Nagar, India). A trained dental intern prepared the anesthetic cartridges. To ensure blinding, the cartridges were masked and coded. A clear plastic tape was used to cover the code to protect it from subsequent water bath immersion. The cartridge code was noted along with the patient code.

To administer supplementary intraligamentary injections, the rubber dam was removed. The gingival sulcus was thoroughly cleaned with an antiseptic solution. A finger pulse oximeter was placed on the index finger of either hand and the resting heart rate was monitored. In the control group, intraligamentary injections of 2% lidocaine with 1:200,000 epinephrine placed at room temperature, were administered using a pressure-type syringe (Osung Deosy, Pearland, Tx, USA) and 30 gauge short needles (Septojet needles, Septodont). The injecting needle was bent to allow for easy insertion in the mesial gingival sulcus at the mesio-buccal line angle of the tooth. The needle was firmly wedged between the involved tooth and the alveolar bone ensuring a firm resistance to the anesthetic deposition. The handle/trigger of the syringe was firmly squeezed to gradually complete three squeezes (which deposited 0.2×3=0.6 mL) under back pressure. If the clinician was not able to feel a back pressure, the needle was repositioned and the injection was repeated till a back pressure was achieved. To prevent the backflow of the solution, the syringe was kept in place for another 20 seconds. Distal root received similar injections of 0.6 mL. In the experimental group, the prepared cartridges were cooled in an ice-water bath using an opaque plastic chiller ice pack. A digital thermometer was used to confirm the temperature at 4±2°C. The cartridges were placed for 15 minutes in the bath before injections. The patients in the experimental group received intraligamentary injections using a similar technique used in the control group. To blind the cartridges of the control group, the cartridges were placed in a similar plastic box filled with water at room temperature. A dental intern measured the heart rate at 30-second intervals for a total duration of 5 minutes after the intraligamentary injections. In case of pain during the treatment, the heart rate readings were discarded (owing to an increase in heart rate corresponding to the stress of the pain). The endodontic treatment was re-initiated under a rubber dam. The anesthetic success was again defined as no pain or faint/weak/mild pain during endodontic access preparation and instrumentation (HP VAS score <55 mm).

Statistical analysis

The age of the patients was analyzed using the Mann-Whitney U test. The gender, type of tooth, and anesthetic success

TABLE 1. Comparison of age, gender, and type of tooth

	2% lidocaine at room temperature	2% lidocaine at 4°C	p
Age	36.8 years±8.2 years, range- 23–51 years	33.8 years±10.2 years, range- 26–48 years	0.42
Gender	18 males	23 males	
	26 females	21 females	0.28, χ^2=1.14, df=1
Type of tooth	First molar=32	First molar=28	
	Second molar=12	Second molar=16	0.36, χ^2=0.84, df=1

df: Degree of freedom

TABLE 2. Group-wise comparison of the anesthetic success rates

	vs. (%)	The difference in success rates, %	p	95% confidence intervals		Chi-square, degree of freedom (X^2, df)
				Lower bound, %	Upper bound, %	
2% lidocaine at room temperature 26 out of 44 patients (59.1%)	2% lidocaine at 4°C 23 out of 44 patients (52.27)	6.83 %	0.52	–13.44	26.33	0.41, 1

TABLE 3. Pair-wise comparison of the change in heart rates before and after injections

	Mean of heart rates at baseline	Mean of maximum heart rate after injections	Difference post-injection vs. Pre-injection	95% confidence intervals		T score, p
				Lower bound	Upper bound	
2% lidocaine at room temperature	70.2	81.6	–11.45	–14.0	–8.9	T= –8.8 p<0.0001 Significant at 5% and 1%
2% lidocaine at 4°C	68	80.8	–12.54	–15.5	–9.6	T= –8.4 p<0.0001 Significant at 5% and 1%
Comparison of 2% lidocaine at room temperature vs. 2% lidocaine at 4°C Baseline heart rate			1.88	–1.1	4.90	T=1.2 p=0.2 Non-significant
Comparison of 2% lidocaine at room temperature vs. 2% lidocaine at 4°C Maximum heart rate			0.79	–1.6	3.3	T=0.64 p=0.52 Non-significant

rates were analyzed with the Pearson chi-square test using Sigma-Stat 3.1 software (Systat Software, Erkrath, Germany). The heart rate changes were analyzed using a t-test. The significance level was kept at 5%.

RESULTS

Out of the initial one hundred and thirty-eight patients, fifty patients presented with successful anesthesia (36% success rate). Eighty-eight patients with failed primary IANB participated in the trial. The difference between age, gender, and the type of tooth is presented in Table 1. There were no statistically significant differences between these variables. The intraligamentary injections with anesthetic solutions at room temperature presented a success rate of 59.1% (26 out of 44 patients), while the injections with a solution at 4°C gave a success rate of 52.27% (23 out of 44 patients). There were no significant differences between the success rates of the groups (χ^2=0.41, p=0.52). The detailed comparison is presented in Table 2.

The comparison of the baseline and maximum heart rate after intraligamentary injections is presented in Table 3. There were no differences between the two solutions at baseline (T=1.2, p=0.2) or after injections (T=0.64, p=0.52).

DISCUSSION

The initial IANB was successful in 36% of cases. The success rate was similar to studies evaluating an IANB during endodontic management of symptomatic mandibular molars (1, 6, 10, 17, 28). This low success rate can be attributed to the activation of certain receptors such as tetrodotoxin-resistant receptors and capsaicin-sensitive transient receptor potential vanilloid type 1 (1, 29, 30). These receptors get activated by the presence of inflammatory mediators (29), and exhibit resistance to the local anesthetic solutions (1, 29–31). To achieve successful anesthesia, supplementary injections are needed (31). A plausible method to improve endodontic anesthesia will be to deposit the anesthetic solution near the root apex. Since a thick buccal cortical plate impedes the anesthetic flow, intraligamentary injection can be used as a minimally invasive method. It can be used with a routine dental syringe (6) or with a pressure syringe (17). The injection aims to force the anesthetic solution from the periodontal space to the cancellous bone surrounding the root apex using strong back pressure (11). Earlier, the mechanism of action of intraligamentary injections was thought to be the strong back pressure similar to intrapulpal anesthesia (32). However, this was refuted by Moore et al. (33) in 1987. The authors injected saline and 2% lidocaine with 1:100,000 epinephrine, in mandibular first premolars, using an intraligamentary technique. After 10 minutes of injections, 42% of teeth in the lidocaine group were anesthetized compared to 0.0% in the saline group (33). Later, Tagger et al. (34) investigated the spread of anesthetic solution in intraligamentary injections using a dye and histological sections. The authors reported that the anesthetic solution had reached the alveolar crest and entered the bone marrow (34). The authors noted that the solution did not spread into the periodontal ligament or in the root canal but diffused out of the periodontal space, via small channels in the alveolar socket. Smith and Walton (35) noticed that the spread of the solution is more like an intraosseous injection.

As the local anesthetic solution reaches the medullary cancellous bone, it is subjected to rapid uptake by blood circulation. The solution is absorbed in the blood circulation, thus decreasing the concentration and the amount of the anesthetic solution. This was evident in the data of the pilot study where it was noted that all patients receiving an intraligamentary injection without a vasoconstrictor reported either no anesthesia or anesthesia of very short duration (1–2 minutes). To overcome this effect and to increase the duration of action of the local anesthetic agent, a vasoconstrictor is added to the solution (36). The vasoconstrictor, also known as a chemical tourniquet, causes peripheral vasoconstriction. This leads to reduced uptake of the anesthetic solution. The most common vasoconstrictor used in dentistry is epinephrine. It stimulates both alpha and beta-adrenergic receptors. Because of its beta stimulation, it may produce some complications (19). When a single injection of an anesthetic solution with epinephrine is given, the risk of an adverse reaction is minimal. However, the risk increases if multiple injections are given (20). The same is true for intraligamentary injections, as there is a rapid uptake of the solution contents in the bloodstream. A study has reported that within 2 minutes of an intraligamentary injection, the peak blood level of anesthetic agents was up to 25% of the intravenous dose. Hence, it is important to find a method to decrease the uptake of local anesthetic solution in intraligamentary injections without increasing the epinephrine dose.

A rather simple way to possibly cause local vasoconstriction is to inject the cooled local anesthetic solutions. Cooling causes significant peripheral vasoconstriction via adrenoceptors (21). There is another important aspect of the cooling of anesthetic solutions. It has been reported that cooling can potentiate the lidocaine inhibition of median nerve sensory fibers (23). Butterworth et al. (23) suggested that cooling the anesthetic solution can delay the uptake of local anesthetic by peripheral circulation. Cooling itself has been shown to reduce the conduction in both myelinated and non-myelinated axons (37). It has also been shown that the pKa of lidocaine increases with a decrease in temperature. Sanchez et al. (38) reported that a decrease in the temperature of lidocaine led to an increase in its pKa, ionic strength, and buffer capacity. Similar results have been reported in other studies (21, 39, 40). Thus, injection of a cooled lidocaine solution will lead to the presence of more ionized anesthetic ions rather than base form. Rosenberg and Heavner (22) reported that cooling of lidocaine potentiated its dose-dependent blocking action in terms of an increased duration/ latency of the compound action potential of rat sciatic nerves. In a human trial, Ince et al. (41) evaluated a 1:1 mixture of 2% lidocaine and 0.5% bupivacaine at three different temperatures (4°C, 25°C, and 37°C) on the duration of sensory and motor blocks in infraclavicular brachial plexus nerve block. The authors reported that the solutions at low temperatures had a long duration of action than solutions at room temperatures. In an endodontic setup, Dabarakis et al. (24) evaluated the onset and duration of 3% mepivacaine infiltrations in maxillary premolars. In the first appointment, the anesthetic solution had a temperature of 20°C, while at the subsequent appointment, the temperature of the solution was 4°C. The anesthesia was evaluated using an electric pulp tester. The authors reported that the duration of anesthesia was significantly more in the 4°C groups (22.3 min vs 17.3 min).

Because cooling the local anesthetic solution may increase its duration and potency, the current research aimed at evaluating the anesthetic efficacy of 2% lidocaine with 1:200,000 epinephrine, cooled at 4°C and administered as a supplementary intraligamentary anesthesia after a failed primary IANB. The injections administered with an anesthetic solution at room temperature gave a success rate of 59%. Cooling the anesthetic solution did not improve the anesthetic success rate (52%). The intraligamentary injections were administered under strong back pressure. It took more than a minute to inject 0.6mL of anesthesia via the periodontal space. When a cold solution is injected into the body tissues, it slowly warms to the body temperature. The slow rate of the injections may lead to the warming of the solution in the body tissues, thus negating the cooling of the solution. As stated before, the medullary space is highly vascular. The copious blood flow would have warmed the slowly deposited anesthetic solution. Regarding the success of the individual solution, the success rate was similar to studies evaluating supplementary

intraligamentary injection. Chen et al. (6) reported success rates of 69–80% after administering one or two sets of intraligamentary injections after a failed primary IANB.

CONCLUSION

In conclusion, cooling the 2% lidocaine with 1:200,000 epinephrine to 4°C does not increase the anesthetic success rate of supplemental intraligamentary injections, given after a failed primary IANB.

Disclosures

Conflict of interest: The authors deny any conflict of interest.

Ethics Committee Approval: This study was approved by The Jamia Millia Islamia, New Delhi Ethics Committee (Date: 07/07/2020, Number: 24/5/330/XXX/IEC/5/2020).

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