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ORIGINAL ARTICLE

Effect of Intraligamentary Tramadol Hydrochloride on Anesthetic Success During Endodontic Management of Mandibular Molars: A Randomized Clinical Controlled Trial

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ABSTRACT

Objective: Tramadol hydrochloride has shown local anesthetic properties similar to lidocaine, apart from a central analgesic effect. The present study evaluated the effect of the administration of tramadol alone or in addition to 2% lidocaine, as supplementary intraligamentary injections.

Methods: One hundred and five patients, with a failed primary inferior alveolar nerve block (IANB), were randomly allocated to one of the three supplementary intraligamentary groups: 2% lidocaine with 1:80,000 epinephrine; tramadol hydrochloride (50 mg/mL); and 2% lidocaine with 1:80,000 epinephrine plus tramadol hydrochloride. Patients received 1.2 mL doses (0.6 mL of each root). Patients reporting pain ≤54 on Heft Parker visual analogue scale (Heft-Parker VAS), were categorized as successful anesthesia. A finger pulse oximeter was used to measure the heart rates. The anesthetic success rates, gender, and type of tooth were compared using the Pearson chi-square test. The heart rates and age were statistically evaluated using the one-way analysis of variance test. The level of significance was set at 0.05 ($p=0.05$).

Results: The initial IANB was successful in 31% of cases. There were significant differences in the anesthetic success rates of different supplementary intraligamentary injections ($\chi^2= 33.6$, $p<0.001$, $df=2$). The 2% lidocaine-plus-tramadol resulted in significantly higher success rates than the two groups. There were no significant changes in the baseline heart rates of all groups ($p>0.05$).

Conclusion: The addition of tramadol to 2% lidocaine with 1:80,000 epinephrine, given as supplementary intraligamentary injection, can help in achieving successful anesthesia during the endodontic management of mandibular molars with irreversible pulpitis resistant to IANB injections.

Keywords: Epinephrine, irreversible pulpitis, lidocaine, mandibular anesthesia, tramadol

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.
- Adding tramadol hydrochloride to 2% lidocaine, given as intraligamentary injections, provide better anesthesia for endodontic treatment procedures.

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INTRODUCTION

Endodontic treatment is preceded by the administration of local anesthetic solutions. These can be deposited as local infiltrations, nerve blocks, or via other routes such as intraseptal, intraosseous, and intraligamentary (1–6). The local anesthetic agents act by inhibiting the inward flow of sodium, by binding their ionized form to various receptors and open voltage-gated channels on the nociceptors in a reversible manner (7, 8). This prevents depolarization of the nerve cells and further neuronal transmission of the action potential, thus providing a peripheral nerve conduction blockage (9). In the presence of localized inflammation, the activation threshold of the nociceptors is reduced (4). As a result, the nociceptors may fire at a stimulus less than the threshold (4, 10, 11). This reduces the anesthetic efficacy of local anesthetic solutions. In addition to this mechanism, the inflammatory mediators also affect the activation of receptors such as transient receptor potential vanilloid type 1 and tetrodotoxin-resistant receptors (4, 11–13). Activation of these receptors further reduces the action of local anesthetic agents. Clinically, these effects lead to a drastic reduction in the anesthetic success rates in symptomatic teeth with irreversible pulpitis. Especially in mandibular molars, failure rates as high as 80%, have been reported (14–18).

Various anesthetic agents including, lidocaine, articaine, mepivacaine, and bupivacaine, have been used to provide nerve block anesthesia for the endodontic management of symptomatic mandibular molars. These agents have given almost similar success rates when administered as a primary inferior alveolar nerve block (3, 4). Various additives, such as dexamethasone, ketorolac, and other non-steroidal anti-inflammatory drugs (NSAIDs) have also been evaluated. Opioids such as diamorphine and fentanyl also exert some local anesthetic properties. Tramadol hydrochloride is one opioid, which is structurally related to methylmorphine (19). A study evaluated the effect of the topical application of morphine to the de-sheathed saphenous nerve, and reported that the drug reversibly inhibited nerve conduction(20). The local anesthetic effect of tramadol was evaluated by Pang et al. (21, 22) by administering intradermal injections of 0.5 mL of tramadol, lidocaine, and saline on the volar surfaces of the forearms. The authors reported that both lidocaine and tramadol significantly reduce pain perception compared with saline and there were no significant differences between the two test solutions (21). Since then, many studies have evaluated the local anesthetic effect of tramadol used alone or in combination with other local anesthetic agents. The studies have reported that tramadol exerts local anesthetic properties similar to lidocaine (19, 23–27). The majority of these studies have been performed on patients undergoing surgical procedures. Ege et al. (23) compared the anesthetic efficacy of tramadol and lidocaine in maxillary infiltrations. The authors found that both solutions provide similar anesthetic durations. Another study compared their efficacy (1.8 mL of 2% lidocaine and 1.8 mL of 50 mg tramadol) during dental extractions, and concluded that tramadol can be an alternative to lidocaine for providing dental infiltration anesthesia (20).

Limited studies have evaluated the use of tramadol, as a local anesthetic agent, during endodontic treatment (15, 28). Since tramadol has a proven local anesthetic effect and a good analgesic effect, it may be beneficial in painful, irreversible pulpitis cases. To the best of knowledge, no study has evaluated supplementary intraligamentary tramadol injections, either alone or in combination with other anesthetic agents. This prospective clinical trial aims to compare and evaluate the use of tramadol, administered as supplementary intraligamentary injections, after a failed primary inferior alveolar nerve block.

MATERIALS AND METHODS

The clinical trial was designed as a prospective, active-controlled, triple-arm, double-blind randomized control clinical trial. The patients with a failed primary inferior alveolar nerve block were recruited for the study at the Faculty of Dentistry, Jamia Milllia Islamia, New Delhi, India. The study was prospectively approved by the institutional research review committee (FOD/IRRC/106/2022/F) and was registered at the relevant clinical trial registry (NCT05538052). The study was conducted in accordance with the Declaration of Helsinki. The study was completed in 6 months. The initial subjects were recruited from the patients reporting to the dental emergency with symptoms of irreversible pulpitis in mandibular molars. The diagnosis of symptomatic irreversible pulpitis was made by a trained endodontist based on the presence of a carious exposed mandibular first or second molar ;acute and prolonged response to the thermal and electric test. The endodontic procedures and subsequent inclusion in the study (in case of failure of primary nerve block) were explained to the patients and informed written consent was taken from each participant.

The sample size calculations were based on the outcome measures, that is, the anesthetic success rates and the changes in heartbeats. The anesthetic success of the primary IANB was defined as a negative response of electric and thermal pulp sensitivity tests after 15 minutes of injections, and no/mild pain (pain score ≤ of 54 on Heft Parker visual analog scale) during endodontic access cavity preparation and root canal instrumentation (14, 17, 29). Based on the data from a previous study, the α errors and the power were kept at 0.05 and 80% respectively (16). Keeping the anticipated incidence of success rate in the control group at 56%, the sample size calculations suggested including 35 patients per group to determine a difference of 30% in the test groups. The sample size calculations for the heartbeat included the evaluation of continuous data from a previous study. The sample size was determined at 23 patients per group to determine a change of 10 heartbeats from the baseline of 77±12 (30). Since the sample size for anesthetic success was higher, it was taken into account and at least 35 patients were included in every group. Initially, the study included one hundred and fifty-three patients.

The inclusion criteria were: the presence of a carious mandibular first or second molar with pulpal exposure; symptomatic irreversible pulpitis with an acute and prolonged response to electric and thermal tests and presence of vital coronal pulp; American Society of Anaesthesiologists class I or II medical histories (31); and ability of the patient to comprehend and understand the use of pain score sheets. The exclusion criteria were: active pain in more than one tooth; contraindication

to the use of any NSAIDs or opioids of any component of the local anesthetic solution; periodontally compromised or mobile teeth; teeth with anatomical variations; and pregnant/ breastfeeding patients. The diagnosis and evaluation of inclusion/ exclusion criteria were made by a trained clinician, not involved in the actual clinical trial.

All included patients received an intracutaneous test to rule out any sensitivity to the injecting solutions (2% lidocaine with epinephrine and tramadol hydrochloride). The diluted solutions (1/10) were injected via an insulin syringe on the extensor surface of the forearm. The injection area was visually observed to rule out any rash or erythema. The study started with the administration of an IANB of 1.8 mL of 2% lidocaine with 1:80,000 epinephrine (Lidayn, Dentaids, Gautam Buddha Nagar, India). The direct technique, described by Halsted, was used to administer IANB (32). After negative aspiration in two planes, the local anesthetic solution was slowly deposited for over 2 minutes. The patients were subjectively evaluated for the presence of lip numbness after 10 minutes. In absence of lip numbness, the block was considered 'missed' and the patient was excluded. Patients with missed blocks were administered a fresh injection of IANB and the data was not included in the final analysis. Patients reporting profound lip numbness again received electric and thermal pulp sensibility tests. In cases of a positive response, the anesthesia was considered as 'failed', and the data was included as failed anesthesia. Patients with a negative response received endodontic access cavity preparation under a rubber dam. If the patient experienced any pain during the treatment, they were asked to mark the pain on 170mm long Heft Parker Visual Analoge Scale HP VAS (29). The HP VAS has 6 categories (faint, weak, mild, moderate, severe, and intense) marked on a 170 mm long line. The patient marks the pain with cues from the categories on the pain scale. If the patient reported pain more than mild pain (marked as more than 54 mm on the HP VAS), the anesthesia was considered failed anesthesia.

The patients with failed anesthesia (105 out of the initial 153 patients) were alphanumerically coded and were randomly allocated to one of the three treatment groups. The randomization codes were prepared using an online randomization protocol (sealedenvelope.com) involving permuted block stratified randomization series. The gender and the type of teeth were considered stratified blocks. The randomization series were prepared by a clinician from another institute. The codes were sealed in opaque envelopes and the envelope was opened just before the administration of supplementary injections. Three types of supplementary intraligamentary injections were given: 2% lidocaine with 1:80,000 epinephrine, tramadol hydrochloride (50 mg/mL), and an equal combination of lidocaine and tramadol (1:1 v/v). For the lidocaine group, standard 1.8mL cartridges were used. For preparing cartridges with tramadol, standard local anesthetic cartridges were emptied, washed, and autoclaved. One set of empty cartridges was filled with 1.8 mL of tramadol hydrochloride (taken from 2 mL ampoule of tramadol hydrochloride with 50mg/mL, (Tramazac 50 mg, Zydus Cadilla, Ahmedabad, Gujrat, India). The other set received 0.9 mL of 2% lidocaine with 1:80,000 epinephrine followed by 0.9 mL of tramadol hydrochloride (50 mg/mL). All cartridges were masked with opaque paper and were alphanumerically coded. The cartridge code was noted along with the patient code and the codes were broken after the completion of the study. The cartridges were prepared by two trained dental interns who were not involved in the clinical part of the trial. The operator was blind to the contents of the cartridges to ensure double-blinding.

The rubber dam was removed. The gingival sulcus was cleaned with a 5% aqueous solution of povidone-iodine. The resting heart rate was evaluated using a finger pulse oximeter. Intraligamentary injections were given using a pressure-type syringe (Osung Deosy, Pearland, Tx, USA) and 30-gauge short needles (Septojet needles, Septodont). The needle was gently bent in the middle using a pair of tweezers, to allow insertion in the gingival sulcus. The needle was gently inserted in the gingival sulcus of the mesio-buccal line angle of the involved tooth till it was firmly wedged between the tooth and the alveolar bone. After confirming back pressure, three clicks of the syringe were administered (depositing 0.6 mL of the solution). In absence of strong back pressure, which was indicated by the easy flow of anesthetic solution out of the sulcus, the needle was repositioned firmly and the injection was repeated. The needle was firmly kept in the position for another 20 seconds to prevent back-flow of the solution. Similar injections were repeated for the distal root. The heart rate measurements were made at baseline, till the completion of both sets of intraligamentary injections (at 30-second intervals). After completion of the intraligamentary injections, endodontic treatment was started again and the anesthetic success was evaluated using HP VAS.

Statistical Analysis

The age and the heart rate of the patients were analyzed using a one-way analysis of variance and suitable post-hoc tests using Sigma-Stat 3.1 software (Systat Software, Erkrath, Germany). The gender, type of tooth, and anesthetic success rates data were categorical and were analyzed with the Pearson chi-square test at 95% significance.

RESULTS

The initial inferior alveolar nerve block was successful in forty-eight patients(48 out of 153 patients, 31% success rate). The remaining one-hundred and five patients further received one of the three intraligamentary injections. The demographic data (age, gender, and the type of tooth) is presented in Table 1. There were no statistically significant differences among these variables ($p=0.66$, 0.45, and 0.8). The data for the anesthetic success rates were plotted in 2X3 contingency tables and were analyzed using the Pearson Chi-square test (Table 2). There were significant differences between the three groups ($\chi 2=33.6$, $p<0.001$, $df=2$). The tramadol group presented with an 11% success rate, which was significantly lower than those of the 2% lidocaine (54%) and 2% lidocaine-plus-tramadol (80%) groups. The 2% lidocaine-plus-tramadol gave significantly better success rates than the two groups. The comparison of the maximum heart rate after intraligamentary injections is presented in Table 3. There were no significant changes in the baseline heart rates of all groups ($p>0.05$). In the tramadol

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

	2% lidocaine	Tramadol hydrochloride	2% lidocaine plus Tramadol hydrochloride	p
Age	28 years±12 years, range- 18–59 years	26 years±11 years, range- 19–54 years	29 years±12 years, range- 18–57 years	0.66
Gender	21 males 14 females	23 males 12 females	19 males 18 females	0.45, χ^2=1.56, df=2
Type of tooth	First molar=28 Second molar=7	First molar=27 Second molar=8	First molar=29 Second molar=6	0.8, χ^2=0.3, df=2
Successful anesthesia	19 out of 35 patients (54%)	4 out of 35 patients (11%)	28 out of 35 patients (80%)	<0.001, χ^2= 33.6, df=2

There was no significant difference between age, gender, and type of teeth. There were significant differences between the anesthetic success rates. df: Degrees of freedom

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

	vs.	The difference in success rates	p	95% confidence intervals of difference in success rates	Chi-square, degree of freedom (X^2, df)
2% lidocaine	Tramadol hydrochloride	43%	p=0.0001	21% to 60%	14.5, 1
	2% lidocaine plus Tramadol hydrochloride	26%	p=0.02	4% to 45%	5.3, 1
Tramadol hydrochloride	2% lidocaine plus Tramadol hydrochloride	69%	p<0.0001	47% to 81%	33, 1

TABLE 3. Pair-wise comparison of the maximum heart rates

		95% CI		Significance values
	Difference In heartrates	Lower bound	Upper bound	T score, p
2% lidocaine vs Tramadol hydrochloride	9	3.7	14.3	T=3.4 p=0.001 Significant
2% lidocaine vs 2% lidocaine plus Tramadol hydrochloride	1	–6.6	4.7	T=0.34 p=0.7 Non-significant
Tramadol hydrochloride vs 2% lidocaine plus Tramadol hydrochloride	–8	–13.3	–2.7	T=3 p=0.0035 Significant

CI: Confidence intervals

group, there was no significant rise in the heartrates after the intraligamentary injections. The remaining groups presented significantly higher heart rates than the baseline values.

DISCUSSION

The cases with a failed primary IANB received supplementary intraligamentary injections with different solutions. The intraligamentary injections of 2% lidocaine-plus-tramadol were successful in 80% of the cases, which was significantly more than 2% lidocaine or tramadol hydrochloride given alone. Tramadol is a synthetic, weak opioid analgesic, that has a dual mechanism of action: both opioid and non-opioid (33). The dual mechanism is because of its enantiomers: (+) and (-) tramadol. The (+) tramadol metabolizes to (+)-O- desmethyl-tramadol (M1). The (+) tramadol and its metabolite have a central opiate agonist property by acting on the selective mu-receptors, thus inhibiting the release of nociceptive neurotransmitters (33). The selective mu affinity of the metabolite is much higher than the parent (+) tramadol (33, 34). Apart from this, the (+) tramadol also inhibits the reuptake of serotonin. The (-) tramadol inhibits the uptake of nor-epinephrine. The synergistic action of both enantiomers inhibits central pain transmission (34–36). Apart from a central analgesic, tramadol has also shown local anesthetic properties (23). However, this property is not related to its central mechanisms. It shows both analgesic and anesthetic properties when injected locally (28). One of the early studies demonstrating the local anesthetic effect of tramadol involved intradermal injections of 25 mg tramadol, 5mg metoclopramide, 1% lidocaine, and 0.5 ml saline in a set of 10 patients. It was noted that tramadol demonstrated a loss of sensation similar to lidocaine (21). Based on these findings, the authors conducted a new trial on 105 patients, comparing the effect of intravenous injection

of 50 mg tramadol, 60 mg lidocaine, and normal saline, given as 1 minute venous retention (22). The authors reported that tramadol and lidocaine reduced propofol injection pain.

A study evaluated the use of tramadol as a local anesthetic agent during minor surgeries (lipoma excision or scar revision) (24). The patients randomly received subcutaneous injections of either 2mg/kg tramadol or 1mg/kg 2% lidocaine before surgical procedures. The authors documented two-fold advantages for the tramadol group; one provides local anesthetic properties similar to lidocaine; the second decreases the demand for post-operative analgesics. Moreover, it has been shown that tramadol can increase the duration of action of articaine injections (37). Another study evaluated the effect of adding tramadol to bupivacaine solution during axillary brachial plexus block. It was reported that the addition of 100 mg tramadol to 0.25% bupivacaine fastens the onset and prolongs the duration, compared with 0.25% bupivacaine given alone (38). Similarly, local wound infiltration of bupivacaine-plus-tramadol was more effective than bupivacaine alone in decreasing postoperative pain during lower abdominal surgery (39). In dentistry, the local anesthetic efficacy of tramadol has been mainly evaluated during oral surgical procedures. Local infiltrations of 50mg of tramadol were compared with 2% lidocaine during orthodontic extractions (40). The authors reported similar results with both injections. Another study compared tramadol and lidocaine buccal infiltrations in healthy volunteers (40). There were no statistically significant differences between the anesthetic duration.

Interestingly, supplemental infiltration of tramadol given alone gave poor results. Only 4 out of 35 patients presented with successful anesthesia. The reason for this low success can be attributed to a rapid uptake of the anesthetic solution due to the lack of a vasoconstrictor (41, 42). The intraligamentary injection is like an intraosseous injection. The anesthetic solution is forced into the medullary bone via periodontal ligament space. The solution enters the cancellous space through small perforations in the alveolar socket. When the solution reaches the medullary space, it encounters a vast network of fine blood vessels leading to rapid absorption in the bloodstream. It has been shown that after 2 minutes of intraligamentary injections of plain 2% prilocaine, the plasma levels of the anesthetic reached 25% of the levels shown by an intravenous administration of the same drug (43). Another study evaluated the spread of intraligamentary injections in maxillary and mandibular teeth (44). The authors reported that after maxillary intraligamentary injections, there was an extensive palatine vascular spread, in both superior labial and anterior palatine vessels. Spread was also observed extending to the sphenopalatine and greater palatine vessels. In the mandibular teeth, there was spread into the inferior alveolar and incisive vascular bundle, along with rapid filling of trabecular spaces, interdental, and crestal vessels. The authors concluded that intraligamentary injections lead to absorption in the vascular bundle, which is different from simple diffusion. To retard the absorption of local anesthetic agents, vasoconstrictors are added. They act as a chemical tourniquet by acting on the adrenergic receptors and causing the narrowing of the local blood vessels. The presence of vasoconstrictors has been shown to affect the duration of intraligamentary injections (45). A study compared 2% lidocaine with and without 1:50,000 epinephrine, administered as an intraligamentary injection in healthy volunteers (46). It was found that the presence of epinephrine increased the duration of pulpal anesthesia by 25 times. Similar studies in healthy volunteers have reported that the presence of epinephrine can prolong the duration and improve the anesthetic efficacy of intraligamentary injections, irrespective of the anesthetic solution (47, 48). A study evaluated the effect of the amount of epinephrine (1:80,000 vs. 1:200,000 epinephrine in 2% lidocaine) on the anesthetic success of supplementary intraligamentary injections, administered after a primary mandibular block has failed. The solutions with more epinephrine presented significantly better success rates. Regarding the use of a vasoconstrictor along with tramadol, as a local anesthetic agent, very few studies have added epinephrine to the tramadol solution. Ege et al. (23) evaluated plain tramadol solution in maxillary anesthesia, while another study (by the same author) used tramadol with epinephrine during maxillary extractions (40). A possible limitation of the study is the lack of lingual infiltration along with a primary nerve block to anesthetize the possible innervation from the cervical plexus in the patients undergoing treatment for mandibular second molars.

Various routes of tramadol administration, for the management of dental pain, have been reported. The most common being the oral and the submucosal routes. The submucosal administration of tramadol has a limited role in the anesthetic success during endodontic procedures. Studies using 100mg/2ml tramadol as preoperative submucosal injections, did not report a significant improvement in the IANB success rates (49). During third molar surgeries, submucosal administration of tramadol did improve postoperative analgesia but did not affect the anesthetic duration (50). Similarly, oral administration of tramadol reduced postoperative pain during oral extractions (51, 52). There have been some reports of adverse effects of tramadol injections. The most common being nausea and dizziness. In the present study, none of the patients receiving tramadol presented with any adverse effects.

CONCLUSION

The addition of tramadol hydrochloride to 2% lidocaine with 1:80,000 epinephrine, given as supplementary intraligamentary injection, can improve the anesthetic success rates.

Disclosures

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

Ethics Committee Approval: This study was approved by The institutional Research and Review Committee (Date: 14/04/2022, Number: FOD/IRRC/106/2022/F).

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