Original Article

Evaluation of three different drugs administered through intraligamentary route for reduction of intraoperative pain of symptomatic irreversible pulpitis in mandibular molars – A randomized triple-blind single-center clinical study

Manan Shroff, Karkala Venkappa Kishan[1], Nimisha Shah, Shreya Volety, Supreet Kaur[2], Niral Kotecha

Department of Conservative Dentistry and Endodontics, K. M. Shah Dental College, Sumandeep Vidyapeeth, Vadodara, Gujarat, [1]Department of Conservative Dentistry and Endodontics, Srinivas Dental College and Hospital, Mangalore, [2]Department of Conservative Dentistry and Endodontics, Manipal College of Dental Sciences, Karnataka, India

Abstract

Introduction: Managing intraoperative pain while initiating root canal treatment necessitates the use of supplementary injection techniques.

Aim: The study sought to assess and compare the anesthetic efficacy of 0.5% bupivacaine and 50 mg/ml tramadol hydrochloride versus 2% lignocaine administered as supplemental intraligamentary injection as an adjuvant to an inferior alveolar nerve block (IANB) for mandibular molars with symptomatic irreversible pulpitis (SIP) and normal apical tissues during access cavity preparation.

Materials and Methods: Two hundred and two individuals with mandibular molars diagnosed with SIP with normal apical tissues and exhibiting moderate-to-intense pain were given 2 ml of IANB containing 2% lignocaine and 1:80,000 epinephrine. The Visual Analog Scale (VAS) was used to record intraoperative discomfort. Individuals who scored more than 5 on the VAS were deemed to need further anesthesia. The intraligamentary medication was given to 99 of these patients after they were randomly assigned to 3 groups (2% lignocaine, 0.5% bupivacaine, and 50 mg/ml tramadol). VAS score was again recorded. If the patient reported no pain during the opening of the access, it was deemed a success. The *post hoc* Tukey's test, paired *t*-test, and one-way analysis of variance were the statistical methods used to examine the data.

Results: Maximum reduction in pain was in bupivacaine followed by lignocaine and tramadol ($P < 0.05$). Subgroup analysis using *post hoc* Tukey's honestly significant difference test showed a maximum difference between bupivacaine and tramadol (1.273, $P > 0.05$) (95% confidence interval [CI]), followed by lignocaine and bupivacaine (−1.182, $P < 0.05$) (95% CI) and lignocaine and tramadol (0.091, $P > 0.05$) (95% CI).

Conclusion: Bupivacaine was most effective in reduction of intraoperative pain when used as an intraligamentary drug during access cavity preparation followed by lignocaine. Tramadol was the least successful drug for achieving effective pulpal anesthesia.

Keywords: Bupivacaine; intraligamentary injection; lignocaine; tramadol

Address for correspondence:
Dr. Karkala Venkappa Kishan,
Department of Conservative Dentistry and Endodontics, Srinivas Dental College and Hospital, Mukka, Surathkal, Mangalore, Karnataka, India.
E-mail: drkishankv@yahoo.co.in

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INTRODUCTION

Sufficient anesthesia is highly critical in endodontic procedures. It is important to note that dental anesthetic injections do not assure a 100% success rate in achieving anesthesia. For instance, the inferior alveolar nerve block (IANB) normally has an anesthetic success rate between 40% and 60%.[1] Effective pulpal anesthesia is even more difficult to achieve when the patient experiences preoperative discomfort. Failure to achieve effective pulpal anesthesia might often result in increased operator time, giving a false sense of inefficiency in the mind of the patient. Therefore, in such cases, the use of supplemental anesthesia has been recommended for optimal anesthesia.[2] Intraligamentary and intraosseous injections are commonly utilized as supplemental injections. Intraligamentary injections, being less invasive compared to intraosseous injections, involve the application of pressure to deposit the drug into the periodontal space.[3] Up to 84% of cases where intraligamentary injection has been administered have achieved anesthetic success.[3] However, only a few studies have evaluated the efficacy of different solutions. Furthermore, majority of the studies have focused on asymptomatic teeth, and there is limited research on its effectiveness in symptomatic teeth.[4] Maxillary tooth extractions have been successfully performed under anesthesia with the use of tramadol.[5] However, its use as a local anesthetic in endodontics has been limited. To date, bupivacaine has not been utilized as an intraligamentary medication, despite its demonstrated efficacy as a long-acting local anesthetic.[6]

The objective of this triple-blind study was to evaluate the anesthetic efficacy of 50 mg/ml tramadol hydrochloride, 0.5% bupivacaine, and 2% lignocaine when given as an additional intraligamentary injection in cases where the primary IANB was insufficient to produce adequate pulpal anesthesia. The secondary goal was to determine tramadol efficacy as a local anesthetic delivered via the intraligamentary route. The different anesthetic drugs used will have no effect and no difference in their effectiveness as an intraligamentary drug was the null hypothesis.

MATERIALS AND METHODS

Study design

This study has been reported as per the Preferred Reporting Items for RAndomized Trials in Endodontics 2020 guidelines [Figure 1]. It was a triple-blind, parallel-arm, superiority, single-center randomized clinical study. The Institutional Ethics Committee (SVIEC/ON/DentBNPG20/D21042) approved the proposal which was then registered in the Clinical Trials Registry of India (CTRI/2021/04/032666). The participants were informed about treatment steps, potential risks involved in the procedure. The signed consent form was recorded. The treatments were carried out in the Department of Conservative Dentistry and Endodontics by a single operator of 2 years' experience in the duration from February 2021 and October 2022.

Eligibility criteria and sample size calculation

Two hundred and two patients participated in this study. Mandibular molars diagnosed as symptomatic irreversible pulpitis with normal apical tissues with an immediate and lingering response to electric pulp tests and cold test having class I or II medical history (American Society of Anesthesiologists) who were able to comprehend pain scales were included. Patients giving a history of drug abuse, those with known allergies to the test medications, pregnant females, and those taking any medications in the past 72 h that might have impacted the way they perceived pain were excluded from the study. An explanation regarding the pain scales (Visual Analog Scale [VAS]) and the procedure was made to the patient, and consent was obtained. All clinical procedures were carried out by a single experienced (2 years of postgraduation) operator. Patients were given primary IANB injections of 1.8 mL 2% lidocaine with 1:80,000 epinephrine utilizing the direct Halsted method in which the inferior alveolar nerve is reached by an intraoral access before it penetrates the mandibular canal. Once the lips, gingiva, and mucosa of the ipsilateral side were completely numb, root canal therapy was started. After isolation with rubber dam, excavation of caries was initiated. If any discomfort was experienced, patients were advised to indicate the same. They were asked to rate their discomfort level. Only patients who experienced a score of 5 or higher were included. Data of a published study[7] were used to determine the sample size. A total sample size of 99 was established, at 95% confidence and 80% power with a standard deviation of 0.5. There was a 1:1:1 allocation ratio.

Randomization and blinding

This study comprised 99 individuals who experienced moderate-to-severe pain (5 or above) during their access opening. They were further randomized into three groups (n = 33) as per computer randomization software (https://www.randomizer.org/) using a permuted block stratified randomization. Preparation of customized cartridges was done previously following all aseptic procedures. For blinding purposes, an uninvolved investigator removed the manufacturer's label from the cartridges that contained the two anesthetic agents and then placed another opaque, plain label on each cartridge that covered the entire glass part of the cartridge, masking the extent of the rubber stopper inside. The autoclaved cartridges were filled from the back end (rubber stopper) with 2.5 mL of the test drug. An intraligamentary unit with the cartridge containing any of the three test drugs mounted on it was handed over to the primary investigator (M.S).

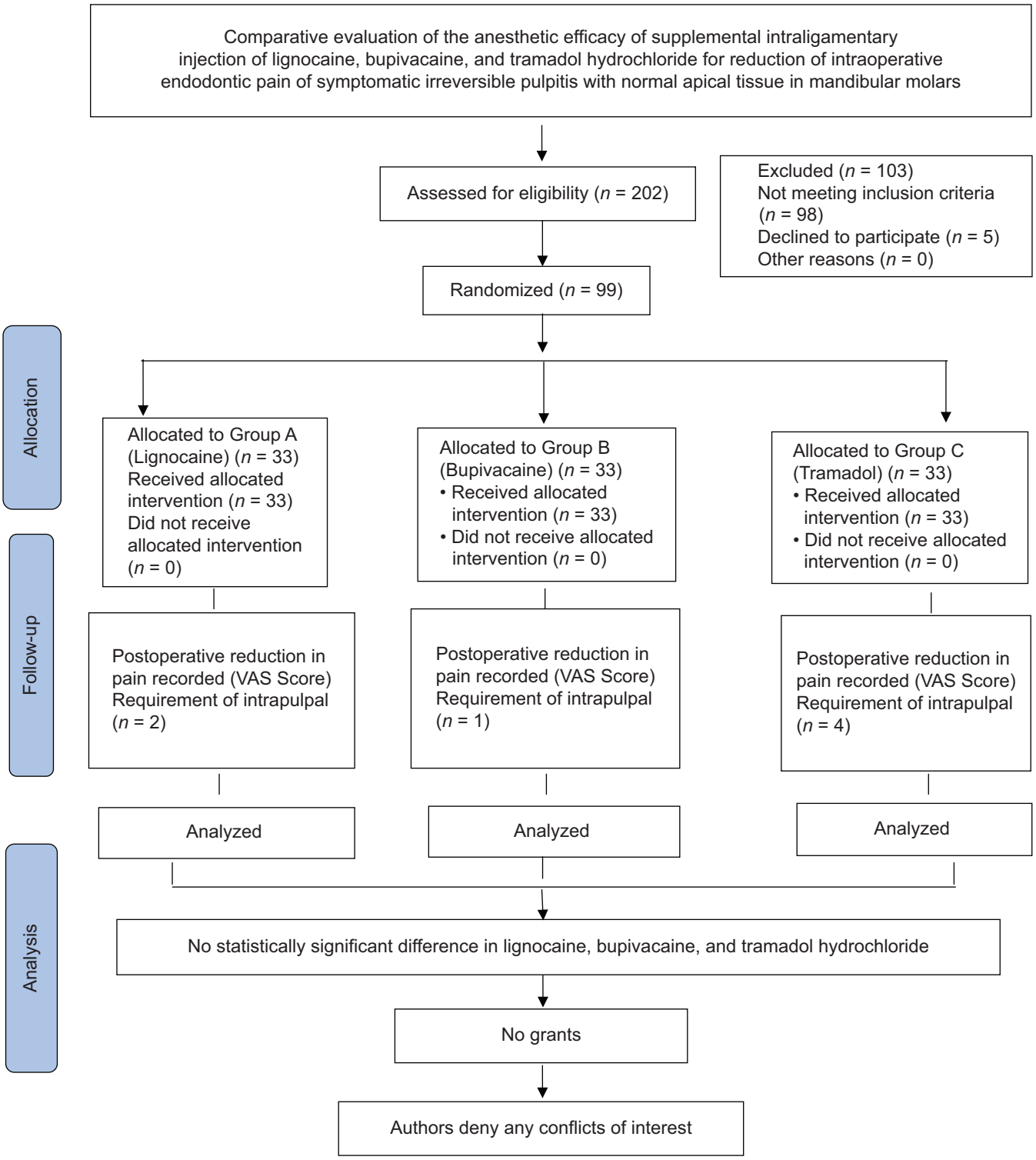

Figure 1: Preferred Reporting Items for RAndomized Trials in Endodontics 2020 flow diagram

Clinical procedure

Administration of the drug was done using a pressure-type syringe (CricDental, Mumbai) and short 30-G Septojet needles (Septodont, USA). This needle was inserted firmly between the tooth and the alveolar bone at a 30° angle from the long axis at the mesiobuccal line angle in the gingival sulcus.[8] Under intense pressure, the trigger was squeezed 3 times, depositing 0.2 × 3 = 0.6 mL of the drug. For the distal root, a similar procedure was repeated. After a waiting period of 3 min, reapplication of the rubber dam was done and treatment was continued. To assess the effectiveness of supplementary injection, the VAS score was recorded immediately after the access bur drop into the pulp chamber was achieved. Success was characterized

as having no pain or very little pain throughout the preparation of the endodontic access. Working length was assessed using the #10-K file (Mani Inc., Japan) and an apex locator (J. Morita, USA) set to 0.5 mm from the tooth's apex. The entire root canal process was completed during the subsequent session.

Outcome assessment

The ability to complete the access opening with little to no pain was deemed the intervention's "success or failure." The presence of moderate-to-severe pain was considered failure of anesthesia. If the patient yet experienced minimal pain after administration of the intraligamentary drug, then intrapulpal injection was administered as a last resort. However, these cases were not excluded and the pain levels in such patients were recorded and assessed.

Statistical analysis

Using SPSS 20.0, (Armonk. NY: IBM Corp.) descriptive statistics were done, including mean, standard deviation, one-way analysis of variance with *post hoc* test, and paired *t*-test. It was assumed that $P = 0.05$ indicated statistical significance.

RESULTS

Of the 202 patients that took part in this study, 48% of the cases had success with the IANB, i.e. the patient did not require any supplemental injection and entry to the pulp chamber was possible. The highest mean values of reduction in pain were seen in Group Bupivacaine (6.12 ± 1.27) followed by Group Lignocaine (4.94 ± 1.46) and Group Tramadol Hydrochloride (4.85 ± 1.75). Subgroup comparisons applying the *post hoc* Tukey's honestly significant difference test revealed that Group Bupivacaine versus Tramadol had the most substantial difference between the groups (1.273), which was not significant. Group Lignocaine versus Bupivacaine had the second-highest difference (−1.182, significant), followed by Group Lignocaine versus Tramadol (0.091, not significant) [Table 1]. When the mean pretreatment pain score values are compared to the values immediately following pulp chamber access, the difference is statistically significant, with $P < 0.001$ for each of the three groups [Figure 2 and Table 2].

DISCUSSION

There was a significant reduction in the intensity of pain after administration of the intraligamentary injection of lignocaine, bupivacaine, and tramadol hydrochloride. As a result, the null hypothesis was rejected. Zanin *et al*.'s systematic review found that clinically irreversible pulpitis was linked to increased gene and protein expression of interleukin-8, tumor necrosis factor-alpha, matrix metalloproteinase-9, and receptor for advanced glycation end products in pulp tissue.[8] Walton and Abbott found an initial success rate of 71%; however, the success rate increased to 92% with reintroduction of the intraligamentary medication.[9] According to Cohen *et al*., reinjection enhanced success to 96% of the time, whereas supplementary intraligamentary injections were effective 74% of the time.[10]

Comparison of the parameter of age between the three groups showed no significant difference between the three groups (test value of 0.997 and $P = 0.373$). A comparison of the parameter pretreatment pain score between the three groups showed no significant difference between the three groups (test value of 1.74 and $P = 0.181$). Each group had 33 participants where Group Lignocaine had 23 females and 10 males, Group Bupivacaine had 18 females and 15 males, and Group Tramadol had 20 females and 13 males.

Lignocaine has been clinically tested as an intraligamentary drug, whereas tramadol has only been administered orally and bupivacaine has been used successfully as IANB.[11] During intraligamentary injection administration, the solution is guided into the surrounding cancellous bone instead of being pushed through the periodontal ligament all the way down to the tooth apex.[12] The vessels supplying the periodontium facilitate this diffusion of the anesthetic agent.[13] The evaluation of preoperative pain and reduction in intraoperative pain was assessed by the operator using the VAS. With a considerable advantage over other comparable tools, the VAS's ability to evaluate differences in pain intensity at two distinct time points accurately reflects the disparity in pain magnitude.[14]

The study employed computer randomization software (https://www.randomizer.org/) to allocate participants into three groups. Each group received either lignocaine, bupivacaine, or tramadol hydrochloride. To minimize bias, the operator, patient, and statistician were unaware of the administered drug, making it a triple-blind study. Neither the patients' ages ($P = 0.373$) nor the preoperative pain levels ($P = 0.181$) differed significantly

Table 1: One-way ANOVA and *post hoc* Tukey's test

	Group 1 (n=33), mean±SD	Group 2 (n=33), mean±SD	Group 3 (n=33), mean±SD	F/Welch statistics	P
Age	37.55±14.32	33.21±11.47	34.3±12.96	0.997	0.373
Pretreatment pain score	7.88±1.02	7.94±1	8.27±0.72	1.74	0.181
Just after gaining access to pulp chamber	2.94±1.52	1.82±1.1	3.42±1.89	11.385*	<0.001
Difference in pain	4.94±1.46	6.12±1.27	4.85±1.75	7.338	0.001

*Welch's t-test. SD: Standard deviation

Table 2: Difference in Visual Analog Scale scores in all the groups using paired *t*-test

Group	Parameter	*n*	Mean±SD	Mean difference±SD	*t*	*P*
Lignocaine	Pretreatment pain score	33	7.88±1.02	4.94±1.46	7.88±1.02	<0.001
	Just after gaining access to pulp chamber	33	2.94±1.52		2.94±1.52	
Bupivacaine	Pretreatment pain score	33	7.94±1	6.12±1.27	7.94±1	<0.001
	Just after gaining access to pulp chamber	33	1.82±1.1		1.82±1.1	
Tramadol	Pretreatment pain score	33	8.27±0.72	4.85±1.75	8.27±0.72	<0.001
	Just after gaining access to pulp chamber	33	3.42±1.89			

SD: Standard deviation

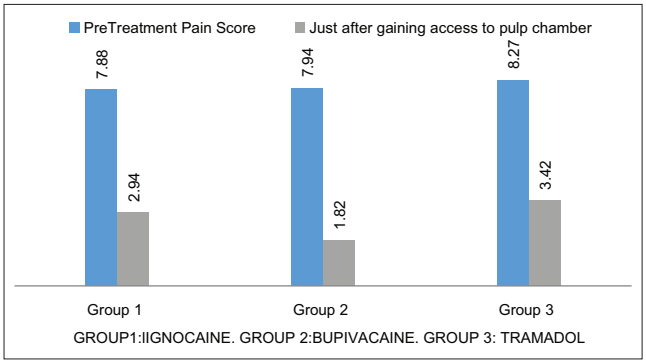

Figure 2: Difference in Visual Analog Scale scores in all the groups

across the three groups. Following the intraligamentary medication injection, there was a statistically significant decrease in pain for all three groups ($P < 0.001$). Notably, the group receiving bupivacaine exhibited the most substantial reduction (mean value: 6.12 ± 1.27).

Bupivacaine, with a therapeutic ratio of 2:0, has a higher anesthetic potency due to its increased lipid solubility, facilitating better diffusion across the nerve sheath.[15] Its higher affinity for proteins in sodium channels also enhances its anesthetic action, particularly in cases involving "hot tooth."[16] This finding aligns with Fernandez *et al*.'s study, which showed significant efficacy differences between bupivacaine and lignocaine as IANBs.[15] Yano *et al*. also found that, in an *in vitro* experiment, phasic block in a single giant axon needed a concentration of lidocaine 16 times higher than bupivacaine, indicating a significant difference in their efficacy and affinity for sodium channels.[17] Bupivacaine, owing to its high lipid solubility (about eight to nine times that of lidocaine), contributes to its increased tissue permeability and stronger interaction with sodium channels.[18]

According to a study by Jendi *et al*., tramadol has been shown to be a safe anesthetic option, free from systemic toxicity and with fewer side effects.[19] Additionally, if it is inadvertently injected into a peripheral nerve, there is less chance of negative consequences. According to some research, tramadol may influence nerve conduction by elevating the activation threshold of voltage-dependent channels and raising extracellular calcium (Ca^{+2}) levels.[20,21] The central nervous system's opioid receptors are bound by tramadol and its active metabolite, which inhibits pain signals from reaching the brain and encourages the absorption of norepinephrine and serotonin. These neurotransmitters are connected to pain alleviation and are a part of the descending inhibitory pain pathway.[22,23] In spite of being used successfully as an anesthetic agent in oral surgery,[21,23-25] according to the findings of this study, its anesthetic effect in symptomatic teeth is debatable.

Since pain is a subjective experience, its validity is debatable even after controlling majority of the confounding factors. Taking these limitations into account, it was determined that the intraligamentary medication administration resulted in a significant ($P = 0.001$) decrease in pain levels. However, when it came to reducing intraoperative pain, there was no statistically significant difference between lignocaine, bupivacaine, and tramadol hydrochloride. Clinically, bupivacaine was the most successful drug. Furthermore, long-term clinical studies with an increased sample size and other anesthetic agents can be carried out. Furthermore, the effect of these drugs on postoperative pain can also be investigated.

CONCLUSION

Within the limitations of this study, there was a reduction of intra-appointment pain in all the experimental groups. Intraligamentary injections in our study had a success rate of 91% and can be used successfully for the reduction of intraoperative endodontic pain during access opening. Bupivacaine was better compared to the others in the amount of reduction of pain in patients with symptomatic irreversible pulpitis when evaluated using the VAS. Tramadol can also be used as an adjuvant to IANB as an intraligament injection in eliminating intra-appointment pain and can be used as an alternative to lignocaine, but it is not as effective as bupivacaine.

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Conflicts of interest
There are no conflicts of interest.

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