Effectiveness of tramadol compared to lignocaine as local anesthesia in the extraction of firm teeth: a randomized controlled trial

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Background: The aim of this study was to compare the local anesthetic effect of tramadol with that of lignocaine in the extraction of immobile (grade 0) maxillary first molars.
Methods: This was a randomized, double-blind, equally balanced, controlled trial conducted on a sample population of 116 patients. The patients were randomly divided into two groups: group A (control) and group B (study). Group A and group B participants received 1.8 ml of 2% lignocaine without adrenaline and 1.8 ml of 5% tramadol, respectively through the supra-periosteal infiltration technique before extraction. Intraoperative pain was recorded on the Visual Analog Scale (VAS) and was evaluated using two unpaired t-tests.
Results: Intraoperative pain was evaluated in both the control and study groups. In the control group, the mean VAS score was 0.71 ± 0.81, while in the study group, the mean intraoperative VAS score was 1.21 ± 0.86, with the difference between the two mean values being statistically significant ($P = 0.001$).
Conclusion: Tramadol has a less potent local anesthetic effect than lignocaine. As a higher dose of tramadol is required to obtain the desired anesthetic effect, it should be used as a supplement to lignocaine in extensive surgical procedures. It can also be used in patients allergic to lignocaine.

Keywords: Lidocaine; Local Anesthesia; Pain; Randomized Controlled Trials; Tramadol.

INTRODUCTION

Dental extraction remains the most common procedure performed in dental clinics, despite efforts to save the teeth by conservative and preventive treatments. Most patients feel anxious because of the belief that tooth extraction procedures are painful, making it difficult for both the patient and the physician. A pain-free dental procedure is mandatory to reduce fear and anxiety among patients. Local anesthetic drugs have been introduced to control pain during treatment since 1884. The first local anesthetic agent was cocaine. Many local anesthetic agents, such as lignocaine, bupivacaine, and mepivacaine, have been introduced as effective pain control therapy during treatment. Although the specific receptor theory is widely accepted, many pain control theories have been proposed. Local anesthesia blocks sodium channels present in the membranes of neurons, thus reducing the influx of sodium ions, which prevents the firing threshold from being attained [1]. This hampers nerve conduction, leading to an anesthetic effect.

Tramadol is an opioid analgesic and a 4-phenyl piperidine analog of codeine. It acts centrally in the nervous system and is mainly used in palliative treatment for moderate to severe pain [2,3]. The local anesthetic effect of tramadol has been mentioned in recent literature [4-6], and has been proven to be an adjuvant to a local anesthetic drug [7]. Tramadol was first introduced as a local anesthetic agent during circumcision by Shrestha and Bista [8].

Among all the other local anesthetic drugs, lignocaine is the most commonly used by dentists to achieve local anesthesia in dental practice. According to the literature, tramadol has been reported to induce peripheral anesthesia after supraperiosteal injection; therefore, the aim of this study was to compare the local anesthetic effect of tramadol to that of lignocaine because lignocaine is considered the gold standard in local anesthesia used for extraction in dentistry. In previous studies, a comparison of the local anesthetic effect of tramadol with lignocaine in dental extraction was performed; however, no criteria for the mobility of teeth were included in the trials. Therefore, the primary objective of this study was to compare the local anesthetic effect of tramadol with that of lignocaine without adrenaline in the simple extraction of immobile (grade 0) maxillary first molars. Therefore, the two-tailed hypothesis is that the local anesthetic effect of tramadol is different from that of lignocaine in the simple extraction of a firm tooth.

METHODS

1. Design and setting

This was a double-blind, controlled trial with balanced randomization (1:1) with a parallel study conducted at Swargiya Dadasaheb Kalmegh Smruti Dental College and Hospital, Nagpur, India. Approval for this trial was obtained from the Institutional Ethical Committee with the approval number IEC/Rep/STRG/03022020, followed by its registration at the Clinical Trial Registry–India, with registration number CTRI/2021/02/031509. This

trial followed the CONSORT statement guidelines and the guidelines of the Declaration of Helsinki.

A detailed case history was recorded and maintained for each patient, with informed written consent for inclusion in the trial.

2. Sample size determination

Based on a previously published study by Al-Haideri et al. [1], the sample size was determined by considering the difference in mean intraoperative pain score between the two groups as the primary outcome. It was estimated that 58 individuals per group were required to be randomized to reliably test our hypothesis, given $\alpha = 0.05$ and a power of 80%. To account for incomplete data or withdrawal criteria, 60 patients were randomly assigned to each group. Therefore, 120 patients were included in the intention-to-treat (ITT) population. The ITT population was randomly divided into two groups: the control group (group A) and the study group (group B).

3. Inclusion criteria

1) Patients aged 18–60 years.
2) Both male and female were participants were included.
3) Presence of an immobile (Grade 0) maxillary first molar that was indicated for extraction.

4. Exclusion criteria

1) Medically-compromised individuals
2) History of alcoholism and smoking
3) Pregnancy or breastfeeding for females
4) Allergy to the drugs used in the trial
5) Patients not willing to consent for the study were also excluded.

5. Randomization

The participants were randomly divided into two groups of 60, each using the permuted block randomization method. A predetermined computer-generated random allocation plan was followed for this purpose. Thirty blocks of size four each were used in this method.

6. Blinding

This was a double-blind trial in which the operating surgeon and patients were blinded. The third surgeon was assigned to take the case history, prepare for the procedure, and prepare syringes for tramadol and lignocaine. The operating surgeon remained the same during the trial and was unaware of the drug injected for local anesthesia.

7. Masking

The use of the permuted block randomization method prevented the researcher from crediting the treatment assignment, which helped in masking the effect.

8. Outcome methods

The pain experienced by the patient during the extraction procedure was recorded using a visual analog scale (VAS), with the score ranging from 0 to 10, where 0 indicated no pain and 10 indicated the worst possible pain [9]. The patient was informed about the scale before the start of the procedure.

9. Interventions

Group A participants received 1.8 ml of 2% lignocaine through the supraperiosteal infiltration technique. In group B, 1.8 ml of 5% (namely, 50 mg/ml) tramadol, which is commercially available, was used as a local anesthetic and was also given through supra-periosteal infiltration before extraction.

After injecting the drug supraperiosteally in both the groups, only the objective signs of local anesthesia were checked. No subjective signs were recorded as the local anesthetic agent was injected supraperiosteally. The patient was advised to score the pain (if elicited) while checking the objective signs before extraction. The objective sign was checked by eliciting pain in the buccal and palatal gingiva associated with the tooth to be extracted in the trial. The extraction procedure was initiated only when the preoperative pain VAS score was 0, which was achieved 3–5 min after drug administration

in both the groups. If during extraction in both the groups, the patient experienced pain with an intensity of less than 3 on the VAS scale, the extraction was completed; however, if the score was more than 3, an additional injection (0.5 ml) was administered supraperiosteally to complete the extraction. If the patient still experienced pain, no further reinjection was carried out in the trial, and those patients were excluded from the study. Dental extraction in the excluded patients was completed after administering a conventional nerve block local anesthetic of 2% lignocaine with 1:80,000 adrenaline. The entire procedure was conducted under universal aseptic precautions. The number of injections required until the completion of the extraction process was also recorded and compared between the groups.

A patch test was performed before the commencement of each procedure, undertaking all aseptic precautions. Only those patients who tested negative in this patch test continued with the extraction.

The primary endpoint to be evaluated in this trial was intraoperative pain measured using the VAS, which is a categorical, ordinal parameter with a binary outcome. This parameter is a continuous variable. The data obtained from the trial were analyzed using the statistical software STATA 10.1 (2011). The significance of the difference in means between the two groups was assessed using two independent-sample t-tests.

Values of $P < 0.05$ were considered statistically significant.

RESULT

Of the total sample of 120 patients aged 18–60 years, 68 were males and 52 were females (Table 1). The ITT population was initially 120; however, with the dropout of four patients from the ITT population, the available per-protocol population was 116. Of the four dropouts, one was from the control group and three from the study group. These four dropout patients had a VAS score $\geq$ 3, which required more than 2 injections of local

Table 1. Demographic details of the study population

	Study	Control
Age [Mean ± SD]	39.36 ± 10.34 (39)	39.08 ± 9.95 (40)
Sex ratio (M : F)	35:22	31:28

SD, standard deviation.

Table 2. Intraoperative VAS scores in group A and group B after adequate numbers of injections

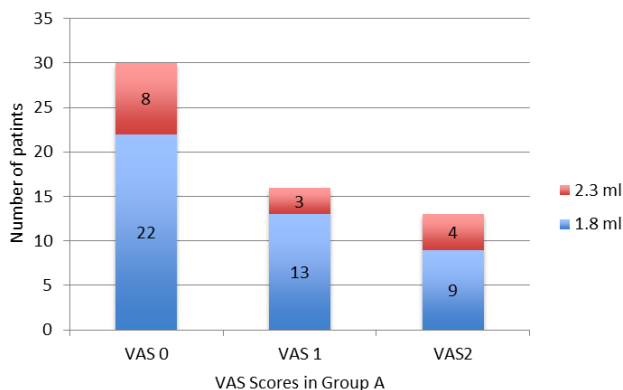| Amount of solution / VAS scores	VAS 0	VAS 1	VAS 2	Total	P value
Group A					
1.8 ml	22 (37%)	13 (22%)	9 (15%)	44	
2.3 ml	8 (14%)	3 (5%)	4 (7%)	15	
Total	30	16	13	59	0.001
Group B					
1.8 ml	11 (19%)	8 (14%)	12 (21%)	31	
2.3 ml	5 (9%)	7 (12%)	14 (25%)	26	
Total	16	15	20	57	

VAS, Visual Analog Scale.

Fig. 1. Graph showing the distribution of samples in group A. VAS, Visual Analog Scale
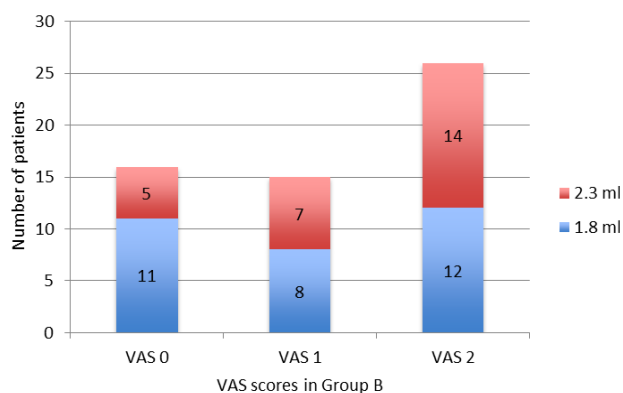

Fig. 2. Graph showing the distribution of samples in group B. VAS, Visual Analog Scale

anesthetic drugs in their respective groups. Pain was recorded with the help of the VAS ranging from 0 to 10. Patients were asked to use the VAS scale to score the pain they felt according to their perception of the success of anesthesia after local anesthetic injections in both groups. As per the trial protocol, four patients were excluded from the trial. None of the patients in either group showed any adverse reactions to the local anesthetic drugs.

In this trial, intraoperative pain was evaluated in both control and study groups. In group A, the mean VAS score was 0.71 ± 0.81. In group B, the mean intraoperative VAS score was 1.21 ± 0.86. The difference between the mean values of the two groups was statistically significant (P = 0.001).

In group A, 22 participants had a VAS score of 0 with minimum number of injections, that is, 1.8 ml of lignocaine (Table 2). Whereas, in group B, 14 had a VAS score of 2 even after the maximum number of injections, that is, 2.3 ml of Tramadol (Table 2). Therefore, maximum scattering was seen for 1.8 ml with a VAS score of 0 in the control group (Fig. 1) and for 2.3 ml with a VAS score of 2 in the study group (Fig. 2).

DISCUSSION

Pain is the most commonly reported symptom by patients during extraction. Therefore, performing pain-free procedures is vital for healthcare professionals. Many studies have been performed on pain-free procedures. One way to achieve a pain-free procedure is to use local anesthesia. Local anesthesia (generally used in dentistry) is a molecule with an amide or ester group. However, the most commonly used local anesthetic agent is lignocaine, which is an amide. This is due to its chemical configuration and its low systemic toxicity.

According to Bennett [10], there are many other compounds that show local anesthetic activity different from those of local anesthetic agents, such as anti-histamines, analgesics, tranquilizers, and antiarrhythmic drugs. Even alcohols, anticonvulsants, barbiturates, and narcotics have the potential to cause conduction blockage in the nerves [11]. The local anesthetic properties of opioids such as meperidine, fentanyl, sufentanil, and tramadol are well documented in the literature [12-15].

Tramadol is a synthetic opioid analgesic that acts centrally. It is generally used in post-surgical pain, such as obstetric pain, terminal cancer pain, and pain of coronary origin [16]. Tramadol has been reported to block peripheral nerves [4].

In 1999, Pang et al. [5] demonstrated that tramadol was effective in reducing propofol injection pain; therefore, they postulated that tramadol has peripheral analgesic activity. In 2001, Tsai et al. [17] studied the effect of tramadol on the sciatic nerves in rats and concluded that fully reversible inhibition of nerve conduction was made possible by using tramadol in a dose-dependent manner without any deleterious neurological effects. In a study by Altunkaya et al. [18], tramadol provided local anesthesia that was equivalent to that provided by lidocaine when injected subcutaneously for the excision of skin lesions and provided the benefit of prolonged postoperative analgesic effects, thereby reducing the analgesic requirement.

The first use of tramadol as a local anesthetic agent in oral and maxillofacial surgery was in the extraction of maxillary first molars by Yahya A. A, Al-Haideri [1], who concluded that tramadol could be effective as a local anesthetic when used only with adrenaline. In an in vitro study, Mert et al. [19] found that tramadol had a weaker local anesthetic effect than lidocaine and a mechanism different from that of lidocaine for producing conduction blockade. Haeseler [14] explained two distinct effects of opioids on membrane excitability: a non-specific local anesthetic-like effect in which there is depression of both the sodium conductance and potassium conductance and a selective decrease in sodium conductance alone due to the activation of stereospecific opioid drug receptors. Mert et al. [20] proposed that tramadol might follow a hydrophobic pathway, such as benzocaine, by passing through the nerve membrane and blocking the sodium channels. Tsai et al. [17] showed that the changes in somatosensory evoked potentials induced by tramadol were not reversed by naloxone, suggesting that the local anesthetic effect of tramadol is not mediated by opioid receptors. Mustafa et al. (2005) proposed that tramadol followed a hydrophilic pathway as lignocaine and produced a nerve conduction block by blocking Na+ channels. In addition, tramadol blocks K+ channels more effectively than lignocaine [21].

The primary objective of this study was to evaluate the local anesthetic efficacy of tramadol compared to that of lignocaine in the extraction of immobile maxillary first molars. In this study, lignocaine and tramadol were used without adrenaline to evaluate the actual potency of tramadol compared to that of lignocaine without any supplementary effect of vasoconstrictors. Twenty-six patients in group B required at least an additional injection of tramadol in contrast to 15 patients in group A. Even after additional injection in both the groups, 14 out of 26 patients in group B had a maximum VAS score of 2, while only 4 out of 15 in group A had a VAS score of 2 (Table 2). These results indicate that lignocaine is more potent than tramadol when used as a local anesthetic.

Altunkaya et al. [22] found that tramadol (5%) has a local anesthetic effect that is as potent as that of prilocaine (2%) when administered intradermally. The extended duration of analgesia with tramadol reduced the demand for postoperative analgesia. These results encouraged us to check the efficiency of tramadol as a local anesthetic agent for the simple extraction of teeth and to compare it with the commonly used local anesthetic agent, lignocaine. In contrast, no significant difference in postoperative analgesia was found by Polat et al. [23].

A similar study was conducted by Yahya A.A. Al-Haider [1] in 2013, who used tramadol hydrochloride (HCL) with adrenaline (1:80,000) for the extraction of maxillary molars through the closed method and concluded that tramadol HCl with adrenaline (1:80,000) exhibits a local anesthetic effect when performing the painless extraction of a tooth when infiltrated supra-periosteally [1]. Alsandook [24] also studied the anesthetic effect of tramadol in the form of a nerve block for the performance of conventional and surgical dental extraction.

The results of our trial suggest that tramadol has weaker local anesthetic properties than lidocaine, which is similar to the results of Polat et al. [23]. The weaker anesthetic properties were due to the difference in the pKa values of both drugs. Bennett [10] mentioned that a drug with a higher pKa value provides a relatively poorer quality of local anesthesia. The pKa value for lignocaine was 7.9, while that for tramadol was 9.41 [25, 26]. Similar findings have been reported in the literature, which shows that tramadol has an local anesthetic effect that is weaker than that of lignocaine [19,20]. Therefore, owing to the relatively weaker anesthetic property of tramadol, there was a significant difference in intra-operative pain between the two groups in our study.

In addition, the dose of tramadol required for local anesthesia is higher than that of lignocaine. Thus, the use of tramadol as a local anesthetic has been avoided mainly due to its side effects. The most common symptoms were nausea (6.1%) and vomiting (1.7%). The reported side effects of tramadol, when used intravenously, are skin rash and burning sensations at the injection site [4]. Pang et al. [5] observed more skin reactions with tramadol in the form of erythema and/or wheal than with lidocaine. Similarly, Altunkaya et al. [22] also reported an allergic reaction with intradermal tramadol. However, Kargi et al. [7] and Vahabi et al. [27] did not report any such skin reactions upon local infiltration of tramadol, which was similar to the findings of this trial.

A limitation of this trial was that only the immobile maxillary first molars were selected for extraction; however, while extracting the mobile tooth, tramadol can be as potent as lignocaine if the periodontal attachment is compromised. Previous studies on the local anesthetic efficacy of tramadol in extraction have not specified the periodontal condition of the tooth in the trial protocol [28].

In conclusion, although tramadol has been found to have a local anesthetic effect, it is less potent than lignocaine. Therefore, it can be used in patients allergic to lignocaine to achieve sufficient anesthesia. An increased dose of tramadol to achieve its local anesthetic effect should not outweigh its adverse effects. Further studies should be carried out to check the efficiency of tramadol as a local anesthetic so that it may be used as an alternative to vasoconstrictors or without vasocon-strictors.

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