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Tramadol hydrochloride: An alternative to conventional local anaesthetics for intraoral procedures- a preliminary study

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ABSTRACT

Purpose: To evaluate and compare the soft tissue anaesthesia produced by tramadol hydrochloride on gingival tissues in maxilla.

Methods: A total of 50 ASA physical status I subjects between 18 and 35 years of age, both male and female were included in the study. Each individual received 0.5 ml of 50 mg tramadol in the soft tissues over maxillary canine tooth as local infiltration on one and 0.5 ml of 20 mg lignocaine on the contralateral side in a double-blinded fashion. After completing the injection, the author recorded pain on injection, the onset of action, duration of anaesthesia, side effects, and feedback from patient.

Results: The mean onset of anaesthesia for tramadol was 172.00 s (standard deviation 39.898) while for lignocaine it was 162.60 s (standard deviation 35.098) and there was no statistically significant difference between the two groups ($p = 0.214$). The mean duration of anaesthesia for tramadol group was 45.70 min with a standard deviation of 8.512 min whereas for lignocaine group it was 44.70 min with a standard deviation of 8.107 min. There was no statistical relevant difference between the two groups in duration of anaesthesia ($p = 0.549$). None of the subjects reported any side effect in both the groups. There was no significant difference in pain on injection between the two groups.

Conclusions: Tramadol has a local anaesthetic effect similar to lignocaine when injected as infiltration in oral soft tissues.

1. Introduction

Opioids have been shown to have a local anaesthetic (LA) effect in both in vivo and in vitro studies. The LA property of opioids like meperidine, fentanyl, sufentanyl, tramadol and others are documented in the literature.[1–5] Since more than two decades tramadol has been shown to have a LA effect similar to lignocaine by many researchers. It has been used as a sole anaesthetic agent for excision of soft tissue tumour, circumcision procedure and for tendor repair surgery in hand injuries.[6–8] It has been tested in the extraction of upper molar tooth in a war torn country of Iraq in 2013 and this was the first study of its kind where tramadol HCl had been administered intraorally as a local anaesthetic agent for tooth extraction.[9] However the evaluation of performance of tramadol in comparison with lignocaine would rather exhibit the effectiveness of tramadol as a LA agent for intraoral procedures since lignocaine is a gold standard[10] for the comparison of all other LAs. So, this in vivo study was conducted to evaluate and compare the LA action of tramadol with that of lignocaine in intraoral soft tissues.

2. Material and method

The study was approved by the institutional ethical committee and review board. The study was explained to all the subjects in their vernacular language before their enrollment and a written informed consent was obtained from each subject. A total of 50 ASA physical status I subjects between 18 and 35 years of age, both male and female were included in the study. The subjects excluded were pregnant females, lactating mothers, medically compromised individuals and those who were allergic to the drugs used in this study. Every patient underwent drug allergy testing for those drugs which were to be injected as infiltration anaesthesia. 0.1 ml of test dose was injected intradermally under all aseptic precaution on the forearm of right hand using sterile 1 mL tuberculin syringe with a short needle. The intradermal

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(intracutaneous) injection was performed by inserting the needle tip, bevel up, just underneath the surface of the skin and injecting 0.1 mL of the drug. The formation of "bleb" was an indication that the injection was performed properly.

2.1. Evaluation of the response

Each injection site was evaluated for 15–20 min.

The response was measured by the diameter of skin change or wheal, if present.

Scale: 0 = no reaction.

1 = mild rash.
2 = erythema.
3 = urticaria.

If there was no allergic reaction to the drug injected, then intraoral injection was performed. Each individual received 0.5 ml of 50 mg tramadol HCl in the soft tissues over maxillary canine tooth as local infiltration on one side and 0.5 ml of 20 mg lignocaine (vasoconstrictor-free) on the contralateral side in a double-blinded fashion using 27 gauge needles under all aseptic precaution. This was a randomized split-mouth design study. Both the investigator and the participant were unaware of the drug being injected. No treatment was performed on these subjects. After the injection was completed, each injection site was assessed for the following parameters:

2.2. Pain on injection

The individuals were explained about the Visual Analogue Scale (VAS) before the start of procedure that ranged from 0 to 10, where 0 indicates no pain and 10 means worst pain possible. Each individual was asked to interpret the pain experienced during injection as per VAS on each injection site and the pain scores were recorded.

2.3. Onset of action

One minute after the completion of injection the objective onset of anaesthesia was checked at every 10 s interval with a dental probe by pricking at the site of injection and on the lip mucosa opposite to the area of injection and pain was assessed using VAS.

2.4. Total duration of anaesthesia

The patient was evaluated every 5 min after the completion of injection to check the disappearance of anaesthesia by pricking with a dental probe at the injection site until the return of normal sensations in the area of injection.

2.5. Possible side effects

Side effect if any was recorded at the time of injection and also when the subjects were recalled for follow up after 24 h.

2.6. Feedback from participants

Feedback from participants was recorded as bad, fair, good, very good when they were recalled after 24 h for follow-up.

Descriptive statistics were expressed as mean ± standard deviation (SD) for each group. The two groups were compared for onset and duration of anaesthesia by Independent 't' test. The association among responses from patient (patient feedback) between the groups was calculated by Chi Square Test. In the above tests, p value less than 0.05 ($p < 0.05$) was taken to be statistically significant. All analyses were performed using SPSS software version 17.

Table 1
Comparison between two groups for onset of action (in seconds) by Independent 't' test.

Group	Onset of action (in seconds)	Onset of action (in mins)	t value	Mean Difference	p value
			1.251	9.400	0.214*
Tramadol	172.00 ± 39.898	2.867 ± 0.665			
Lignocaine	162.60 ± 35.098	2.71 ± 0.585			

*p value < 0.05 is statistically significant.

3. Result

A total of 50 subjects were included in the study of which 20 were females and 30 were males. The mean age of the participants was 27.52 years (with standard deviation of 4.102). In both the groups, none of the patient showed any untoward response on the forearm after the administration of the respective drugs. The mean onset of anaesthesia for tramadol was 172.00 ± 39.898 s (2.867 ± 0.665 min) while for lignocaine it was 162.60 ± 35.098 s (2.71 ± 0.585 min) and there was no statistically significant difference between the two groups ($p = 0.214$) [Table 1]. The mean duration of anaesthesia for tramadol group was 45.70 min with a standard deviation of 8.512 min whereas for lignocaine group it was 44.70 min with a standard deviation of 8.107 min. There was no statistical relevant difference between the two groups in duration of anaesthesia ($p = 0.549$) [Table 2]. 37 subjects in tramadol group and 35 subjects in lignocaine group experienced no pain on injection while 13 subjects in tramadol group and 15 subjects in lignocaine group experienced mild pain on injection ($p = 0.656$) [Table 3]. 11 subjects in tramadol group and 12 subjects in lignocaine group considered the procedure as fair, while 25 in tramadol group and 26 in lignocaine group considered the procedure as good whereas 14 subjects in tramadol group and 12 subjects in lignocaine group considered the procedure as very good ($p = 0.897$) [Table 4]. None of the subjects reported any side effect in both the groups; neither at the time of injection nor at the follow up after 24 h.

4. Discussion

Tramadol is centrally acting, synthetic, weak opioid analgesic that has a multimodal mechanism of action. It was synthesized by Grunenthal GmbH, a pharmaceutical company headquartered at Stolberg, near Aachen in Germany in 1962 and has been available for treatment of pain since 1977. This drug was registered in UK and US in 1994 and 1995 respectively. Tramadol hydrochloride is a racemic (1:1) mixture of the (+) and (−) enantiomers. It has a multimodal mechanism of action as on one hand the two enantiomers (+) and (−) act on the serotonin and noradrenaline reuptake, and on the other hand the O-desmethyl metabolite of tramadol (known as M1 or ODT) acts on the mu opioid receptor.[11,12] The recommended dosage for tramadol is 50–100 mg every 4–6 h not to exceed 300–400 mg/day. It may be administered orally or parenterally. Dosage adjustments may be required in patients with renal or hepatic impairment and in individuals > 75

Table 2
Comparison between two groups for Duration of Action (in minutes) by Independent 't' test.

Group	Duration of action (in min)	t value	Mean Difference	p value
		0.602	1.000	0.549*
Tramadol	45.70 ± 8.512			
Lignocaine	44.70 ± 8.107			

*p value < 0.05 is statistically significant.

Table 3
The association of pain on injection among groups by Chi Square Test.

Group	No pain	Mild pain	Total	p value
				0.656*
Tramadol	37 (74%)	13 (26%)	50 (100%)	
Lignocaine	35 (70%)	15 (30%)	50 (100%)	

*p value < 0.05 is statistically significant.

Table 4
The Comparison of feedback between two groups by Chi Square Test.

Group	Fair	Good	Very Good	Total	p value
					0.897*
Tramadol	11 (22%)	25 (50%)	14 (28%)	50 (100%)	
Lignocaine	12 (24%)	26 (52%)	12 (24%)	50 (100%)	

*p value < 0.05 is statistically significant.

years of age. For pediatric patients, the recommendations for its use may differ between individual countries. For instance, in UK tramadol is not recommended for use in patients < 12 years of age.[11–13] It is contraindicated in patients with diminished respiratory function.[11] Tramadol is rapidly and almost completely absorbed after oral and intramuscular administration. It is rapidly distributed in the body.[11–13] It is known to cross the blood brain barrier and has a vasodilating property.[14,15] The plasma protein binding for this drug is approximately 20%[11] and is poorly lipophilic.[16]

Tramadol is known for its strong analgesic effect and has been used in dentistry for pain relief since many years. Intramuscular or submucosal tramadol before surgery extended the duration of anaesthetic effect and improved the quality of postoperative analgesia in third molar surgery.[17] TH was shown to be effective in preventing acute pain when compared with control group in third molar extraction when administered postoperatively submucosally.[18] When applied submucosal tramadol preoperatively it increased articaine activity in teeth with irreversible pulpitis.[19] Tramadol is known to provide profound postoperative analgesic effect of tramadol when used intramuscular or before surgery.[6] However, several other studies evaluated the LA efficacy of tramadol alone because it has a neurotransmission blocking properties. Pang et al. was the first to report on the local anaesthetic efficacy of tramadol when compared with lignocaine on the skin of forearm.[20] The studies of Al Haideri and Al Sandook examined the effect of tramadol with adrenaline in comparison with lignocaine containing adrenaline in minor oral surgical procedures and found that tramadol with vasoconstrictor provides effective anaesthesia similar to lignocaine containing vasoconstrictor.[21] In another trial, Al Haideri evaluated the effect of tramadol with versus without adrenaline for extraction of maxillary molars under supraperiosteal infiltration and found that tramadol with adrenaline provided profound anaesthesia when compared with that provided by tramadol alone and suggested that tramadol can be used as an alternative to lignocaine for tooth extraction.[9] But what is the effect of tramadol alone (without vasoconstrictor) on the oral soft tissues like gingiva when compared to that of lignocaine (without vasoconstrictor)? Only one study compared the effect of tramadol alone with plain lignocaine in oral soft tissue and suggested that tramadol can be a good alternative to lignocaine for oral surgical procedures.[22]

In the present study, we evaluated and compared tramadol versus lignocaine in terms of allergic reaction, pain on injection, onset and duration of anaesthesia, side effect and response of the participants. True allergic reactions and systemic anaphylactoid reactions to opioids are rare.[23] Altunkaya et al. reported local skin reaction (rash) with intradermal injection of tramadol.[24] However in the study of Kargi et al. it was found that tramadol did not have any significant local side effects when injected as local infiltration on skin.[25] Vahabi et al. also showed that tramadol did not have any significant local skin reactions when injected subcutaneously.[6] In the present study, none of the patient showed any untoward reaction to either drugs used. Kargi et al. and Vahabi et al. showed that there was no significant difference in local reaction between lignocaine and tramadol when injected as local infiltration.[6,25] Our results are in accordance with those of Kargi et al. and Vahabi et al. No form of allergy testing is 100% reliable, however intradermal (intracutaneous) test is the primary mode of assessing a patient for LA allergy and it is claimed that this test is 100 times more sensitive than other cutaneous tests. Also the accuracy of this test is comparatively more and the risk for anaphylactic reaction is also very low.[10] Hence, intradermal testing was used in this study to assess for drug allergy. None of our patients showed any skin reaction to either tramadol or lignocaine.The author assessed pain on injection using VAS ranging from 0 to 10. There was no significant difference in pain on injection between the two groups suggesting that the pH of the two drugs might be similar. There are no studies in the literature with which we can compare this finding. According to Ege et al. there was a significant difference in anaesthesia onset between tramadol and lignocaine. Lignocaine was more effective at 20 and 40 s while tramadol was more effective at 15, 20 and 30 min.[22] However in our study there was no statistical difference in onset of anaesthesia between the two drugs and is in accordance with the findings of Al Sandook et al.[21] The onset of anaesthesia in the present study for tramadol was 2.867 ± 0.665 min. The onset of action for tramadol according to Al Sandook et al. after inferior alveolar nerve block is 2.95 min.[21] The duration of anaesthesia depends upon the technique of injection and the amount of vasoconstrictor present in the solution. It is well-known that nerve blocks have longer duration of action than infiltration.[26] The solution containing a vasoconstrictor like adrenaline has a longer duration of anaesthesia comparatively.[26,27] Thus it is clear that vasoconstrictor enhances the effect of anaesthetic drugs. Therefore, the present study compared the LA effects of plain (without adrenaline) lignocaine and plain (without adrenaline) tramadol to compare the actual efficacies. Also Pang et al. proposed that commercially available tramadol has a LA effect which is comparable to lignocaine.[20] The duration of action for tramadol as a LA has been reported by Alsandook et al.to be about 117.38 min when administered along with adrenaline while for lignocaine with adrenaline it is about 300 min using conventional inferior alveolar nerve block and there was no significant difference between the duration of action of lignocaine and tramadol.[21] In the present study the duration of action for tramadol was found to be 45.70 ± 8.512 min while for lignocaine it was 44.70 ± 8.107 min and there was no significant difference in duration of action between two drugs.

The most common adverse events with single or multiple dose oral or parenteral tramadol administration is nausea (6.1%) and vomiting (1.7%).[9,13] In a study conducted by Alsandook et al. tramadol (with adrenaline) induced nausea in 6.45% and vomiting in 1.61% of patients while lignocaine (with adrenaline) induced nausea in 2.23% of patients with no incidence of vomiting and there was no statistical significant difference between the two groups.[21] In the present study none of the participant experienced any side effect when evaluated even after 24 h. None of the participant in both the groups considered the procedure as bad experience. All the participants tolerated the procedure well.

How this potent analgesic exhibits LA action is still not well understood. However, different opinions exist in the literature on this aspect. Like benzocaine, tramadol may follow hydrophobic pathway by passing through the nerve membrane and blocking the sodium channels.[28] In one study it was shown that the changes in somatosensory evoked potential by tramadol was not reversed by naloxone thereby suggesting that the local anaesthetic effect of tramadol was not mediated through opioid receptors.[29] Mert T et al., in 2007 reported a similar finding.[30] Mustafa G. and colleagues in 2005 hypothesized that tramadol may produce nerve conduction block by exerting a local anaesthetic effect by blocking Na^+ channels following a hydrophilic

pathway as lignocaine and it blocks K^+ channels more than lignocaine.[31]

5. Conclusion

The authors conclude that tramadol has a local anaesthetic effect similar to lignocaine when injected as infiltration in oral soft tissues. Like diphenhydramine, tramadol can also be used as an alternative to conventional local anaesthetic agents in intraoral minor surgical procedures.

Compliance with Ethical Standards:

Disclosure of potential conflicts of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in this study (involving human participants) were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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References

1. Brau ME, Koch ED, Vogel W, Hempelmann G. Tonic blocking action of meperidine on Na^+ and K^+ channels in amphibian peripheral nerves. *Anesthesiology.* 2000;92(1):147–155.
2. Mert T, Gunes Y, Ozcengiz D, Gunay I, Polat S. Comparative effects of lidocaine and tramadol on injured peripheral nerves. *Eur J Pharmacol.* 2006;543(1-3):54–62.
3. Haeseler G, Foadi N, Ahrens J, Dengler R, Hecker H, Leuwer M. Tramadol, fentanyl and sufentanil but not morphine block voltage-operated sodium channels. *Pain.* 2006;126(1-3):234–244.
4. Dalkilic N, Tuncer S, Bariskaner H, Kiziltan E. The effect of tramadol on the rat sciatic nerve conduction: a numerical analysis and conduction velocity distribution study. *Yakugaku Zasshi.* 2009;129(4):485–493.
5. Jaffe RA, Rowe MA. A comparison of the local anesthetic effects of meperidine, fentanyl and sufentanil on dorsal root axons. *Anesth Analg.* 1996;83(4):776–781.
6. Vahabi S, Heidari M, Ahmedinejad M, Akhlaghi J, Birjandi M. Comparison of local anesthetic effects of tramadol and lidocaine used subcutaneously in minor surgeries with local anesthesia. *Middle East J Anesthesiol.* 2011;21(1):9–14.
7. Kargi E, Isikdemir A, Tokgoz H, et al. Comparison of local anesthetic effects of tramadol with prilocaine during circumcision procedure. *Urology.* 2010;75(3):672–675.
8. Kargi E, Babuccu O, Altunkaya H, et al. Tramadol as a local anaesthetic in tendon repair surgery of the hand. *J Int Med Res.* 2008;36(5):971–978.
9. Al-Haideri YA. Comparison of local anesthetic efficacy of tramadol hydrochloride (with adrenaline) versus plain tramadol hydrochloride in the extraction of upper molar teeth. *J Oral Maxillofac Surg.* 2013;71(12):2035–2038.
10. Malamed SF. *Handbook of Local Anesthesia.* sixth ed. St.Louis: Mosby; 2013.
11. World Health Organization. Tramadol update review report. Available at: www.who.int/medicines/areas/quality_safety/6_1_Update.pdf; 2014.
12. Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet.* 2004;43(13):879–923.
13. Scott LJ, Perry CM. Tramadol: a review of its use in perioperative pain. *Drugs.* 2000;60(1):139–176.
14. Raimundo JM, Pontes LB, Antunes F, Sudo RT, Trachez MM, Zapata-Sudo G. Comparative effects of tramadol on vascular reactivity in normotensive and spontaneously hypertensive rats. *Clin Exp Pharmacol Physiol.* 2008;35(10):1197–1203.
15. Kitamura A, Higuchi K, Okura T, Deguchi Y. Transport characteristics of tramadol in the blood-brain barrier. *J Pharmacol Sci.* 2014;103(10):3335–3341.
16. Chrubasik J, Chrubasik S, Mather L. *Postoperative Epidural Opioids.* Heidelberg, New York: Springer-Verlag Berlin; 1993.
17. Pozos AJ, Martinez R, Aguirre P, Perez J. Tramadol administered in a combination of routes for reducing pain after removal of an impacted mandibular third molar. *J Oral Maxillofac Surg.* 2007;65(8):1633–1639.
18. Gönül [1] O, Satılmış [2] T, Bayram [2] F, Göçmen [2] G, Sipahi [2] A, Göker [2] K. Effect of submucosal application of tramadol on postoperative pain after third molar surgery. *Head Face Med.* 2015 Oct 14;11:35.
19. De Pedro-Muñoz [1] A, Mena-Álvarez [2] J. The effect of preoperative submucosal administration of tramadol on the success rate of inferior alveolar nerve block on mandibular molars with symptomatic irreversible pulpitis: a randomized, double-blind placebo-controlled clinical trial. *Int Endod J.* 2017 Dec;50(12):1134–1142.
20. Pang WW, Mok MS, Chang DP, Huang MH. Local anesthetic effect of tramadol, metochlopramide, and lidocaine following intradermal injection. *Reg Anesth Pain Med.* 1998;23(6):580–583.
21. Alsandook TA, Haideri YAA. A pilot double blinded clinical trial to compare between tramadol HCl and lidocaine HCl as local anaesthesia amongst hospital-outpatient adult dental attendees mosul-Iraqi. *Journal of Oral and Dental Research.* 2013;1(1):13–16.
22. Ege B < sup > 1 < /sup > , calisir M < sup > 2 < /sup > , Al-Haideri Y < sup > 3 < /sup > , Ege M < sup > 4 < /sup > , gungormus M < sup > 5 < / sup > . Comparison of local anesthetic efficiency of tramadol hydrochloride and lidocaine hydrochloride. *J Oral Maxillofac Surg.* 2018 Apr;76(4):744–751.
23. Fukuda Kazuhiko. Opioid analgesics. eighth ed.In: Miller RD, ed. *Miller's Anesthesia.* vol. 2. Philadelphia: WB Saunders; 2015:864–914.
24. Altunkaya H, Ozer Y, Kargi E, Babuccu O. Comparison of local anaesthetic effects of tramadol with prilocaine for minor surgical procedures. *Br J Anaesth.* 2003;90(3):320–322.
25. Kargi E, Babuccu O, Altunkaya H, et al. Tramadol as a local anaesthetic in tendon repair surgery of the hand. *J Int Med Res.* 2008;36(5):971–978.
26. Bennett CR. *Monheim's Local Anesthesia and Pain Control in Dental Practice.* seventh ed. Ontario: B.C.Decker; 1990.
27. Pitt Ford TR, Seare MA, McDonald F. Action of adrenaline on the effect of dental local anaesthetic solutions. *Endod Dent Traumatol.* 1993;9(1):31–35.
28. Mert T, Gunes Y, Guven M, Gunay I, Ozcengiz D. Blocking action of tramadol on nerve conduction. *Internet J Pharmacol.* 2001;1(2).
29. Tsai YC, Chang PJ, Jou IM. Direct tramadol application on sciatic nerve inhibits spinal somatosensory evoked potentials in rats. *Anesth Analg.* 2001;92(6):1547–1551.
30. Mert T, Gunes Y, Gunay I. Local analgesic efficacy of tramadol following intraplantar injection. *Eur J Pharmacol.* 2007;558(1-3):68–72.
31. Guven M, Mert T, Gunay I. Effects of tramadol on nerve action potentials in rat: comparisons with benzocaine and lidocaine. *Int J Neurosci.* 2005;115(3):339–349.