

Determine the Effect of Tramadol Injection as Adjuvant Anesthetic and Analgesia Following Surgical Removal of Mandibular Third Molar

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ABSTRACT

Objective: To establish the efficacy of mean pain control after submucosal tramadol injection compared to placebo after surgical removal of the impacted third molar.

Study Design: Quasi-experimental study.

Place and Duration of Study: Department of Maxillofacial Surgery, Armed Forces Institute of Dentistry, Rawalpindi Pakistan, from Feb to Aug 2018.

Methodology: All the patients had symmetrical bilateral impactions of the third molar on an orthopantomogram. The surgical site was randomly selected, and those in Group-T received Tramadol injection submucosally adjacent to the extraction socket immediately after the first tooth extraction, and Group-P received Saline. After the second extraction, Group-T received a Saline injection, and Group-P received Tramadol in the same manner. Patients were followed 24 hours post-operative for pain grading at 2, 4 and 24 hours, frequency and concentration of analgesic intake and duration of anaesthesia.

Results: Mean age of participants was 23.80±2.80 years. Means of pain intensity of Group without Tramadol after 2, 4 and 24 hours of extraction are 8.40±0.90, 6.30±0.40 and 2.10 ± 0.40, respectively, and those with Tramadol are 5.90±0.50, 4.50±0.30 and 1.60±0.40 respectively.

Conclusion: Our study concluded that Tramadol was more effective in providing analgesia after third molar surgery than local anaesthesia alone.

Keywords: Impacted third molar extraction, Local anaesthesia, Post-extraction pain, Submucosal injection, Tramadol

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INTRODUCTION:

Extraction of the third molar is a routinely performed procedure in oral and maxillofacial surgery.¹ It affects patients' quality of life due to associated complications with the dental procedure such as facial swelling, pain and trismus.² These complications are caused by the release of different inflammatory mediators like Interleukin-6 (IL-6), triggered by surgical trauma.³ The severity and possibility of post-operative complications are directly associated with the level of difficulty of extraction.⁴ The analgesic effect of post-operative sub mucosal Tramadol administration after impacted third molar surgery is documented to be threefold more in symptomatic patients as compared to asymptomatic patients.⁵ Third molar extraction is a common model in determining the efficacy of analgesics for acute dental pain relief.⁶

It is documented that effective control of post-surgical pain and inflammation enhances recovery in terms of oral functions and lifestyle and is very

relevant to the procedure technique.⁷ In dentistry, post-operative pain is effectively relieved by different analgesics and anti-inflammatory drugs or a combination of both.⁸ Non-steroidal anti-inflammatory drugs are known to cause various reactions. Therefore, they are not used in medical conditions like peptic ulcer disorder, bleeding disorder, patients taking anticoagulants and those with a history of intolerance or allergic reaction to drugs like Aspirin.

Opioid analgesics are alternative for such patients. Among opioids, Tramadol is an excellent substitute because it lacks respiratory depressant and sedative effects. Tramadol hydrochloride is a centrally acting synthetic opioid analgesic. Although classified as a weak opioid regarding its analgesic effects, it exhibits a dual action as an opioid and non-opioid. The pain-relieving effect of Tramadol is due to receptor antigen-mediated events of the cycle, which is independent of the route of administration. Tramadol and its active metabolite M1 possess a weak and selective binding affinity for μ opioid receptors. At the same time, it prevents the neuronal reuptake of serotonin and nor-adrenaline, preventing nociceptive inputs at the spinal cord.^{9,10}

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In this study, we compared the pain intensity following third molar removal after the submucosal administration of tramadol injection and placebo injection. Our research aims to establish mean pain control after submucosal tramadol injection compared to placebo after surgical removal of the impacted third molar.

METHODOLOGY

The quasi-experimental study was conducted from February 2018 to August 2018, at the Department of Oral and Maxillofacial Surgery, Armed Forces Institute of Dentistry, Rawalpindi Pakistan. Prior to the data collection, approval from the Institutional Ethical Committee was taken (IERB No. 905/Trg-ABP1K2). All the participants signed an institutionally approved consent form.

Inclusion Criteria: Patients aged greater than 18 years, having symmetrical bilateral impactions of the third molar on orthopantomogram diagnosed by Pell and Gregory method of impaction and with no record of psychological sickness and hypersensitivity to different medicines like Mepivacaine, Tramadol and Flurbiprofen were included in the study.

Exclusion Criteria: Patients with the use of analgesics and anti-inflammatory medicines a day before treatment, with history of seizures, lactating and pregnant women were excluded.

The sample size was calculated using G power 3.1.9.2 software, keeping the value of effect size as 0.8, alpha error as 0.05, beta error as 0.2, probability and power 0.8, and a sample size of 50 was calculated.

As a protocol, all patients presenting to the Armed Forces Institute of Dentistry, Rawalpindi Pakistan, were examined in the Outpatient Department, and those patients who fulfilled the criteria were sent to the Department of Oral and Maxillofacial Surgery. The patients underwent history, especially about the use of NSAIDs, psychiatric disorders and allergies, followed by a complete oral examination.

The type of impacted molars was categorized as devised by Pell and Gregory, determined from an orthopantomogram. The same surgeon carried out both extractions with a minimum gap of 1 weeks between extractions. A maximum of three 1.8 ml ampules of 2% Mepivacaine with 1: 20,000 Levnorfedrin were used as a local anaesthetist during surgery. In order to make access to the third molar, a full mucoperiosteal flap was elevated on the buccal aspect of the third

molar extending from the distal side of the second molar to backwards. Osteotomy and tooth sectioning, where required, were then carried out. Continuous saline irrigation was carried out throughout the procedure. Curettage and thorough irrigation of alveolus was done after tooth extraction. 4-0 silk suture was applied to achieve primary closure. Block randomization was done, and an equal number of patients were allotted to two groups, i.e., T-Group and the P-Group. Group -T received 2ml 100mg Tramadol injection submucosally adjacent to the extraction socket immediately after the first tooth extraction on a randomly selected side, and Group-P received a Saline injection. After the second extraction, Group-T immediately received saline injection submucosally adjacent to the extraction socket, and Group-P received Tramadol in the same manner.

Another maxillofacial surgeon administered medication to guarantee double blindness. Patients were given post-operative advice and were told to fill up a 3-fraction feedback form i.e., A) Assessment of pain intensity by utilizing a 10-mm visual analogue scale (VAS) at 4, 8 and 24 hours after surgery, with the lowest range (0) marked as "no pain" and uppermost range (10) marked as "very extreme pain" 18, B) Quantity of pain killer utilization and instant of taking of medicine, C) Interval of the effect of anaesthesia, taking into account the instant termination of lip's loss sensation compared with the similar feeling on the opposites lip, as the duration of anaesthesia ends. Pain-relieving effectiveness was evaluated corresponding to 4 endpoints i.e., average duration beyond primary ingestion of the rescue medication, the entire amount of pain-relieving medicine utilized through the initial 24 hours following surgery, and a complete assessment of the pain assessment.

Pain assessment was carried out using VAS after 4, 8 and 24 hours. The number of analgesics consumed and duration of anaesthesia were asked from the patient and recorded accordingly. The time period between the commencement of the anaesthetic effect on the lip and the return of normal consciousness was considered as the time interval of the sensory loss. Statistical Package for Social Sciences (SPSS) version 20.0 was used for the data analysis. Descriptive statistics were summed up for both qualitative and quantitative variables. Paired sample t-test was utilized to evaluate the differences between the two groups. The p -values ≤ 0.05 was considered significant.

RESULTS

Hundred patients were included in our research. The age of patients varies from 19 to 30 years. The mean age of participants was 23.80±2.80 years. Gender distribution among participants was shown in Table-I.

Table-I: Demographics of Study Participants (n=100)

Demographics	Frequency
Gender	
Male	55
Female	45

There was not much difference in the complexity and duration of surgical procedures among groups. No complications were encountered during the extraction procedure. Assessment of pain as experienced by the patients after 2, 4 and 24 hours of surgery evaluated on the visual analogue scale (VAS) from 0-10 is shown in Figure-1, where 0 was measured as “no pain” and ten was measured as “very severe pain”.

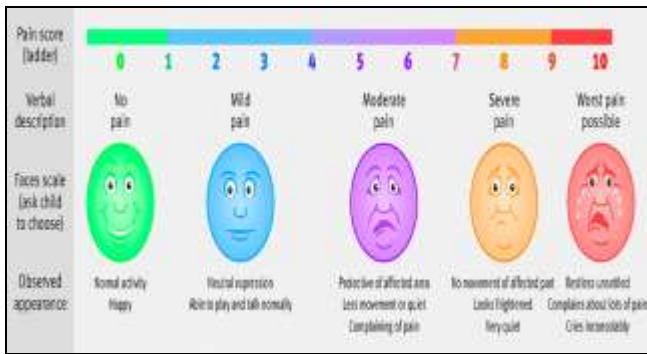


Figure -1: Visual Analogue Scale (0-10mm)

As evident from Figure-2, patients who were given post-operatively 2ml 100mg tramadol injection submucosally experienced less pain as compared to those who were given placebo (Saline).

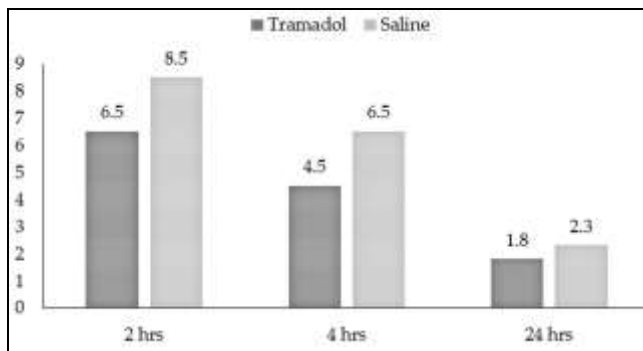


Figure-2: Pain Intensity observed over 2, 4 and 24 hours as assessed on VAS (0-10), (n=100)

Table-II showed the pain assessed on VAS by patients in both groups after 2, 4, and 24 hours of surgical extraction as the *p*-value was significant (<0.05), which showed there was a significant difference between the means of pain intensities in patients who were given Tramadol and means of pain intensities in patients who were given placebo (Saline). Patients administered submucosal Tramadol post-operatively experienced less pain than those administered placebo (Saline).

Table-II: pain intensities assessed on Visual Analogue Scale (0-10) after 2, 4 and 24 hours after injection of tramadol and placebo (n=100)

	After 2 Hours	After 4 Hours	After 24 Hours	<i>p</i> -value
	Mean±SD	Mean±SD	Mean±SD	
Without Tramadol	8.40±0.90	6.30±0.40	2.10±0.40	<0.001
With Tramadol	5.90±0.50	4.50±0.30	1.60±0.40	

DISCUSSION

Patients feel moderate to severe pain in the early post-operative phase after the impacted third molar extraction procedure. Therefore, effective post-operative analgesia is required to improve patient satisfaction and provide ease in the early post-operative period. In the current study, after doing extraction of the impacted third molar 2ml, 100 mg Tramadol was injected locally in sub mucosa, which was more effective in controlling pain than placebo. Although the central effect of Tramadol is well established, it can also be administered locally, where it acts through different known and unknown peri-pher-al mechanisms.

Many researchers explained the results of Tramadol after systemic administration while its local pain-relieving result came to light in 1998. Several scholars have described the potential events of the cycle after local administration of tramadol.^{11,12} Anesthetic results similar to Lidocaine,¹³ and Prilocaine,¹⁴ were also documented. Tramadol is also being used in addition to local anaesthetic articaine in impacted third molar removal procedures, enhancing the effect of anaesthesia.¹⁵

Third molar extraction is associated with medium to severe pain. Pain intensity reaches its maximum in about 3-5 hours following surgery when the efficacy of local anaesthesia declines.¹⁶ Tramadol is an effective analgesic in relieving moderate pain after day-case oral surgeries. Gonul *et al.*¹⁷ showed did a study that morphine and Tramadol can provide effective relief in

extremely severe pain. Despite administering higher than usual doses of Tramadol, it produces few side effects compared to more commonly used opioids like morphine. Pozos *et al.* also showed that Tramadol acts as an adjunctive pain-relieving medicine, potentiating the effectiveness of peri-operative analgesia in impacted molar removal procedures.¹⁵

One of the main causes of its superior analgesic action after local administration at the wound site is elevated medicine concentration at the surgical procedure site, devoid of distribution throughout the body or elimination, resulting in loss of drug from the body.^{18,19}

Ceccheti *et al.*, illustrated that if the degree of complexity of the surgical procedure were high, then the local submucosal administration of the drug tramadol would be more effective in alleviating post-surgical pain after surgical removal of the impacted third molar.¹³ Ceccheti *et al.* results confirmed that increased pain intensity and difficulty of procedure were quite effectively managed by administration of Tramadol. They also stated that VAS illustrated a pain-relieving effect for only 3.5 to 4 hours after surgical procedure. Seventy-five per cent of samples reported the worst post-operative surgical pain experience when a placebo was used as an analgesic. Our study showed that there was less requirement for intake of post-operative analgesics in patients given Tramadol submucosally providing evidence of the efficacy of Tramadol as an adjuvant anaesthetic when used along local anaesthesia. This was also shown by Kanto *et al.*²⁰ When Tramadol was used, patients had less preoperative anxiety, leading to decreased need for analgesics. It is also renowned and accepted that tramadol submucosally augments the anaesthetic efficiency of Mepivacaine along with epinephrine in the inferior alveolar nerve blockage.²¹

In a study, after extraction of the impacted third molar, Tramadol was given systemically and applied locally at the extraction site. It showed that both systemic and local administration of Tramadol increases the duration of anaesthesia and the efficacy of post-operative analgesia.²² In a study, 10mg oral ketorolac was used with 50mg submucosal Tramadol and was found effective in relieving post-operative pain, and less amount of analgesia was required when compared to oral ketorolac and placebo (Saline).²³ Number of theories have been given to clarify the events of cycles occurring during the mechanism of action of

Tramadol. Some recommended that Tramadol acts on voltage-gated Na⁺ channels (as do local anaesthetists) and adrenergic alleyways (as do vasoconstrictors).²⁴ A number of current researchers recognized the job of imprecise voltage-dependent K⁺ channels and the nitric oxide pathway.²⁵

Our study showed that when Tramadol was used, there was a positive pain response, less post-operative anxiety and less need for post-operative analgesics. Unfavourable effects of Tramadol usually accounted for were vomiting, nausea, diarrhoea, dizziness, xerostomia and perspiration. In the study, no appreciable adverse effect was noted except a small amount of gastric discomfort, which could be due to sympathetic flush related to surgical procedure. In addition, we noticed that there was no local inflammatory process exacerbation, necrotic process or delayed healing. In this study, after 2 hours, the mean pain intensity of the Group without Tramadol was 8.5, whereas the Tramadol Group had a mean intensity of 6.5. Similarly, the pain intensity mean of Group without Tramadol after 4 hours is 6.5 and of Group with Tramadol was 4.5. However, there is no such a large mean difference between the pain intensities of Group without Tramadol and Group with Tramadol after 24 hours, i.e. the mean of Group without Tramadol was 2.3 and of Group with Tramadol was 1.8 as the *p*-value was significant (<0.05), it showed that there was a significant difference between the mean pain intensities in patients who were given submucosal Tramadol and administered placebo (Saline).

CONCLUSION

Pain control and reduction in post-operative discomfort have been a matter of interest for many researchers. Our study was conducted to test one of the modalities of effective pain management. We concluded that submucosal administration of Tramadol along with local anaesthesia is more effective in providing effective and prolonged analgesia following impacted third molar extraction surgery when compared to local anaesthesia alone. One of the loopholes of our study was that it only provides evidence of the benefit of local administration of Tramadol into maxillofacial operating locations, but events of cycles occurring during the mechanism of action of the drug remain vague. Research evaluating the effect of Tramadol with other systemic analgesic and local anaesthetic drugs is needed.

Conflict of interest: None.

Author's Contribution

KK: Conception of idea, design of research, formulation of manuscript, AB: Supervisor, conception of idea, design or

research, SY: Data collection and compilation, WM: Interpretation and analysis of data, formulation of manuscript.

REFERENCES

1. Akbulut N, Üstüner E, Atakan C, Çölok G. Comparison of the effect of naproxen, etodolac and diclofenac on postoperative sequels following third molar surgery: a randomised, double-blind, crossover study. *Med Oral Patol Oral Cir Bucal* 2014; 19(2): e149-e156. doi: 10.4317/medoral.19518.
2. Perez-Urizar J, Martínez-Rider R, Torres-Roque I, Garrocho-Rangel A, Pozos-Guillen A. Analgesic efficacy of lysine clonixinate plus tramadol versus tramadol in multiple doses following impacted third molar surgery. *Int J Oral Maxillofac Surg* 2014; 43(3): 348-354. doi: 10.1016/j.ijom.2013.08.003.
3. Singh P, Rastogi S, Bansal M, Kumar S, Singh R, Nishad SG, et al. A prospective study to assess the levels of interleukin-6 following administration of diclofenac, ketorolac and tramadol after surgical removal of lower third molars. *J Oral Maxillofac Surg* 2015; 14(2): 219-225. doi: 10.1007/s12663-013-0609-1.
4. Lee CT, Zhang S, Leung YY, Li SK, Tsang CC, Chu CH. Patients' satisfaction and prevalence of complications on surgical extraction of third molar. *Patient Prefer Adher* 2015; 9: 257-263. doi: 10.2147/PPA.S76236.
5. Slade GD, Foy SP, Shugars DA, Phillips C, White Jr RP. The impact of third molar symptoms, pain, and swelling on oral health-related quality of life. *J Oral Maxillofac Surg* 2004; 62(9): 1118-1124. doi: 10.1016/j.joms.2003.11.014.
6. Isiordia-Espinoza MA, Pozos-Guillen A, Martinez-Rider R, Perez-Urizar J. Comparison of the analgesic efficacy of oral ketorolac versus intramuscular tramadol after third molar surgery: A parallel, double-blind, randomized, placebo-controlled clinical trial. *Med Oral Patol Oral Cir Bucal* 2016; 21(5): e637-e643. doi: 10.4317/medoral.21077
7. Paiva-Oliveira JG, Bastos PR, Pontes ER, da Silva JC, Delgado JA. Comparison of the anti-inflammatory effect of dexamethasone and ketorolac in the extractions of third molars. *J Oral Maxillofac Surg* 2016; 20(2): 123-133. doi: 10.1007/s10006-015-0533-2.
8. Mony D, Kulkarni D, Shetty L. Comparative evaluation of preemptive analgesic effect of injected intramuscular diclofenac and ketorolac after third molar surgery-a randomized controlled trial. *J ClinDiagn Res* 2016; 10(6): ZC102. doi: 10.7860/JCDR/-2016/17696.8045.
9. Isiordia-Espinoza MA, de JesúsPozos-Guillén A. Analgesic efficacy and safety of single-dose tra-madol and non-steroidal anti-inflammatory drugs in operations on the third molars: a systematic review and meta-analysis.Br *J Oral Maxillofac Surg* 2014; 52(9): 775-783. doi: 10.1016/j.bjoms.2014.05.005.
10. Gönül O, Satılmış T, Bayram F, Göçmen G, Sipahi A, Göker K. Effect of submucosal application of tramadol on postoperative pain after third molar surgery. *Head Face Med* 2015; 11(35): doi: 10.1186/s13005-015-0090-9
11. Gopalraju P, Lalitha RM, Prasad K, Ranganath K. Comparative study of intravenous Tramadol versus Ketorolac for preventing postoperative pain after third molar surgery-A prospective randomized study. *J Craniomaxillofac Surg* 2014; 42(5): 629-633. doi: 10.1016/j.jcms.2013.09.004.
12. Pang WW, Huang PY, Chang DP, Huang MH. The peripheral analgesic effect of tramadol in reducing propofol injection pain: a comparison with lidocaine. *Reg Anesth Pain* 1999; 24(3): 246-249.
13. Cecchetti MM, Negrato GV, de Melo Peres MP, Deboni MC, da GraçaNaclério-Homem M. Analgesic and adjuvant anesthetic effect of submucosal tramadol after mandibular third molar surgery. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2014; 117(3): e249-e254. doi: 10.1016/j.oooo.2012.05.015.
14. Altunkaya H, Ozer Y, Kargi E. Comparison of local anaesthetic effects of tramadol with prilocaine for minor surgical procedures. *Br J Anaesth* 2003; 90(3): 320-322. doi: 10.1093/bja/aeg079.
15. Pozos AJ, Martinez R, Aguirre P, Perez J. The effects of tramadol added to articaine on anesthesia duration. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; 102(5): 614-617.
16. Shipton EA, Roelofse JA, Blignaut RJ. An evaluation of analgesic efficacy and clinical acceptability of intravenous tramadol as an adjunct to propofol sedation for third molar surgery. *Anesth Prog* 2003; 50(3): 121-128.
17. Gönül O, Satılmış T, Ciftci A, Sipahi A, Garip H, Göker K. Comparison of the effects of topical ketamine and tramadol on postoperative pain after mandibular molar extraction. *J Oral Maxillofac Surg* 2015; 73(11): 2103-2107. doi: 10.1016/j.joms.2015.05.012.
18. Singh J, Dixit P, Singh P, Kedia NB, Tiwari MK, Kumar A. Pain perception and personality trait toward orthodontic treatment. *J Int Soc Prev Community Dent* 2017; 7(6): 377-380. doi: 10.4103/jispcd.JISPCD_419_17.
19. Dionne RA, Haynes D, Brahim JS, Rowan JS, Guivarc'h PH. Analgesic Effect of Sustained-Release Flurbiprofen Administered at the Site of Tissue Injury in the Oral Surgery Model. *J Clin Pharmacol* 2004; 44(12): 1418-1424. doi: 10.1177/009127000-4265703.
20. Kanto D, Salo M, Happonen RP, Vahlberg T, Kanto J. Tramadol premedication in operative extraction of the mandibular third molar: a placebo-controlled crossover study. *Acta Odontol Scand* 2005; 63(1): 43-49. doi: 10.1080/00016350510019685.
21. Isiordia-Espinoza MA, Orozco-Solis M, Tobías-Azúa FJ, Méndez-Gutiérrez EP. Submucous tramadol increases the anesthetic efficacy of mepivacaine with epinephrine in inferior alveolar nerve block. *Br J Oral Maxillofac Surg* 2012; 50(2): 157-160. doi: 10.1016/j.bjoms.2011.02.010.
22. Pozos AJ, Martínez R, Aguirre P, Pérez 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. doi: 10.1016/j.joms.2006.06.267.
23. Isiordia-Espinoza MA, Pozos-Guillén AJ, Martínez-Rider R, Herrera-Abarca JE, Pérez-Urizar J. Preemptive analgesic effectiveness of oral ketorolac plus local tramadol after impacted mandibular third molar surgery. *Med Oral Patol Oral Cir Bucal* 2011; 16(6): e776-780. doi: 10.4317/medoral.16854.
24. Mert T, Gunes Y, Gunay I. Local analgesic efficacy of tramadol following intraplanter injection. *Eur J Pharmacol* 2007; 558(1-3): 68-72. doi: 10.1016/j.ejphar.2006.11.055.
25. Yalcin I, Aksu F. Involvement of potassium channels and nitric oxide in tramadol antinociception. *Pharmacol Biochem Behav* 2005; 80(1): 69-75. doi: 10.1016/j.pbb.2004.10.020.