Journal of Population Therapeutics & Clinical Pharmacology

Ketorolac versus Tramadol for pain management after surgical removal of third molar: A prospective randomized study

Osamah So.Al Alawi[1], Sultan Ismail Shammaa[2], Abdulaziz Safar Almotairi[1], Ahmed Hamed Albeladi[2], Nabeel Hamed Albeladi[2], Rafi Husni Alghamdi[2], Ibrahim Mohammed Alsayyed[2]

[1]Medical supply administration, Jeddah, Saudi Arabia
[2]Rabigh general hospital Rabigh, Saudi Arabia

Abstract

Background: Analgesics administered prior to the painful stimulus may inhibit or eliminate the development of pain hypersensitization, resulting in decreased postoperative pain. Tramadol, which is a synthetic analog of codeine, induces pain prevention in both the opioid & non-opioid systems.

Aim: Comparing Tramadol & Ketorolac for pain management following third molar surgery was the objective of this research.

Patients and methods: The subjects of this randomized, triple-blind, controlled trial were 140 patients slated to undergo third molar extraction surgery. The current investigation was carried out within the Oral & Maxillofacial Surgery Department between May 2021 to December 2022.

Results: In terms of age & gender, there were no significant variations among the researches groups. There were Significant variations were observed among the groups under study with regard to the duration of action, onset of analgesia, sum of pain intensity scores over a 12-hour period& the aggregate of all analgesics taken in the five days following the procedure.

Conclusion: Preoperative Ketorolac is more effective than Tramadol in postoperative pain subsequent to third molar extraction, according to our findings.

Keywords: Tramadol, Ketorolac, amputation of the third molar, pain.

Introduction

An impacted mandibular third molar is surgically extracted; the procedure induces edema, trismus & moderate to severe pain. The management of postoperative pain subsequent to third molar surgery has the potential to enhance both oral function& lifestyle recovery **(1).**

Pain is a complicated phenomenon that involves both nerve psychological& mechanisms perceptions. It has been shown that preoperative administration of certain analgesics can decrease the advent of postoperative pain **(2).**

Preemptive analgesia, which refers to the administration of analgesics pre onset of the painful stimulus, it is a potential alternative approach to managing the pain associated with third molar postoperative procedures **(3).**

It is hypothesized that intramuscular administration of ketorolac, a pyrrolo-pyrrolo derivative, would yield analgesic effects comparable to 100 mg of pethidine & at least as effective as morphine **(4).**

Tramadol, which is a synthetic analog of codeine, induces pain prevention in both opioid & non-opioid systems. The opioid constituent of the substance exhibits a preference for μ receptors **(5).**

The mechanism of action of the non-opioid constituent of tramadol is by impeding the reuptake of serotonin & nor-epinephrine, as well as by releasing serotonin that is deposited in the nerve endings **(6).**

The main goal of this research was to compare the analgesic effects of Ketorolac & Tramadol following third molar surgery.

Patients and Methods

The subject of this randomized, triple-blind, controlled trial were 140 cases. who were scheduled for 3rd molar extraction surgery. The current research was carried out at the Oral &Maxillofacial Surgery Department. May 2021 to December 2022.

Inclusion criteria: Healthy patients with ASA 1, both genders, age range of 20 to 30 years and teeth with moderate and extremely difficult (with respective difficulty indices of five to seven & seven–ten). by Pederson difficulty index.

Exclusion criteria: Patients with acute pericoronitis who have not been suggested ASA I and have A medical history of hypersensitive reactions to ketorolac or tramadol, as well as who have been taking another NSAIDs within the previous twenty-one-day period.

Patients were randomized into two categories using random allocation software. Group A (intravenous ketorolac thirty milligrams, ketorolac tromethamine) & Group B (intravenous tramadol hydrochloride fifty milligrams) were administered.

Ethics approval and consent to participate: The current research was conducted in outlined in the Declaration of Helsinki& every procedure occurred in accordance with relevant guidelines & regulations. The protocol for the research received approval from the ethical committee at local level. Written consent with informed consent was obtained from every participant. who were involved in the research.

Methods of randomization: The randomization number was contained in an opaque, sealed envelope, with the principal investigator having exclusive access to the patient's coding. Patients, statisticians (assistant investigator) & the surgeon were all knowledgeable of the drug classes & medications. On the morning of surgery, a principal investigator removed The patient coding& the medication to be administered are enclosed in a sealed envelope.; consequently, the specified drug was inserted into a 2cc syringe. In the datasheet, the assistant investigator documented every parameter. The information relating to both medications was not revealed prior to the research., which defines the triple-blind design of this research.

Sample size Calculation: This research is based on research conducted by **Pathi et al. (7)** The following presumptions were taken into account when calculating the sample size using Epi Info STATCALC: - A two-sided certainty level of ninety-five percent with eighty percent power. & α error of five percent, the final maximum sample size obtained from the Epi-Info output was 125. The mean Onset of analgesia for the Ketorolac group (min) was 14.43±3.072 with The action duration (h) is 9.57±1.51. &the mean Onset of analgesia for the Tramadol group (min) was 3.21±1.085 with Duration of action (h) 4.04±1.44. In order to account for any incidences of dropout during follow-up, the sample size was raised to 140 subjects.

The patients were exposed to orthopantomograms, intraoral periapical radiographs& clinical examinations.

Surgical technique: The cephalic vein in the antecubital fossa was injected with a loaded syringe containing either fifty milligrams per milliliter tramadol or thirty milligrams per milliliter ketorolac fifteen minutes prior to the procedure. All patients had their third molars extracted by an assistant& physician while under local anesthesia (two percent lignocaine 1: 100,000 adrenaline solution) to prevent the nerves of the lingual &long buccal cavity &inferior alveolar nerve from being obstructed. Strict aseptic procedures were adhered to while preparing the surgical field. After incision of the standard T. Wards, a tooth was extracted using osteotomy. & tooth sectioning, the laceration was closed with 3–0 mersilk suture after socket toileting. Antibiotics, rescue oral analgesics (one hundred milligrams of aceclofenac, five hundred milligrams of paracetamol& ten milligrams of serratiopeptidase) & antiemetics were prescribed.

Postoperative procedure: Patients who were confined for a duration of six hours on a daycare basis were requested to provide the time at which they initially experienced pain. Subsequently, The Wong-Baker pain assessment scale was employed to commence an hourly pain evaluation. **(8).**
cases were released from the medical facility once the duration of pain relief was recorded& immediate postoperative complications were deemed to be nonexistent. They were also advised to undergo routine follow-up. In addition, cases were instructed to record the daily consumption of rescue analgesics until the fifth following the procedure. removal of Suture occurred on seventh day following satisfactory healing. The routine follow-up assessment additionally assessed the research's drugs for any possible side effects.

Statistical analysis: The information was entered into the computer & analyzed utilizing version 20.0 of the IBM SPSS software program (Armonk, NY: IBM Corp). Qualitative data were described in terms of percentages & numbers. The Kolmogorov-Smirnov test was employed to assess the distribution's normality. The range (minimum & maximum values), mean, standard deviation, median& IQR were employed to characterize the quantitative data. The statistical data relating to the efficacy of analgesics postoperatively, The Student's t-test was utilized to analyze the onset of action, duration of action, sum of pain intensity& total number of analgesics ingested during the five-day period following the procedure. At ninety-five percent the coefficient interval was established. The calculation of the level of significance was based on the subsequent probability (P) values: One-half of 0.05 was deemed to be significant in statistics.

Results

Table (1): Distribution of demographic data among the studied groups.

	Group A (Ketorolac group) N= 70	Group B (Tramadol group) N=70	test	P value
Age (year) mean± SD	27.6± 6.3	26.94± 6.8	**t**=0.59	0.55
Sex				
male	27 (38.6%)	23 (32.9%)	**X^2**=0.49	0.48
female	43 (61.4%)	47 (68.1%)		

P value >0.05: Not significant, P value <0.05 is statistically significant, p<0.001 is highly significant., SD: standard deviation, t: T test, x2: qui square test.

There was no significant variation observed in terms of gender or age among groups under investigation, as indicated in the table.

Table (2): Distribution of duration of action between the studied groups.

	Group A (Ketorolac group) N=70	Group B (Tramadol group) N=70	test	P value
Duration of action (hour) Mean± SD	9.01±1.62	3.75± 1.38	**t**=20.67	≤0.001

P value >0.05: Not significant, P value <0.05 is statistically significant, p<0.001 is highly significant., SD: standard deviation, t: T test.

This table demonstrates that, with regard to duration of action, there were significant variation among the groups under study.

Table (3): Distribution of Onset of analgesia among the studied groups.

	Group A (Ketorolac group) N=70	Group B (Tramadol group) N=70	test	P value
Onset of analgesia (min) Mean± SD	14.13±3.1	2.94±1.12	**t**=28.4	≤0.001

P value >0.05: Not significant, P value <0.05 is statistically significant, p<0.001 is highly significant., SD: standard deviation, t: T test.

as stated in the data in this table, there was a statistically significant variation among the groups under study regarding the initiation of analgesia.

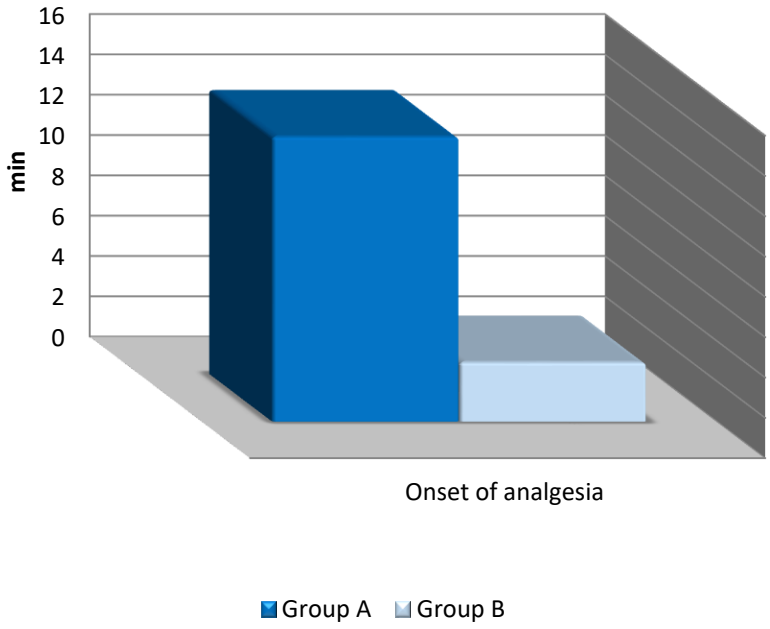

Fig (1): Shows distributions of onset of analgesia between studied groups.

Table (4): Distribution of sum of hourly pain intensity scores of 12 h among studied groups.

	Group A (Ketorolac group) N= 70	Group B (Tramadol group) N=70	test	P value
Sum of pain intensity scores of 12 h mean± SD	32.63±7.65	52.35±5.86	**t**=17.12	≤0.001

P value >0.05: Not significant, P value <0.05 is statistically significant, p<0.001 is highly significant., SD: standard deviation, t: T test.

This table demonstrates that there were significant variation among the researches groups regard to sum of pain intensity scores of 12 h.

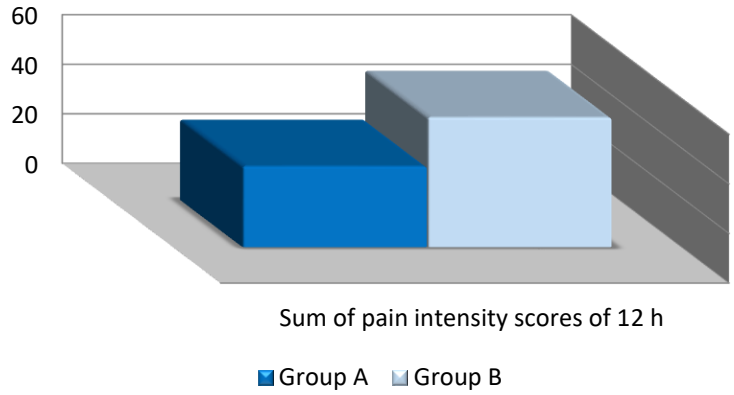

Fig (2): show distribution of sum of pain intensity scores of 12 h among studied groups.

Table (5): Distribution of total number of analgesics consumed during 5 postoperative days among studied groups.

	Group A (Ketorolac group) N= 70	Group B (Tramadol group) N=70	test	P value
Total number of analgesics consumed during 5 postoperative days mean± SD	3.05±2.5	7.91±3.02	**t**=10.37	≤0.001

P value >0.05: Not significant, P value <0.05 is statistically significant, p<0.001 is highly significant., SD: standard deviation, t: T test.

This table demonstrates that there were statistically significant variations among the researches groups regarded total quantity of analgesics taken in the five days following the procedure

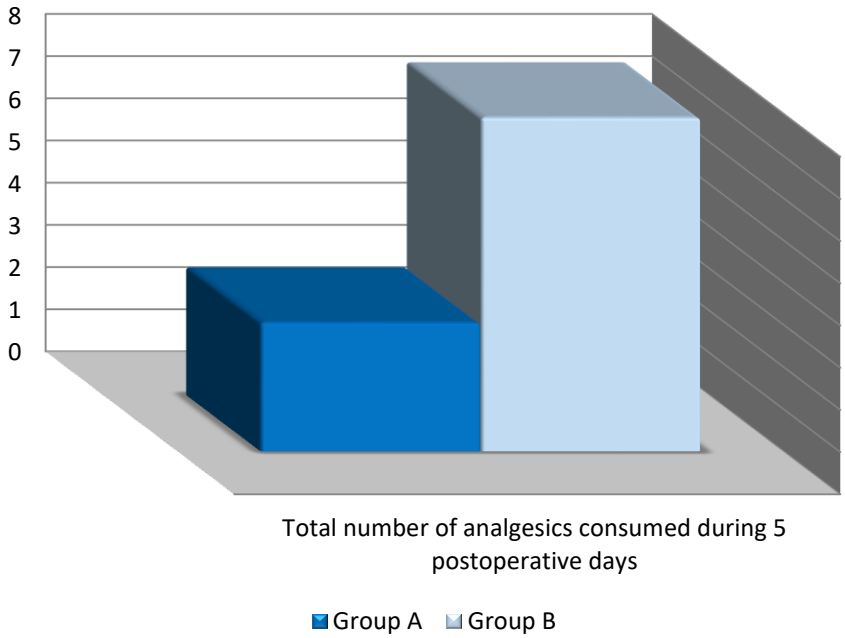

Fig (3): show distribution of total quantity of analgesics taken in the five days following the procedure among studied groups.

Discussion

The intrinsic nervous system's second-order neurons in the spinal cord become more excitable in response to noxious stimuli induced by injury at a more central level. &decreases threshold of nociceptive afferent nerve terminals. The notion of preemptive analgesia has developed as a consequence of this. **(9).**

By administering analgesics pre to the painful stimulus, it is possible to mitigate or eliminate the occurrence of pain hypersensitization, which would subsequently lead to a reduction in postoperative pain. **(10).**

Preemptive analgesia may have been not effective due to pain that had already developed central sensitization pre to surgery; thus, the current research investigation included a group of asymptomatic impacted mandibular third molars. **(4).**

The demand for clinical treatment that effectively represent the effectiveness of different analgesics in clinical practice is growing. Commonly, the efficacy of analgesics is evaluated using third molar surgery as the model because The surgical procedure generates pain of a basically regular intensity., enabling accurate differentiation among feeble & potent analgesics **(11).**.

Ketorolac, which was recently incorporated as a parenteral NSAID for management pain following the procedure, has demonstrated analgesic efficacy comparable to that of morphine. Additionally, comparative research has demonstrated which ketorolac suppositories exhibit greater potency than diclofenac **(12).**

Tramadol can be used frequently despite being an opioid due to its inability to induce drug tolerance & respiratory depression. Tramadol, which has the same analgesic efficacy as ketorolac, is thought to operate through multiple mechanisms **(13).**

The main results of this study were as follows:

The present research reported that the mean age of ketorolac group was 27.6± 6.3 years, 27 (38.6%) cases were males& 43 (61.4%) cases were females while average age of tramadol group 26.94± 6.8 years, 23 (32.9%) cases were males& 47 (68.1%) cases were females. We found that there were no significant variations in age or gender among the groups under study. Similarly, our results in agreement with **Pathi et al. (7)** who compared This study compares the analgesic effectiveness following the procedure IV ketorolac for avoiding pain following the procedure with tramadol. They disclosed that there were no statistical significant variations in age or gender among the groups under study.

Also, our results in line with **Gopalraju et al. (14)** who assessed the impact of two distinct analgesic regimens—a preoperative IV dose of Ketorolac or Tramadol administered 10 minutes pre operation—on clinical recovery following third molar surgery. In terms of age & gender, they discovered no statistically significant variations among the groups under study.

The findings of the present research demonstrated a significant distinction among the groups under investigation with regards to the duration of action, with the ketorolac group exhibiting better outcomes.

Also, our findings in line with **Pathi et al. (7)** who reported that In contrast to the tramadol group, the ketorolac group exhibited a substantially longer duration of action (9.57 hours) and achieved superior results (4.04 hours).

Similarly, our findings in consistent with **Kapoor et al. (15)** who contrasted pain relievers Tramadol & ketorolac following surgical removal of the third molar. It was documented that Group A exhibited a considerably longer duration of action in comparison to Group B.

There was an extremely significant variation among the groups examined in terms of analgesic onset time, with tramadol exhibiting a quicker & more effective onset than ketorolac, according to the current research.

The present research in agreement by **Kapoor et al. (15)** who noted that the rate at which analgesia was initiated was considerably slower in Group B cases than in Group A cases.

In a similar vein, the current study in consistent **Pathi et al. (7)** who demonstrated The analysis of analgesic onset times among the groups revealed that tramadol exhibited a substantially faster & more effective onset than ketorolac.
The findings of our study revealed a significant variation among the groups examined with regards to the sum of pain intensity scores over a period of twelve hours. Also, the current research in line with **Pathi et al. (7)** The participants who reported that the mean of the hourly pain intensity scores across the group responded significantly better to ketorolac as opposed to tramadol.
In a similar vein, our results in consistent with **Kapoor et al. (15)** who reported that ketorolac showed better results than tramadol regarding the hourly pain intensity between the groups.
O Our research findings indicated significant variation among the groups under investigation with regards to the total number of analgesics consumed over course of five days following procedure. Specifically, cases in ketorolac group consumed fewer analgesics in comparison to those in the tramadol group. The present study in agreement with **Pathi et al. (7)** who stated that a significant variation existed among the groups under study with regard for the total number of analgesics consumed. Additionally, they discovered that the individuals in the ketorolac group (3.03 mg/day) used fewer analgesics than those in the tramadol group (7.93 mg/day).
Also, our findings in consistent with **Kapoor et al. (15)** who demonstrated that In contrast to Group B, individuals in Group A consumed a lower quantity of analgesics overall over the course of five postoperative days compared to Group B.
Similarly, our results in line with **Gopalraju et al. (14)** who documented that individuals who were administered Ketorolac exhibited notably reduced pain intensity scores, a considerably extended time to rescue analgesics (500 milligrams of Acetaminophen) & decreased consumption of postoperative analgesics.

Conclusion

Comparing Tramadol & Ketorolac for pain management following third molar surgery was the purpose of this current research. Preoperative Ketorolac is more effective than Tramadol in decreasing postoperative pain subsequent to third molar extraction, according to our findings. However, in order to confirm the findings, additional research trials with a more extensive follow-up period & a larger sample size are required.

References

1. Balamurugan R. Influence of tooth sectioning on postoperative pain, swelling and trismus following surgical removal of impacted mandibular third molar. J Dent Res. 2019;1(1):11–7.
2. Marchand S. Mechanisms challenges of the pain phenomenon. Vol. 1, Frontiers in Pain Research. Frontiers Media SA; 2021. p. 574370.
3. Doleman B, Leonardi-Bee J, Heinink TP, Boyd-Carson H, Carrick L, Mandalia R, et al. Pre-emptive and preventive NSAIDs for postoperative pain in adults undergoing all types of surgery. Cochrane Database Syst Rev. 2021;(6).
4. Shah A V, Arun Kumar K V, Rai KK, Rajesh Kumar BP. Comparative evaluation of pre-emptive analgesic efficacy of intramuscular ketorolac versus tramadol following third molar surgery. J Maxillofac Oral Surg. 2013; 12:197–202.
5. Subedi M, Bajaj S, Kumar MS, Mayur YC. An overview of tramadol and its usage in pain management and future perspective. Biomed Pharmacother. 2019; 111:443–51.
6. Beakley BD, Kaye AM, Kaye AD. Tramadol, pharmacology, side effects, and serotonin syndrome: a review. Pain Physician. 2015;18(4):395.
7. Pathi J, Vidya KC, Sangamesh NC. Tramadol versus ketorolac for pain management after third molar surgery. National Journal of Maxillofacial Surgery. 2020 Jul 1;11(2):236-40.
8. Lanzetta A, Vizzardi M, Letizia G, Martorana U, Sanfilippo A, Osti L, Cervelli C, Coluccia R. Intramuscular tramadol versus ketorolac in patients with orthopedic and

traumatologic postoperative pain: a comparative multicenter trial. Current therapeutic research. 1998 Jan 1;59(1):39-47.
9. Finnerup NB, Kuner R, Jensen TS. Neuropathic pain: from mechanisms to treatment. Physiological reviews. 2020 Nov 3.
10. de Sousa Santos JA, da Silva LC, de Santana Santos T, Júnior LR, de Assunção Oliveira AC, Brandão JR. Comparative study of tramadol combined with dexamethasone and diclofenac sodium in third-molar surgery. Journal of cranio-maxillofacial surgery. 2012 Dec 1;40(8):694-700.
11. Au AHY, Choi SW, Cheung CW, Leung YY. The efficacy and clinical safety of various analgesic combinations for post-operative pain after third molar surgery: a systematic review and meta-analysis. PLoS One. 2015;10(6):e0127611.
12. Magee DJ, Jhanji S, Poulogiannis G, Farquhar-Smith P, Brown MRD. Nonsteroidal anti-inflammatory drugs and pain in cancer patients: a systematic review and reappraisal of the evidence. Br J Anaesth. 2019;123(2):e412–23.
13. Shankariah M, Mishra M, Kamath RAD. Tramadol versus ketorolac in the treatment of postoperative pain following maxillofacial surgery. J Maxillofac Oral Surg. 2012; 11:264–70.
14. 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 Cranio-Maxillofacial Surg. 2014;42(5):629–33.
15. Kapoor M, Samah Bashir DAAS, Gul S. Ketorolac versus Tramadol for pain management after surgical removal of third molar-A prospective randomized study. J Adv Med Dent Sci Res. 2020;8(11).