

Tramadol versus ketorolac for pain management after third molar surgery

ABSTRACT

Objectives: To compare the analgesic efficacy of preoperative intravenous (IV) ketorolac versus tramadol in preventing postoperative pain after mandibular third molar surgery.

Methodology: Two hundred patients in the age group of 18–40 years with asymptomatic impacted mandibular molars were randomly allocated into one of the two groups (100 in each group) and underwent third molar surgery under local anesthesia. Group I received IV ketorolac 30 mg and Group II received IV tramadol 50 mg preoperatively. The difference in postoperative pain was assessed by five primary end points: pain intensity being measured hourly by Wong-Baker pain assessment scale for 6 h, onset of analgesia, duration of action, total number of analgesics consumed, and patient's global assessment.

Results: Throughout the 6 h investigation period, patients reported significantly lower pain intensity scores, longer duration of action, lesser postoperative analgesic consumption, and better global assessment in ketorolac when compared to tramadol group. Patients in the ketorolac group significantly performed better than the tramadol group in terms of all parameters except onset of analgesia. All the drug-related complications were mild and did not require any investigation.

Conclusion: The result of the present study shows that preoperative IV ketorolac 30 mg is more effective than tramadol 50 mg for postoperative pain following third molar surgery.

Keywords: Ketorolac, pain, third molar surgery, tramadol

INTRODUCTION

Surgical removal of an impacted mandibular third molar causes swelling, trismus, and moderate to severe pain.^[1,2] Postsurgery pain control after third molar surgery may lead to improved recovery in terms of lifestyle and oral function.^[1,3] The various analgesics used intravenous (IV) techniques are ketorolac, tramadol, paracetamol, nalbuphine, and buprenorphine.

Ketorolac tromethamine, a member of pyrrolo-pyrrole group, has an analgesic, anti-inflammatory, and antipyretic activity and has been significantly effective for postoperative dental pain, is available for IV, intramuscular, and oral administration.^[4,5]

Tramadol hydrochloride, which is a synthetic analog of codeine, has been proved clinically effective in treating

moderate to moderately severe pain while having a low addiction potential and causing minimal respiratory depression.^[4,6,7]

Since both these drugs have reported the pharmacologic and pharmacodynamic advantages, the present study was carried out to compare the analgesic efficacy of IV ketorolac against tramadol following surgical removal of the third molar.

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METHODOLOGY

The present triple-blind, randomized controlled trial was carried out with a sample size of 200 patients (100 males and 100 females); the sample size was calculated using the formula $N = AB/(E/S)^2$. Patients of both genders of age from 20 to 30 years and with the physical status ASA I were included in the study. Patients were subjected to clinical examination, intraoral periapical radiographs, and orthopantomograms. Winter's WAR lines were drawn, and WHARFE assessment was done. To standardize and select a homogenous sample, moderately difficult and very difficult (difficulty index of 5–7 and 7–10, respectively) samples were chosen. Patients other than ASA I, with a history of allergic reactions to tramadol or ketorolac, who were on other nonsteroidal anti-inflammatory drugs (NSAIDs) within past 21 days, and with acute pericoronitis were excluded from the study. Ethical committee clearance was obtained for the study (KIMS/KIIT/IEC/025/2014).

Individuals who were eligible to participate explained about the study and signed informed consent obtained. Enrolled patients were randomized using random allocation software into two groups. Group I (ketorolac 30 mg IV, ketorolac tromethamine, batch no. DH5015) and Group II (tramadol 50 mg IV, tramadol hydrochloride, batch no. KP949013). An opaque, sealed envelope consisted of randomization number with the patient coding being made assessable only to the principal investigator. Neither the patients, surgeon (assistant investigator), nor the statisticians were aware of the drugs and the groups. This sealed envelope containing the patient coding and the drug to be administered was opened on the day of surgery by a principal investigator; accordingly, the particular drug was loaded into 2cc syringe. Assistant investigator recorded all the parameters in the datasheet. In this study, all the information regarding both drugs was not disclosed until the study, thus characterizing the triple-blind study design.

Loaded syringe containing either ketorolac 30 mg/ml or tramadol 50 mg/ml was administered into the cephalic vein in the antecubital fossa 15 min preoperatively. All the patients underwent extraction of third molars by the same surgeon and an assistant, under local anesthesia (2% lignocaine with 1:200,000 adrenaline) for blocking inferior alveolar nerve and lingual and long buccal nerve. Surgical field was prepared, strict aseptic techniques were followed. Standard T. Wards incision was given, tooth extraction was done by osteotomy and tooth sectioning, followed by socket toileting and wound closure using 3-0 mersilk suture. Rescue oral analgesic (aceclofenac 100 mg + paracetamol 500 mg + serratiopeptidase 10 mg), antibiotics, and antiemetics were prescribed, and postoperative instructions were advised.

Following the surgical procedure, patients were admitted on a daycare basis for 6 h and were asked to report the time when they first experienced the pain, at which point the hourly pain assessment was started using Wong-Baker pain assessment scale.^[8] The time at which the pain subsided was noted and when the immediate postoperative complications were ruled out, patients were discharged and were advised a regular follow-up. Patients were also asked to document the total number of rescue analgesics consumed per day up to 5th postoperative day and suture removal was done on the 7th day after ensuring satisfactory healing. Routine follow-up examination also included evaluation of potential complications associated with the study drugs.

Statistical analysis

It was done using SPSS software version 20.0 (IBM Corp. Armonk, NY, USA). Statistical data in relation to onset of action, duration of action, sum of pain intensity, total number of analgesics consumption during 5 postoperative days, and efficacy of analgesics postoperatively were analyzed by Student's *t*-test.

A $P < 0.05$ was considered statistically significant, $P < 0.01$ highly significant, and $P < 0.001$ very highly significant, while $P > 0.05$ was considered to be statistically insignificant.

RESULTS

The present study included administration of IV ketorolac and tramadol in 100 patients each preoperative to third molar surgery and both drugs were compared for onset of analgesia, duration of action, sum of pain intensity scores for 6 h, total number of analgesics consumed, and global assessment.

The mean age of ketorolac and tramadol was 27 and 25, respectively, which were not significant statistically [Table 1].

Sex wise distribution showed no significant results [Table 2].

Duration of action between the groups showed better results for ketorolac group (9.57 hours) compared to tramadol (4.04 hours) [Table 3].

The onset of analgesia between group showed that tramadol was having better and faster onset as compared to ketarolac [Table 4].

Duration of action between the two drugs was compared and it showed better results for ketorolac (9.57 Hours) than tramadol (4.04 Hours), which was statistically highly significant [Table 5].

Table 1: Age-wise distribution between the groups

Age group (years)	Frequency (%)	Ketorolac	Tramadol	t*	P*	Significance
16-24	87 (43.5)	27.37±6.19	25.73±5.72	1.945	0.299	Not significant
25-32	78 (39.0)					
33-40	35 (17.5)					
Total	200 (100.0)					

Age range: 16-40 years unpaired t-test, P>0.05, not significant

Table 2: Sex wise distribution

Sex	No of case	Percentage	Ketorolac	Tramadol
Male	63	31.5	31 (31%)	32 (32%)
Female	137	68.5	69 (69%)	68 (68%)
Total	200	100		

$\chi^2=0.04$, P>0.05, Not Significant

The sum of hourly pain intensity scores between the group showed better results with ketarolac than tramadol [Table 6].

Patients with ketarolac group (3.03) had consumed less analgesics as compared to tramadol group (7.93) [Table 7].

Patients were requested to grade the surgical procedure and pain relief status using global assessment scale, ketarolac group showed better results (2.09) than tramadol group (3.53) [Table 8].

DISCUSSION

The tissue response to noxious stimuli due to injury results by reducing the threshold of nociceptive afferent nerve terminals and at the more central level, by increasing the excitability of the second order neurons in the spinal cord. Based on this the concept of preemptive analgesia has been evolved. Administration of analgesics before the painful stimulus, the development of pain hypersensitization may be reduced or abolished, thus resulting in less postoperative pain.^[5,9]

It has been postulated that the pain existing before surgery may have already achieved central sensitization, thus making preemptive analgesia ineffective; therefore, asymptomatic impacted mandibular third molars were included in the current study.^[5,10]

There is an increase in need for clinical models that accurately reflect the efficacy of various analgesics commonly used. Third molar surgery is the model commonly used to test the efficacy of analgesics since the procedure induces pain that generally is consistent in severity allowing for good discrimination between weak and strong analgesics.^[11]

Of late, ketorolac has been introduced as a parenteral NSAID for the control of postoperative pain and its analgesic

potency has been shown to be comparable with morphine. Comparative studies have also shown that ketorolac suppositories are more than diclofenac.^[12,13]

In spite of being an opioid, tramadol can routinely be used because of lack of drug tolerance and respiratory depression. With an analgesic efficacy equivalent to ketorolac, tramadol is believed to have a multimodal action.^[12] In the present study, any significance difference between both the study groups in terms of pain is thus attributable to the drug effect.

Ong *et al.* conducted a study on comparison of IV tramadol and ketorolac in terms of analgesic potency after third molar surgery and concluded that the analgesic duration was longer with ketorolac than tramadol, with the overall fewer rescue analgesic consumption.^[10]

The finding of this study was in accordance with the present study. Lanzetta *et al.* compared the pain intensity of these two drugs in orthopedic procedures. Hourly assessment of pain showed that pain relief from the tramadol was sooner as compared to the ketorolac.^[8] The faster onset of action of tramadol could be possibly attributed to its central mode of action.

Postoperative pain was assessed after third molar surgery for a period of 6 h by Ong *et al.* and patients in the ketorolac group experienced significantly less pain throughout the investigation period, as compared to tramadol.^[10]

In our study, preoperative IV ketorolac showed greater pain relief with lesser pain intensity scores. Ketorolac proved to be a better drug for postoperative pain management following third molar surgery, due to its peripheral mechanisms of action. A study conducted by Shaik *et al.* showed that tramadol is a suitable and safe analgesic for the relief of postextraction pain and is more effective than ketorolac with prolonged analgesia and minimal side effects. The difference may be due to oral consumption of analgesics.^[14]

The total number of analgesic consumption was higher in tramadol group as compared to the diclofenac group as observed by Tuzuner *et al.* for pain relief after bimaxillary osteotomy procedures.^[15]

Table 3: Duration of action between the study groups

	Mean ± SD		t*	P*	Significance
	Ketorolac	Tramadol			
Duration of action (H)	9.57±1.51	4.04±1.44	-26.42	0.00	Highly Significant

Table 4: Onset of analgesia between the study groups

	Mean ± SD		t*	P*	Significance
	Ketorolac	Tramadol			
Onset of analgesia (min)	14.43±3.072	3.21±1.085	-34.43	0.00	Highly significant

*The statistical significance was less than 0.0001 so it was considered highly significant. Unpaired t-test, P<0.001, highly significant. SD: Standard deviation

Table 5: Duration of action between the study groups

	Mean ± SD		t*	P*	Significance
	Ketorolac	Tramadol			
Duration of action (h)	9.57±1.51	4.04±1.44	-26.42	0.00	Highly significant

*The statistical significance was less than 0.0001 so it was considered highly significant. Unpaired t-test, P<0.001, highly significant. SD: Standard deviation

Table 6: Sum of hourly pain intensity scores of 12 h between the study groups

	Mean ± SD		t*	P*	Significance
	Ketorolac	Tramadol			
Sum of pain intensity scores of 12 h	33.56±6.98	53.23±4.49	23.678	0.00	Highly significant

*The statistical significance was less than 0.0001 so it was considered highly significant. Unpaired t-test, P<0.05, significant. SD: Standard deviation

Table 7: Total number of analgesics consumed during 5 postoperative days between the study groups

	Mean ± SD		t*	P*	Significance
	Ketorolac	Tramadol			
Total number of analgesics consumed during 5 postoperative days	3.03±2.45	7.93±3.016	11.93	0.00	Highly significant

*The statistical significance was less than 0.0001 so it was considered highly significant. SD: Standard deviation

Table 8: Global assessment between the study groups

	Mean ± SD		t*	P*	Significance
	Ketorolac	Tramadol			
Global assessment	2.09±1.18	3.53±0.577	-10.94	0.00	Highly significant

*The statistical significance was less than 0.0001 so it was considered highly significant. Unpaired t-test, P>0.05, not significant. SD: Standard deviation

Vitterio Colletti *et al.* conducted a clinical trial to compare the postoperative analgesic effect and therapeutic tolerability of tramadol administered by IV injection when compared with that of ketorolac. During the 3 days of trial, the number of ampoules used did not differ significantly. For tramadol, the mean was 1.4 ± 0.1 ampoules on the

day of surgery, decreasing to 0.4 ± 0.1 ampoules on day 1 and 0.1 ± 0.1 ampoules on day 2 postoperatively. For ketorolac, the mean number of ampoules was 1.5 ± 0.1 on the day of surgery, decreasing to 0.6 ± 0.1 on day 1 and 0.1 ± 0.1 on day 2.^[16]

The total postoperative analgesic consumption for preventing postoperative pain after third molar surgery for the ketorolac group was significantly less than the tramadol group as noted by Ong *et al.*^[10]

In the present study, the total number of analgesic consumption was found to be lesser in the ketorolac group compared to the tramadol group. Because Group I has better analgesic efficacy than Group II for third molar surgical pain, maybe that the pathogenesis of dental pain is largely inflammatory and NSAIDs have been shown to elicit excellent dental pain relief where Tramadol does not affect prostaglandin synthesis and it does not have anti-inflammatory effects.

Ong *et al.* conducted a study to compare preoperative IV tramadol and ketorolac for preventing postoperative after third molar surgery, where the patients overall assessment of the surgery in relation to pain showed that most patients in the ketorolac group (43.3%) scored the surgery as excellent in relation to minimum pain after the surgery as compared with Tramadol group.^[10]

Nausea and vomiting are the major adverse effects of tramadol when used for preoperative analgesia. In our study, ten patients complained of nausea and vomiting. Respiratory depression and sweating are also the known adverse events associated with parenteral tramadol. None of the patients in our study complained of sweating upon injection of tramadol. Vickers *et al.* found that there was a drop in the respiratory rate following IV administration of tramadol, but it was noted not only during the first 5 min postinjection, while it was sustained in case of morphine administration. They concluded that tramadol had much less effect on the respiratory system with a higher therapeutic ratio.^[17]

However, Bouloux GF *et al.* in their study rated tramadol as a better drug when compared to ketorolac when used for postoperative pain management following nasal surgeries.^[16]

Shah *et al.* conducted a study to compare the analgesic efficacy of tramadol hydrochloride with diclofenac sodium in dentoalveolar surgery. The purpose of this study was to find a safe and effective analgesic alternative to NSAIDs for patients undergoing dentoalveolar surgery who could not tolerate NSAIDs. The analgesic efficacy of the two drugs was equal, but tramadol did better than diclofenac. Tramadol can be

used for postoperative analgesia after dentoalveolar surgery, especially in situations where NSAIDs are contraindicated.^[18]

In our study, ketorolac rated better than tramadol because of the nature of pain following third molar surgeries. The pathogenesis of dental pain and general surgical pain are different. Dental pain being largely inflammatory is better managed with NSAIDs than with opioids. Most common adverse effects of parenteral ketorolac are pain and skin reactions at the site of injection, but in our study, only five reported of severe pain at the site of injection but none of them had local skin reactions.

CONCLUSION

Although tramadol is an opioid, ketorolac performed better in terms of pain relief following third molar surgery. The possible reason could be the nature of dental pain being largely inflammatory, is better managed with the use of an NSAID than an opioid. With a limited sample size, we conclude that ketorolac could be given priority over tramadol for the management of postoperative pain following surgical removal of impacted mandibular third molars. However, to substantiate the results, further research trials are needed with a larger sample size and a considerable duration of follow-up.

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Conflicts of interest

There are no conflicts of interest.

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