**A double-blind, placebo-controlled randomized comparison of pre and postoperative administration of ketorolac and tramadol for dental extraction pain**

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**Abstract**

**Objective:** To compare the analgesic efficacy and safety of single-dose oral ketorolac and tramadol administered pre and postoperatively for dental extraction pain.  
**Materials and Methods:** 74 patients undergoing third molar extraction (impacted or other causes) were recruited into the study, over a period of 1 year. The patients were divided into six groups and they were given ketorolac (20 mg), tramadol (100 mg), or placebo either preoperatively or postoperatively (half an hour before or half an hour after the procedure). Placebo was glucose powder filled in empty capsule. Pain assessment was done using a modified Verbal Rating Scale (VRS) at 30 min, 2, 4, and 6 h after the procedure. A record of whether rescue analgesic (ibuprofen 400 mg) was taken during the 6 h study period, along with the time it was taken, was made. Record of any adverse effects experienced by the patient was also kept. Maximum pain scores for each of the six study groups, over the 6 h study period, were noted.  
**Results:** Kotorolac and tramadol were significantly better than placebo in relieving molar tooth extraction pain. Postoperative administration of tramadol was found to be more efficacious than preoperative administration in relieving the pain, whereas the preoperative administration of ketorolac was better than its postoperative administration.  
**Conclusion:** This study demonstrated that tramadol is equally effective to ketorolac in relieving pain in the first 6 h after molar extraction and therefore can be tried in patients who are intolerant to nonsteroidal anti-inflammatory drugs.  
**Key words:** Analgesia, dental pain, ketorolac, tramadol

**Introduction**

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.1 Pain of dental extraction produces moderate to severe pain which is routinely treated with nonsteroidal anti-inflammatory drugs (NSAIDs) for 2–3 days.2-4 The NSAIDs have the advantage of being analgesic as well as anti-inflammatory and are therefore the rational choice for pain associated with inflammation.5,6 At the same time the NSAID’s are liable to produce gastrointestinal adverse effects such as gastritis and peptic ulcer and thus should be used cautiously. Analgesics such as tramadol, which are non-NSAIDs, can be tried on such patients.

Dental extraction pain is an excellent clinical model for acute pain, especially third molar extraction pain.5 This study was designed to compare the analgesic efficacy of ketorolac with tramadol for pre and postoperative pain relief as well as their side effect in patients undergoing dental extraction.

**Materials and Methods**

This prospective randomized, placebo-controlled study was conducted on patients for 1 year (Jan 2010–Jan 2011) attending the Dental Outpatient Department of Teerthanker Mahaveer Medical College and Research Centre, Moradabad, UP. Ethical clearance was obtained from the Institutional Ethical Committee. Seventy four patients undergoing tooth extraction were recruited according to the inclusion and
exclusion criterion. They were divided into six groups, i.e., to receive tramadol, ketorolac, or placebo pre or postoperatively. Patients with history of acid–peptic diseases, hemorrhagic diathesis, known hypersensitivity of NSAIDs or tramadol, and epileptic patients were excluded. A total of 74 patients were recruited during the study, 25 each in the tramadol and ketorolac groups and 24 in the placebo group.

Both the investigator and patient were blind. Random allocation of groups was done using computer-generated random numbers. Each drug was coded and packed into identical appearing packets, with only the patient number and whether to be given pre- or postoperatively indicated on the label. Drugs were given by the dental surgeon per orally (PO) as per Table 1.

A verbal rating scale (VRS) was chosen to grade pain for this study because it is very reliable and easy to administer. The first assessment of the pain intensity/relief was done half an hour after the end of the procedure. The 2nd, 3rd, and 4th assessments done at 2, 4, and 6 h postextraction. We devised a modified VRS for grading pain, taking into consideration the use of a rescue analgesic (ibuprofen 400 mg), and it is shown in Table 2.

As placebo is included in this study, it was ethically incorrect not to include the rescue analgesic. Ibuprofen is NSAID with good anti-inflammatory and analgesic activity. It is one of the most commonly used analgesics for dental pain. Therefore, we included ibuprofen as the rescue analgesic in our study. Patients from placebo group were given rescue analgesic when pain becomes intolerant.

Pain scores of patients receiving same drug preoperatively or postoperatively as well as other drug groups were compared using Mann-Whitney’s U test. Age of patients, the amount of rescue medication taken, and time after extraction when rescue medication was taken were compared by ANOVA followed by post-hoc Dunnett’s T3 test. Number of males and females in different groups were compared by Chi-square test, P value. Adverse effects were compared using Chi-square test or Fischer’s exact test as appropriate. All analysis were done using SPSS software 16.0 version. P value < 0.05 was considered significant.

### Results

Out of the 74 patients recruited, 12 patients each were in preoperative group for tramadol, ketorolac, and placebo group; 13 patients each in postoperative group of tramadol and ketorolac; and 12 patients were in postoperative group of placebo. 36 patients were males (48.64%). The mean age of the patients in the study was 31.57 years, ranging from 18–65 years, with 92% of the patients in the 25–45 year age group. Prior to surgery local anesthetic (2% lignocaine) was injected to all patients. The mean dose of the local anesthetic was 2.4 ml ranging from 2 to 8 ml. All except three patients (4%) had antibiotic coverage prior to surgery. The mean duration of the procedure was 15.93 min, ranging from 2 to 70 min. For 59 patients (78%) it took less than 20 min for the completion of the procedure. For two patients (1.5%), it took 70 min. The indications for the third molar extractions were impacted teeth, infected teeth, or both. One patient had a tongue ulcer for which the extraction was indicated. Of the 74 patients, 51 patients (69%) had impacted teeth, 7 patients (9.5%) had infected teeth, and 16 patients (21.5%) had both. All except three (4%) were lower molar extractions. All the six patients group were similar in terms of gender distribution, average age, the amount of local anesthetic administered, the antibiotic coverage given, the position of the molar extracted, and the duration of the procedure.

The results of the analysis of the primary end point namely mean pain scores show that the analgesics (ketorolac and

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### Table 1: Analgesic drugs administration protocol

| Drug  | Dose and route | Timing            |
|-------|---------------|-------------------|
| Tramadol | 100 mg pre- and postoperatively, PO | 30 min before and after extraction |
| Ketorolac | 20 mg pre- and postoperatively, PO | 30 min before and after extraction |
| Placebo  | 20 mg pre- and postoperatively, PO | 30 min before and after extraction |

### Table 2: Modified verbal rating scale used

| Before rescue                          | Score | Rank |
|----------------------------------------|-------|------|
| No pain                                | 1     | 1    |
| Some pain, but no need for rescue      | 2     | 2    |
| Pain severe enough to take rescue      | 3     | 3    |
| After Rescue                           |       |      |
| No pain                                | 4     | 3    |
| Some pain, but less than when rescue was taken | 5     | 3    |
| Pain same as when rescue was taken    | 6     | 3    |
| Pain more severe than when rescue was taken | 7     | 4    |

### Table 3: Adverse effects

| Adverse effects              | No. of patients |
|------------------------------|-----------------|
|                             | Tramadol (n = 25) | Ketorolac (n = 25) | Placebo (n = 24) |
| Sleepy                      | 1               | 1                | 0               |
| Dizziness/giddiness         | 5               | 2                | 0               |
| Weakness/tiredness          | 1               | 0                | 0               |
| Nausea/vomiting             | 0               | 2                | 0               |
| Tingling sensation          | 0               | 0                | 1               |
| Serious adverse events      | 0               | 0                | 1               |
| Total n %                   | 7 (28)          | 5 (19.22)        | 1 (4.16)        |
tramadol) were more efficacious in reducing the pain as compared to placebo [Figure 1]. Mean combined pain score for tramadol plus ketorolac versus placebo at 30 min was 1.261 and 1.312, respectively, and at 6 h was 2.132 and 2.884, respectively. When the pain scores of analgesic group were compared against those of the placebo group separately, the analgesic group was found to have lower maximum pain scores at each time point as compared to placebo, indicating that the analgesics were superior to placebo in producing pain relief.

On comparison of the pain scores of the preoperative group versus the postoperative group of tramadol, postoperative administration was found to reduce the pain score more than preoperative administration at each time point. Mean pain score for preoperative tramadol and postoperative tramadol at 30 min was 1.4 and 1.1, respectively, and at 6 h it was 2.42 and 1.875, respectively [Figure 1]. When preoperative and postoperative ketorolac were compared, there was no significant difference between the maximum pain score (mean pain score for preoperative ketorolac and postoperative ketorolac at 30 min was 1 and 1.545, respectively, and at 6 h it was 2.416 and 1.818, respectively [Figure 1].

The secondary end point in the study was the need for rescue analgesic. When tramadol was compared with placebo (both preoperative and postoperative), the analgesic group needed less rescue drug than the placebo group. The average time taken by the patient from the start of the procedure to the time when pain was severe enough for the patient to feel the need to self administer the rescue analgesic was more in the tramadol than in the placebo group, which indicates that more prolonged pain relief was seen in the analgesic group as compared to those receiving placebo (mean time for rescue analgesic in the tramadol and ketorolac group – 366 min, in the placebo group – 240 min [Figure 2]. On comparison of preoperative placebo with preoperative tramadol, there appeared to be no significant difference in need for rescue analgesic. \( P = 0.241 \) (mean time for rescue in the preoperative placebo group – 245 min and mean time for rescue in the preoperative tramadol group – 313 min). However, on comparison of preoperative placebo and preoperative ketorolac, the need for rescue was significantly lower in the ketorolac group. \( P = 0.006 \) (mean time for rescue in the preoperative placebo group – 245 min and mean time for rescue in the preoperative ketorolac group – 407 min).

When postoperative placebo was compared with postoperative tramadol, the need for rescue analgesic was significantly lower in the tramadol group. \( P = 0.012 \) (mean time for rescue in the postoperative placebo group – 233 min and mean time for rescue analgesic in the postoperative tramadol group – 372 min). On comparison of postoperative placebo with postoperative ketorolac, the need for rescue analgesic was significantly lower in the ketorolac group. \( P = 0.008 \) (mean time for rescue in the postoperative placebo group – 233 min and mean time for rescue in the postoperative ketorolac group – 373 min).

When preoperative tramadol was compared with postoperative tramadol, there was no significant difference in the need for rescue analgesic. \( P = 0.217 \) (mean time for rescue in the preoperative tramadol group – 313 min and mean time for rescue in the postoperative tramadol group – 372 min). When preoperative ketorolac was compared with postoperative ketorolac also, there was no significant difference in the need for rescue analgesic between the two. \( P = 0.766 \) (mean time for rescue in the preoperative ketorolac group – 407 min and mean time for rescue in the postoperative ketorolac group – 373 min).

There were no serious adverse events reported for any of the study groups. Adverse effects seen are tabulated in Table 3. Only 8 patients (16.3%) of the total of 49 reported side effects. Of these eight patients that reported side effects, seven belonged to the tramadol group and one to the placebo group. One patient each from the tramadol
groups complained of sedation. Two patients felt dizziness and five patients had giddiness in the tramadol group. One patient each from the tramadol group and the ketorolac group felt weakness/tiredness. Two patients in the ketorolac group and one patient in the tramadol group felt nausea/vomiting. One patient in the placebo group complained of tingling sensation. Comparison of adverse effect reportage of tramadol versus placebo groups showed that tramadol was significantly more likely to produce adverse effects compared to placebo. Comparison of adverse effect reportage of ketorolac versus placebo groups showed that ketorolac was significantly more likely to produce adverse effects compared to placebo. Comparison of ketorolac and tramadol for adverse effects showed that there was no significant difference between the two.

For purposes of analysis, occurrence of adverse effects was represented as nominal data that is either “any adverse effect occurred” or “no adverse effect occurred.” Pearson’s Chi-square test (without Yate’s continuity correction) showed a significant difference between groups.

**Discussion**

Third molar extraction produces moderate to severe pain and a fair amount of inflammation. It is routinely treated with NSAIDs for 2–3 days. NSAID’s are known to produce side effects such as gastric irritation leading to ulceration and bleeding disorders. Despite the inflammatory component, one of the drugs used in this study was a non-NSAID, so that the side effects produced by the anti-inflammatory analgesics could be avoided. The analgesic efficacy of non-NSAIDs versus NSAID’s to placebo was compared in this study. We also attempted to compare the adverse effects of non-NSAID and NSAID with placebo, when given as single dose. Another aspect, which was looked at in this study, was pre-empting the expected pain by preoperative administration versus countering pain after it sets in by postoperative administration.

This study has succeeded in demonstrating the analgesic efficacy of single oral doses of either tramadol or ketorolac for impacted third molar extraction with an acceptable incidence and severity of side effects, over the first 6 h following extraction. There was no significant difference between the analgesic efficacy of tramadol and ketorolac. The pre- and postoperative administration of ketorolac was found to be equally effective in controlling dental pain. Tramadol was found to be more effective postoperatively than preoperatively.

We looked at whether there is any need for analgesics for postextraction pain as the patient is already receiving a local anesthetic prior to surgery and found that a significant proportion of patients do experience pain severe enough to require analgesics. Single dose of either tramadol or ketorolac was more efficient than placebo in relieving pain, over the first 6 h. Other studies corroborate this finding. Keeping the concept of pre-emptive analgesia in mind, we expected preoperative administration of analgesics to be more efficacious in relieving the pain than postoperative administration. Our results show that postoperative administration of tramadol appears to be more efficacious than preoperative administration in terms of pain relief. Analgesic effect of tramadol begins within 1 h and reaches a peak in approximately 2–3 h. It is likely that the postextraction pain reaches a peak in the first 2–4 h.

Pharmacodynamics and pharmacokinetics of most administered drugs are time dependent. Opioid activity of tramadol is due to both low-affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite to opioid receptors. As it is extensively metabolized by a number of pathways, the bioavailability of the active metabolite is high. It has a quick onset of action. The analgesic effect of tramadol begins within 1 h and reaches a peak in approximately 2–3 h. Though tramadol was given preoperatively with the idea of preempting the expected pain, it appears that it was given too early to be of any benefit and the peak analgesic effect and the time of maximum pain after tooth extraction may not have coincided with each other.

Even though the preoperative administration of ketorolac was found to be effective, it was not significantly better than postoperative administration. Ketorolac inhibits the enzyme cyclo-oxygenase, thereby inhibiting the synthesis of prostaglandins, which is a mediator of inflammation and pain. It is a potent NSAID with a plasma half-life of approximately 4.5–5.5 h. The dose of ketorolac (20 mg) administered in this study was possibly not enough to preempt the pain produce by third molar extraction or that the time of administration was too close to the extraction for the drug to produce any effect. Third molar extraction produces a fair amount of injury to the surrounding tissue, leading to release of arachidonic acid, which is converted into prostaglandin by cyclo-oxygenase. Inhibition of cyclo-oxygenase even before the release of arachidonic acid from injured tissue ensures that the synthesis of prostaglandins is blocked and pain and inflammation is preempted. Sufficient residual pain remains despite adequate local anesthesia.

Tramadol being an Opioid and norepinephrine modulator, more central nervous system-related side effects as expected was found as six patients is tramadol group had CNS-related...
side effects and none in placebo group reported. Comparison of tramadol and ketorolac did not show any significant difference in side effect reportage; however, the organ system affected differed in each case. Ketorolac has been reported to produce nausea, vomiting, dyspepsia, peptic ulceration, and prolongation of bleeding time, whereas tramadol effects on the gastrointestinal tract are fairly minor and its CNS effects are more prominent. Some of the reported side effects include anxiety, confusion, euphoria, sleep disorders, visual disturbance, and dependence.

Pain assessment using a VRS was appropriate for this study. Some studies assessed the utility of 10 indices (including the verbal rating scale) in the subjective experience of acute pain. The results indicated that each of the measures of pain intensity is adequately valid. In other studies, it has been observed that pain intensity is a relatively easy dimension of pain experience for patients to report, most self-report measures of pain intensity are strongly related to one another, and so can probably be used interchangeably in many situations.

As telephonic interviews were needed for the assessment of postoperative pain, patient not accessible by telephone were not included in the study. The fact that this was a single-dose study and pain was assessed only over the first 6 h was another limitation. Ideally, the duration of a study for assessing the analgesic efficacy of drugs is postextraction pain, which should be for a period of 2–3 days, with multiple dosing.

Conclusion

This study demonstrated that postoperative administration of tramadol is equally effective as traditional NSAID’s in relieving pain in the first 6 h after molar extraction, and therefore, it can be tried in patients who are intolerant to NSAIDs. A firm conclusion regarding the time of intervention (i.e., pre and postextraction) for optimal pain control is a point for clarification and needs further analysis.

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