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COMPARISON OF THE ANALGESIC EFFICACY AND SAFETY OF PRE & POST OPERATIVE ORAL KETOROLAC FOR DENTAL EXTRACTION PAIN

Dr. VIPIN KUMAR[1], Dr. HITESH MISHRA[2], Dr. SANJEEV SHARMA[3]

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1. Lecturer, Dept of Pharmacology, S.N. Medical College, Agra.
2. Assistant Professor, Dept of Pharmacology, Teerthanker Mahaveer Medical College & Research Center, Moradabad.
3. Professor, Dept of Pharmacology, Teerthanker Mahaveer Medical College & Research Center, Moradabad.

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Corresponding Author

Dr. Vipin Kumar

Lecturer, Dept of Pharmacology, S.N. Medical College, Agra

Abstract

Objective: To compare the analgesic efficacy and safety of the single-dose oral ketorolac pre & post operatively for dental extraction pain. **Materials and Methods:** 49 Patients who were undergoing third molar extraction (impacted or other causes) were recruited into the study, over a period of one year. The patients were divided into four groups to receive ketorolac (20 mg) or placebo either preoperatively or postoperatively (half – an – hour before or half – an – hour after the procedure). Pain assessment was done using a modified Verbal Rating Scale (VRS), at 30 minutes, 2 hours, 4 hours and 6 hours after the procedure. A record of whether rescue analgesic (ibuprofen 400 mg) was taken during the 6 hours 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 4 study groups, over the 6 hours study period. Secondary end points are time when rescue analgesic was taken, adverse effects observed. **Results:** Ketorolac was significantly better than placebo, in relieving molar tooth extraction pain. Preoperative administration of Ketorolac was found to be more efficacious than postoperative administration in relieving the pain. **Conclusion:** This study demonstrated that Ketorolac, a NSAID's is effective in relieving pain in the first 6 hours after molar extraction and therefore can be tried in patients who are undergoing molar extraction.

INTRODUCTION

What is Pain? Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage[1]. Pain can be acute or chronic. Acute pain is produced by an excessive noxious stimulus, giving rise to an intense and unpleasant sensation.

Pain of dental extraction produces moderate to severe pain which is routinely treated with non-steroidal anti-inflammatory drugs (NSAIDs) for 2-3 days.[2, 3] The NSAIDs have the advantage of being analgesic as well as anti-inflammatory and as such are the rational choice for a condition where pain with inflammation occurs.[4, 5]

The study was conducted on patients attending the dental outpatient department of Teerthankar Mahaveer dental college& Research center.

Dental extraction pain is an excellent clinical model for acute pain, especially third molar extraction pain[4]. The patients were recruited from the TeerthankarMahaveer dental College & Research Centre Hospital's OPD. The head of the Department of dentistry was approached and the study was discussed after which it was initiated.

Ethical clearance was obtained from the Institutional Ethical Committee. The Verbal Rating scale was chosen for this study because it is very reliable and easy to administer. As placebo is included in this study it was ethically incorrect not to include the rescue analgesic.

Ibuprofen is NSAID that has a good anti-inflammatory, analgesic activity. It is one of the most commonly used analgesics for dental pain. Therefore, we introduced ibuprofen as the rescue analgesic. Patient of placebo group were given rescue analgesic when pain becomes intolerant. Inclusion & exclusion criteria were made to select the patient for the study. Pain intensity was scored and assessed using a Verbal Rating Scale (VRS). Treatment differences were calculated using Kruskal – Wallis & Mann – Whitney U tests for rank transferred data. Adverse effects were compared using Pearson's Chi squared test.

RESULTS

A total of 49 patients were recruited during the study. Eight patients were excluded

from the efficacy analysis. (Seven patients could not be contacted on the telephone and one patient was found to have high blood pressure after the drug was administered). Of the 49 patients included in the study 24 were males (48.97%). The mean age of the patients in the study was 31.57y, ranging from 18y-65y, with 92 % of the patients in the 25-45 y age group. The mean duration of the procedure was 15.93 minutes, ranging from 2-70 minutes. For 38 patients (78%) it took less than 20 minutes for the completion of the procedure while for 1 patient (2 %) it took 70 minutes. Local anesthetic (2% lignocaine) was injected to all patients, prior to surgery. The mean dose of the local anesthetic was 2.4 ml ranging 2-8 ml. All except 3 patients (6%) had antibiotic coverage prior to surgery. 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 49 patients, 34 patients (69%) had impacted teeth, 4 patients (9.5%) had infected teeth, and 9 patients (19%) had both. All except 2(4%) were lower molar extractions. All the four 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.

Analgesic efficacy:- (Figure 1)

The results of the analysis of the primary end point namely mean pain scores show that the Ketorolac was more efficacious in reducing the pain as compared to placebo. Mean pain score of Ketorolac group and placebo group at 30 minutes was 1.272 and 1.312 and at 6 hours was 2.117 and 2.884 respectively. (Kruskal-Wallis Chi-square = 17.2413; P=0.0041).

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 ketorolac, there was no significant difference between the maximum pain score. Mean pain score for preoperative ketorolac and postoperative

ketorolac at 30 minutes was 1 and 1.545 and at 6 hours it was 2.416and 1.818 respectively (Mann Whitney U with Z correction = 1.0218; p = 0.306).

Need for rescue analgesic – (Figure 2)

The secondary end point in the study was the need for rescue analgesic. When Ketorolac was compared with placebo (both preoperative and postoperative), the analgesic group needed rescue drug less 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 ketorolac than in the placebo group, indicates that, more prolonged pain relief was seen in the analgesic group as compared to those receiving placebo (meantime for rescue analgesic in the ketorolac– 366 minutes, in the placebo group – 240 minutes (Kruskal – Walis Chi-Square = 17.7; p = 0.00337)

It was seen that on comparison of preoperative placebo with preoperative ketorolac, there appeared to be significant difference in need for rescue analgesic. (Mean time for rescue in the preoperative placebo group- 245 minutes, mean time for rescue in the preoperative ketorolac group – 407 minutes) Mann Whitney U – 7.4; p = 0.006)

When postoperative placebo was compared with postoperative ketorolac, the need for rescue analgesic was significantly lower in the Ketorolac group. (Mean time for rescue in the postoperative placebo group –233 minutes, mean time for rescue analgesic in the postoperative ketorolac group 373 minutes) (Mann Whitney U Test = 7; p = 0.008).

When preoperative ketorolac was compared with postoperative ketorolac, there was no significant difference in the need for rescue analgesic (Mean time for rescue in the preoperative ketorolac group - –407 minutes, mean time for rescue in the postoperative ketorolac group – 373 minutes) (Mann Whitney U test = 0.1; p = 0.766).

Adverse events: (Table-1)

There were no serious adverse events reported for any of the study groups. Only 8 patients (16.3 %) of the total of 49 reported side effects. Of these 8 patients that reported side effects, 7 belonged to

the Ketorolac group and 1 to the placebo group. Five patients in the Ketorolac group felt dizziness/giddiness. One patient from the Ketorolac group felt weakness/tiredness. One patient in the Ketorolac group felt nausea/vomiting one patient in the placebo group complained of tingling sensation.

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'. Pearsons chi square test (without Yale's continuity correction) showed a significant difference between groups (Chi square – 12.6083; p =0.0018)

Comparison of adverse effect reportage of Ketorolac versus placebo groups showed that Ketorolac was significantly more likely to produce adverse effects, compared to placebo (Fisher's exact test; p = 0.0006)

DISCUSSION

Third molar extraction produces moderate to severe pain and a fair amount of inflammation. It is routinely treated with non-steroidal anti-inflammatory drugs (NSAIDs) for 2-3 days. The analgesic efficacy of NSAIDs to Placebo was compared in this study. We also attempted to compare the adverse effects of 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 administrative.

This study has succeeded in demonstrating the analgesic efficacy of single oral doses of Ketorolac, for impacted third molar extraction, with an acceptable incidence and severity of side effects, over the first 6 hours following extraction. The postoperative and preoperative administration of ketorolac was found to be equally effective in controlling dental pain.

We looked at whether there is any need for analgesics for post extraction 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 ketorolac was more efficient than placebo in relieving pain, over the first 6 hours.

We did not come across any study, with dental extraction as pain model using ketorolac as study drugs. Therefore we

discuss here the conclusions of other investigators using major rather than minor surgery as pain models. However, we fell that their conclusions are relevant to our study. In a comparison study between ketorolac and morphine for treatment of postoperative pain after cholecystectomy, ketorolac produced significantly less analgesia than morphine on day 1, but on day 2 the two drugs produced a similar effect. [6] Although ketorolac is a potent anti-inflammatory drug, use of ketorolac for more than 5 days is associated with a significant incidence of peptic ulceration and renal impairment. The consequences of any patient that develop nephrotoxicity are not to be taken lightly, since it could eventually lead to analgesic nephropathy and chronic renal failure requiring dialysis. We emphasize here, that our choice of ketorolac was because; molar extraction is a minor surgical procedure producing short lived pain, requiring analgesic for not more than 2-3 days in all. [7]

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. In our study we found that timing of administration appeared not to significantly affect its efficacy. Pharmacodynamics and pharmacokinetics of most administered drugs are time dependent.

Even though the preoperative administration of Ketorolac was found to be effective, it was no significantly more so than postoperative administration. We can explain this by taking into account the pharmacokinetic and the pharmacodynamic properties of Ketorolac. Ketorolac being an NSAID inhibits the enzyme cyclo-oxygenase, thereby inhibiting the synthesis of Prostaglandin's, which is a mediator of inflammation and pain. It is a potent NSAID with a plasma half-life of approximately 4.5-5.5 hours[8] It is likely that the dose of Ketorolac (20mg) administered in this study is too less to pre-empt the pain produce by third molar extraction. It is also possible that the time at which the dose was administered, was too close to the procedure for the drug to produce any effect in the body, by the time pain sets in.

From our results showing that analgesic group required the rescue drug (Ibuprofen 400 mg) less than the placebo group, we

once again demonstrated that the pain following impacted tooth extraction is severe enough to require analgesics.

Our results showed preoperative Ketorolac to be more efficient than preoperative placebo in producing longer lasting analgesia, as seen by the reduced need for rescue in the preoperative Ketorolac group. 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 Prostaglandin's is blocked and pain and inflammation is preempted.

When postoperative placebo and Ketorolac were compared, Ketorolac was found to be more efficacious as indicated by the lower need for rescue in the analgesic groups. This result reinforces that sufficient residual pain remains despite adequate local anesthesia.

Overall, the side effects reported by Ketorolac group were significantly more than that reported by the placebo group. Ketorolac has been reported to produce nausea, vomiting, dyspepsia, peptic ulceration, prolongation of bleeding time, and impairment of renal function.

Pain assessment using a verbal rating scale (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.[9, 10] the results indicated that each of the measures of pain intensity is adequately valid. In other studies,[11, 12] 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 used interchangeably in many situations. Our result emphasizes the fact that NSAID's are effective in ameliorating the acute pain as proved in this study.

As telephonic interviews were needed for the assessment of postoperative pain, patient not accessible by telephone could not be included in the study. The fact that this was a single dose study and pain was assessed only over the first 6 hours, was another limitation. Ideally the duration of a study for assessing the analgesic efficacy of

drugs is post extraction pain, should be for a period of 2-3 days, with multiple dosing.

CONCLUSION

This study demonstrated that Ketorolac, a NSAID's is effective in relieving pain in the first 6 hours after molar extraction and therefore can be tried in patients who are undergoing molar extraction. A firm conclusion regarding the time of intervention (i.e., pre-extraction; post – extraction) for optimal pain control is a point for clarification and needs further analysis.

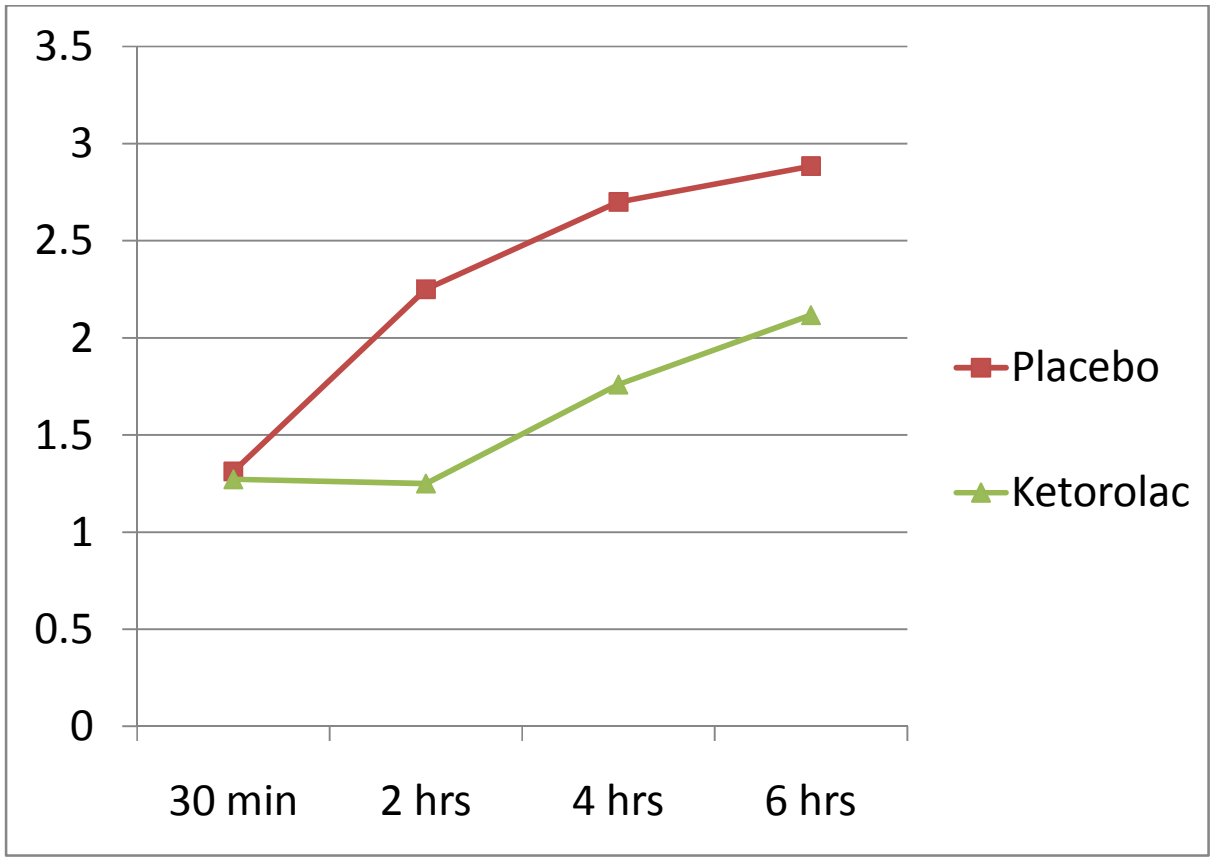

Figure 1 Change in mean pain scores (preoperative and the postoperative group combined) for Ketorolac and Placebo over the 6 hour study period.

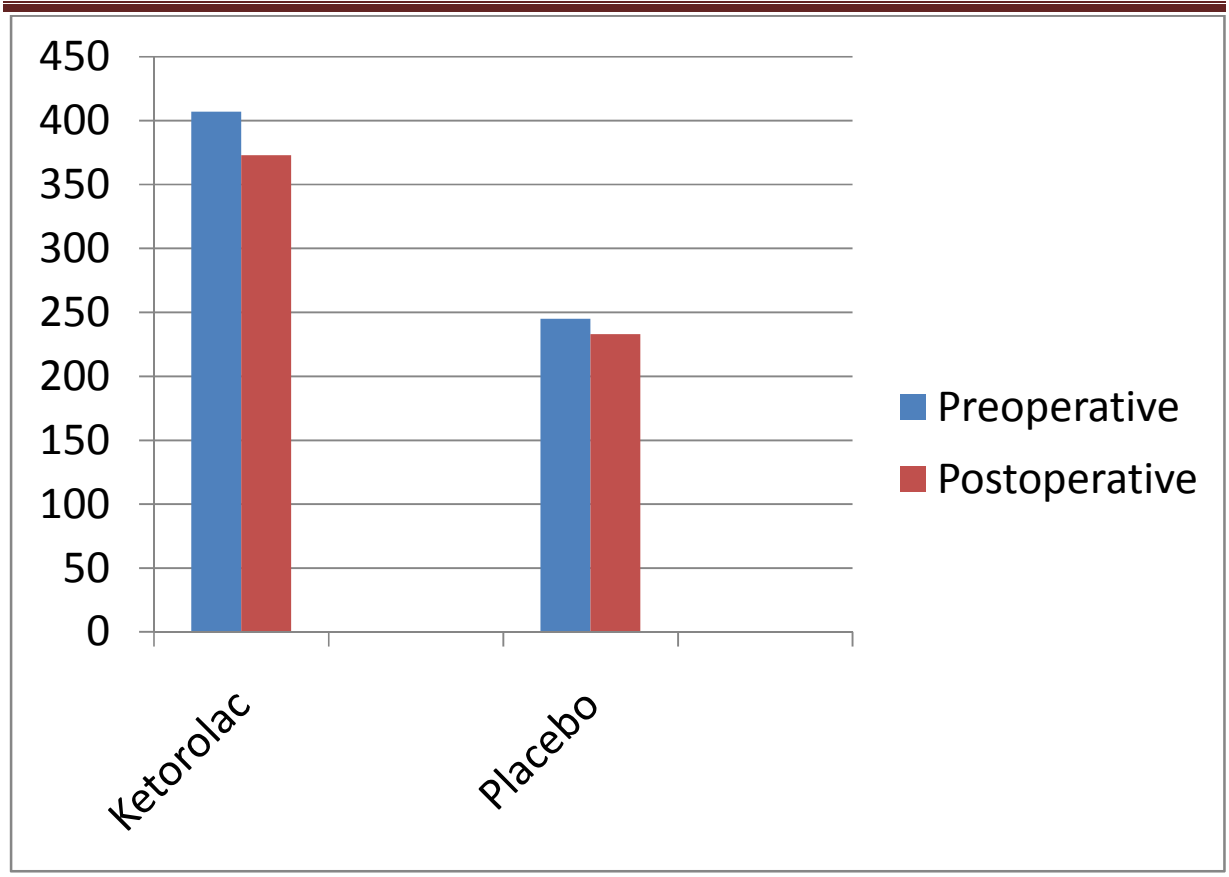

Figure 2 Need for rescue analgesic in the Preoperative versus Postoperative groups of Ketorolac and placebo as indicated by mean time (in minutes) at which the rescue drug was self administrated.

Table 1

Adverse Events

Adverse Effects	Ketorolac n = 25	Placebo n = 24
Sleepy	0	0
Dizziness/giddiness	5	0
Weakness/Tiredness	1	0
Nausea/Vomiting	1	0
Tingling sensation	0	1
Serious adverse events	0	0
Total n %	7(28)	1(4.16)

Table 2

Modified Verbal Rating Scale Used

Modified Verbal Rating Scale Used

Before Rescue	Score	Rank
No Pain	1	1
Some Pain but no need of 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	5	3
Pain same as when rescue was taken	6	3
Pain more severe than when rescue was taken	7	4

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