Comparative Evaluation of Pre-Emptive Analgesic Efficacy of Intramuscular Ketorolac Versus Tramadol Following Third Molar Surgery

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Abstract Pre-emptive analgesia aims at preventing the central nervous system from reaching a hyper-excitabile state known as central sensitization, in which it responds excessively to afferent inputs. The clinical implication would be more effective pain management, thereby reducing post-operative pain and analgesic requirements. This study aimed at investigating the existence of pre-emptive analgesia and to compare the pre-emptive analgesic efficacy of im ketorolac [NSAID] versus tramadol [SYNTHETIC OPIOD] for post-operative pain management following third molar surgery. Fifty patients under the age group of 16–25 years with asymptomatic, symmetrically impacted mandibular third molars were equally divided into 2 groups and underwent third molar surgery under local anesthesia. Ketorolac 30 mg and tramadol 50 mg were used in the study group, while sodium chloride 0.9 % was used in the control group. Study parameters

included pain intensity scores for 12 post-operative hours, time to 1st rescue analgesia, total number of analgesics consumed during the 5 post-operative days and patients' self assessment of efficacy of the surgery with regards to pain. Statistically, the data are presented as the mean values with their standard deviations and a 95 % confidence interval [p is significant, if $p < 0.05$] for the mean are applicable. Incidences of adverse events like pain on injection of the study drug, local reactions, nausea and vomiting were noted. Patients in the study group significantly performed better than the control group in terms of all the parameters; while among the study group, ketorolac fared better than tramadol. All the drug related complications were mild and did not require any intervention. Pre-operative ketorolac or tramadol in comparison to placebo resulted in a significantly better post-operative pain management. However as against tramadol, ketorolac is a better choice as a pre-emptive analgesic agent for the post-operative pain management following third molar surgery.

Keywords Third molar surgery · Ketorolac · Tramadol · Pre-emptive analgesia

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Introduction

Pre-emptive analgesia may be defined as an anti-nociceptive treatment that prevents the establishment of altered central processing of afferent input from the sites of injury. By administering an analgesic before the painful stimulus [referred to as pre-emptive analgesia], the development of pain hypersensitization may be reduced or abolished, thus resulting in less post-stimulus pain.

Ketorolac [a pyrrolo-pyrrolo derivative] when administered intramuscularly is believed to possess an analgesic

efficacy equivalent to pethidine 100 mg and at least as efficacious as morphine [1–3].

Tramadol is a synthetic analogue of codeine and causes activation of both the opioid and non-opioid pain inhibition systems. The effect of non-opioid component of tramadol is mediated through the inhibition of reuptake of serotonin and nor-epinephrine and by displacing the stored serotonin from the nerve endings. Its opioid component has an affinity for μ receptors [4]. Tramadol causes minimal respiratory depression and few gastrointestinal effects and has less potential for opiate like physical dependence or abuse [5, 6].

Surgical removal of third molar teeth is the most common operation in oral surgery and reports indicate that 18–40 % of all extracted third molars are asymptomatic. Impacted asymptomatic third molars are prophylactically removed in order to prevent the anticipated complications like cystic transformations, pericoronitis, periodontal lesions of the distal surfaces and root resorption of second molars [7].

This study aimed at investigating the existence of pre-emptive analgesia and to compare the pre-emptive analgesic efficacy of intramuscular ketorolac versus tramadol following surgical removal of asymptomatic impacted mandibular third molars.

Aims and Objectives

Aims of the Study

- To investigate the efficacy of pre-emptive analgesia by comparing the analgesic efficacy of ketorolac and tramadol versus normal saline.
- To compare the pre-emptive analgesic efficacy of intramuscular ketorolac versus tramadol following third molar surgery.

Objectives of the Study

- To compare the analgesic efficacy of a single dose of pre-operative ketorolac versus tramadol in preventing pain after third molar surgery.
- To investigate the efficacy of pre-emptive analgesia by comparing the analgesic efficacy of ketorolac and tramadol versus normal saline, by comparing the active treatment groups for:
 1. The pain intensity scores.
 2. The time to 1st rescue analgesia.
 3. Total amount of analgesics consumed during 5 post-operative days.
 4. Global assessment by the patients.

Methodology

Source of Data

Patients reporting to the Department of Oral, Maxillofacial & Reconstructive Surgery of Bapuji Dental College & Hospital, Davangere, for the surgical removal of impacted mandibular third molars.

Methods of Data Collection

After the protocol for the study was approved by the ethics committee of local institution, a sequential enrollment of 50 patients reporting from January 2007 to August 2008, for the surgical removal of asymptomatic impacted mandibular third molars was done with an informed/written consent.

Inclusion Criteria

Fifty patients under ASA-1 category in the age group of 16–25 years requiring surgical removal of asymptomatic impacted mandibular third molars in an out patient setting.

Exclusion Criteria

Patients with a history of pain, signs of infection or other related problems in the week before surgery were excluded, as it has been hypothesized that pain existing before the surgery may have already achieved central sensitization, thus making pre-emptive analgesia ineffective.

Sequence of Patient Care

On initial presentation, patients were clinically and radiographically examined to rule out the presence of signs of infection. Pell and Gregory classification was applied and the difficulty of the operative procedure was predicted based upon Pedreson's difficulty index.

Study Design

Selected patients were equally divided into two groups as study group [group 1] and control group [group 2].

Each patient in the study group with bilaterally symmetrical impacted mandibular third molars underwent third molar surgery under local anesthesia [2 % lignocaine with 1:80000 adrenaline] on two separate occasions with a wash out period of minimum of 3 weeks and received ketorolac 30 mg on the 1st occasion and tramadol 50 mg on the 2nd occasion gluteally 20 min before the incision. Sodium chloride 0.9 % was used in the control group. Post-operatively, rescue oral analgesic and antiemetic included Tab

Biozobid plus [diclofenac potassium 50 mg/paracetamol 500 mg/serratiopeptidase 10 mg] and Tab Ondem [ondansetron 4 mg] respectively.

Follow Up Design

Post-operative pain assessment was done on day 1 at hours 1, 3, 5, 8 and 12 using a numerical rating scale with anchor points as 0-no pain to 10-worst pain possible. The numerical rating scale was categorized as [0]-no pain, [1–3]-mild pain, [4–6]-moderate pain and [7–10]-severe pain. Time to 1st rescue analgesia, total number of analgesics consumed during the 5 post-operative days and patients' self assessment of overall evaluation of the efficacy of the surgery with regard to no pain were recorded. Incidences of adverse events like pain on injection of the study drug, local reactions, nausea and vomiting were noted.

Statistical Analysis

Statistically, the data are presented as the mean values with their standard deviations and a 95 % confidence intervals for the mean are applicable. The difference in the pain intensity scores and the total number of analgesics consumed during the 5 post-operative days were analysed using Wilcoxon's signed rank test. The time to 1st rescue analgesia and the duration of surgery are presented with the paired *t* test while the patients' self assessment of overall surgical procedure referred to as the Global assessment was evaluated using the χ^2 test.

Results and Observations

Both the study and control groups were statistically balanced for the demographic variable. The difference of mean age and sex ratios of the patients of all three groups i.e., ketorolac, tramadol and control groups is statistically insignificant (Tables 1, 2). Study parameters included pain intensity scores at hours 1, 3, 5, 8 and 12, time to first rescue analgesia, total number of rescue analgesics consumed during 5 post-operative days and patients' overall self assessment in terms of no pain which is designated as global assessment. During the statistical analysis, *p* values

Table 1 Comparison of mean value of age between study and control groups

Age (Years)	Mean $\pm$ SD	<i>t</i> * value	Significance
Controls	20.8 $\pm$ 1.47	0.28	<i>p</i> > 0.05 Not significant
Study group	20.68 $\pm$ 1.55		

* Unpaired *t* test

Table 2 Comparison of sex ratios of the study and control groups

Sex	Controls	Study group
Male	11 (44)	13 (52)
Female	14 (56)	12 (48)

$\chi^2 = 0.08$ *p* > 0.05 Not significant

of <0.05 or <0.01 were considered as significant, while a *p* value of <0.001 suggested a highly significant value and *p* > 0.05 was considered statistically insignificant.

In this study, patients when treated with ketorolac reported considerable pain relief at hours 1, 3, 5 and 8 with significantly lower pain intensity scores than when treated with tramadol. At hour 12, the difference was not statistically significant [*p* > 0.05] (Table 3) (Wilcoxon's signed rank test). Placebo group was compared with the patients in the study group when treated with ketorolac and with tramadol individually and at hour 1, 3, 5, 8 and 12. Both the study drugs proved better than placebo in terms of pain relief, though at hours 8 and 12 the *p* value was not statistically significant (Table 3) (Wilcoxon's signed rank test/Mann–Whitney *U* test).

When the mean time to first rescue analgesic was assessed, patients in the study group reported a longer pain free interval than the control group with the mean time being 2.42 ± 1.70 , 8.86 ± 0.91 and 7.43 ± 1.15 h for control, ketorolac and tramadol treatments respectively. Comparison among the study group significantly favored ketorolac over tramadol [*p* < 0.001] (Table 4) (Wilcoxon's signed rank test/*t* test).

Patients in the control group consumed maximum number of rescue analgesics during the 5 post-operative days as against the study group, but with an individual comparison, a statistically significant value was noted when control group was compared with ketorolac unlike with tramadol. Ketorolac proved more efficient than tramadol with patients in the former treatment consuming fewer rescue analgesics than when treated with tramadol [*p* < 0.001] (Table 4) (Wilcoxon's signed rank test/*t* test).

Global assessment showed that patients in the study group, on 22 occasions (88 %) of ketorolac treatment and on 5 occasions (20 %) of tramadol treatment rated the overall surgical procedure as good, while 44 % of them did in the control group. One patient when treated with tramadol scored as 3 (very good) while none of them did when ketorolac was administered. Under pre-operative ketorolac occasion, none of the patients considered the procedure as poor as against 1 occasion in tramadol group. Fifty-two percentage patients in the control group, rated the procedure as fair, while in the study group, on 3 occasions (12 %) of ketorolac treatment and 18 occasions (72 %) of tramadol treatment, the rating was fair (Table 5) (χ^2 test).

Table 3 Comparison between study and control groups in terms of pain intensity scores

Pain score	Mean $\pm$ SD			Control–study group		p^* value	
	Controls	Ketorolac	Tramadol	Mean difference (C and K)	Mean difference (C and T)	C and K	C and T
Hour 1	1.8 $\pm$ 1.63	0.32 $\pm$ 0.48	0.72 $\pm$ 0.74	1.48	1.08	$p < 0.001$ HS	$p < 0.01$ S
Hour 3	3.16 $\pm$ 1.28	1.24 $\pm$ 0.52	1.72 $\pm$ 0.98	1.92	1.44	$p < 0.001$ HS	$p < 0.001$ HS
Hour 5	3.36 $\pm$ 1.73	1.44 $\pm$ 0.77	1.8 $\pm$ 0.96	1.92	1.56	$p < 0.001$ HS	$p < 0.001$ HS
Hour 8	3.6 $\pm$ 1.97	3.04 $\pm$ 1.06	3.76 $\pm$ 1.13	0.56	−0.16	$p > 0.05$ NS	$p > 0.05$ NS
Hour 12	2.64 $\pm$ 1.46	2.44 $\pm$ 0.92	2.36 $\pm$ 0.95	0.2	0.28	$p > 0.05$ NS	$p > 0.05$ NS

* Mann–Whitney U test**Table 4** Comparison between study and control groups in terms of time to 1st rescue analgesia, duration of surgery and total number of analgesics consumed during 5 post-operative days

	Mean $\pm$ SD			Control–study group		p^* value	
	Control	Ketorolac	Tramadol	Mean difference (C and K)	Mean difference (C and T)	C and K	C and T
Time to 1st rescue analgesia (hours)	2.42 $\pm$ 1.70	8.86 $\pm$ 0.91	7.43 $\pm$ 1.15	−6.4	−5.01	$p^* < 0.001$ HS	$p^* < 0.001$ HS
Duration of surgery (hours)	0.99 $\pm$ 0.29	0.96 $\pm$ 0.30	1.04 $\pm$ 0.28	0.026	0.045	$p^* > 0.05$ NS	$p^* > 0.05$ NS
Total no. of analgesics consumed during 5 post-operative days	10.76 $\pm$ 3.03	7.36 $\pm$ 1.7	8.92 $\pm$ 1.91	3.4	1.84	$p^\# < 0.001$ HS	$p^* > 0.05$ NS

* Unpaired t test# Mann–Whitney U test**Table 5** Comparison of the global assessments by the patients between study and control groups

Global assessment	Controls	Ketorolac	Tramadol
0	0	0	1 (4)
1	13 (52)	3 (12)	18 (72)
2	11 (44)	22 (88)	5 (20)
3	1 (4)	0	1 (4)
4	0	0	0
Total	25 (100)	25 (100)	25 (100)
X^2 value	–	$X^2 = 36.75$ $p < 0.001$ highly significant	$X^2 = 15.64$ $p = 0.001$ highly significant

The adverse effects like nausea, vomiting, pain and local reactions at the site of injection were documented. One patient in the study group, when treated with ketorolac experienced severe pain at the site of injection and consumed the rescue analgesic for the same while 4 patients after receiving tramadol complained of nausea and demanded the rescue antiemetic. None of the patients had

any local reactions at the site of injection of the study drug and there was no incidence of vomiting reported.

Discussion

Injury to the tissues causes an exaggerated response to noxious stimuli on both a peripheral basis, by reducing the threshold of nociceptive afferent nerve terminals and at a more central level, by increasing the excitability of the second order neurons in the spinal cord. Based on the aforementioned observations, the concept of pre-emptive analgesia has evolved. By administering an analgesic before the painful stimulus, the development of pain hypersensitization may be reduced or abolished, thus resulting in less post-operative pain [8].

It has been postulated that the pain existing before surgery may have already achieved central sensitization, thus making pre-emptive analgesia ineffective [9]. Therefore asymptomatic impacted mandibular third molars were included in the current study. Patients in both the study and control groups did not differ in their demographic characteristics and the surgical factors including the operating

time; both of which can potentially affect the outcome measures. Any significant difference between both the study and the control groups in terms of pain is thus attributable to the drug effect.

The mean time to first rescue analgesia in the study group of 8.86 h with ketorolac treatment, 7.43 h with tramadol treatment and 2.42 h in control group is clinically significant as pain following third molar surgery is usually most severe between 6 and 8 h after the surgery. The lower pain intensity scores in the study group as compared to the control group, at all the assessment intervals, longer duration to first rescue analgesia, lesser amount of post-operative analgesic consumption, are highly suggestive of existence of pre-emptive analgesia. Ong et al. [9] in their study found that pre-operative ketorolac produced post-operative analgesia for 8.9 h which is consistent with our result; while the duration of action of ketorolac when administered post-operatively is 6.9 h. The longer duration to first rescue analgesic may be due to a pre-emptive effect as the study drugs were given before the surgical incision suggestive of a relatively longer post-operative pain free interval without actually increasing the dosage or the dosing frequency of the study drug.

Most common adverse effects of parenteral ketorolac are pain and skin reactions at the site of injection. In our study, only one patient reported severe pain at the site of injection but none of them had local skin reactions.

Due to interference with renal and platelet function [8], ketorolac is preferably used in patients without any risk for the renal dysfunction and in the procedures that involve a minimal amount of blood loss.

Tramadol is a synthetic analogue of codeine that causes minimal respiratory depression and few gastrointestinal disturbances and also has a lesser potential for opiate like dependence than morphine. The definitive role of tramadol as a pre-emptive analgesic was proved by Guillen et al. [10]. The main finding of their trial was that pre-emptive tramadol caused a longer time to rescue medication and lesser total post-operative analgesic consumption, thus suggestive of pre-emptive analgesic effect.

Nausea and vomiting are the major adverse effects of tramadol when used for post-operative analgesia. In our study 4 patients complained of nausea, but none of the patients reported of vomiting. Respiratory depression and sweating are also the known adverse events associated with parenteral tramadol. None of the patients in our clinical trial complained of sweating upon injection of tramadol. Vickers et al. [6] found that there was a rapid drop in the respiratory rate following intravenous administration of tramadol, but it was noted only during the first 5 min post injection while it was sustained in case of morphine administration. They concluded that tramadol has much less effect on the respiratory system, with a higher therapeutic ratio.

We also compared ketorolac with tramadol in terms of analgesic efficacy and ketorolac fared better in terms of pain scores, time to first rescue analgesia, total post-operative analgesic consumption and patients' self assessment in terms of no pain, consistent with the results observed by Ong and Tan [11] who compared the analgesic efficacy of intravenous ketorolac versus tramadol for third molar surgery. In contrast to our results Colletti et al. [12] in their study rated tramadol as a better drug when compared to ketorolac when used for post-operative pain management following nasal surgeries. Putland and McCluskey [13] also observed better post-operative pain relief with tramadol as against to ketorolac following day case laparoscopic sterilization. In our clinical trial ketorolac fared better than tramadol because of the nature of the pain following third molar surgeries. The pathogenesis of dental pain and the general surgical pain are different. Dental pain being largely inflammatory is better managed with NSAID's than with opioids.

In conclusion, the results of our study suggest that pre-operative intramuscular ketorolac and tramadol are better than placebo, thus signifying the possible existence of pre-emptive analgesia and when compared with each other ketorolac is better than tramadol for post-operative pain management following mandibular third molar surgeries.

Summary and Conclusion

Pre-operative treatment with a parenteral NSAID like ketorolac results in a prolonged duration of pain relief post-operatively which is more than the expected duration of the action of the drug signifying the existence and importance of pre-emptive analgesia. Although ketorolac is one of the most commonly used injectable NSAID, it has a variety of significant adverse effects due to the inhibition of COX-1 enzyme that produces the eicosanoids known to be responsible for the physiologic functions namely secretion of mucus for the protection of gastric mucosa, hemostasis and maintenance of renal functions. COX-2 specific inhibitors spare the COX-1 enzyme at therapeutic concentrations and inhibit the inducible COX-2 enzyme. The COX-2 specific inhibitor is probably a better NSAID to be administered for pre-emptive analgesia, as it does not impair the platelet function and has a lower risk of intra-operative and post-operative bleeding problems than the conventional NSAID's like ketorolac [9].

Pre-emptive use of tramadol has also shown acceptably good results compared to placebo; but the increased incidence of adverse effects, like nausea, warrants its extensive use for post-operative pain management.

A larger sample size with various minor surgical procedures need to be studied with a reasonable follow-up

time to evaluate the efficacy of the aforementioned drugs. With a limited number of samples and study, we hereby conclude that pre-emptive intramuscular ketorolac 30 mg and tramadol 50 mg are better than saline, though used as a placebo, for effective post-operative pain management following third molar surgery in carefully selected patients.

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