Original Article

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Pre-emptive analgesia efficacy of piroxicam versus tramadol in oral surgery

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Background: This double-blind randomized controlled trial (RCT) was conducted to evaluate the pre-emptive analgesia and anti-inflammatory efficacy of piroxicam compared with tramadol in patients undergoing oral surgery.
Methods: Seventy-eight patients who required extraction of impacted mandibular third molars were randomized into three treatment groups of 26 patients each: group I received 100 mg of tramadol, group II received 20 mg of piroxicam, and group III received a placebo. Drugs were administered intramuscularly 30 min prior to the extraction procedure.
Results: Pain intensity, time to first analgesic administration, total analgesic consumption, facial edema, and trismus were the outcomes of interest. The group receiving 20 mg of piroxicam showed significantly lower pain intensity, increased time to first analgesic, and reduced edema from preoperative to postoperative day seven than those in the tramadol and placebo groups.
Conclusion: The findings of this study showed that piroxicam had significant pain relief efficacy after third molar surgery compared with that in tramadol.

Keywords: Piroxicam; Preemptive Analgesia; Third Molar; Tooth Extraction; Tramadol.

INTRODUCTION

Pain is a sensory experience and an evolutionary necessity for sensing unpleasant stimuli, soreness, or distress. Pain due to tissue damage and inflammation is classified as nociceptive or pathological [1]. Pain can be clinically described by its 1) intensity- mild, moderate, or severe; 2) quality- sharp, burning, or dull; 3) duration- transient, intermittent, or persistent; and 4) area of distribution- superficial/deep or localized/diffuse [1]. Surgical extraction of mandibular third molars is a common minor dental procedure performed in outpatient settings. Postoperative pain, which can be intense, often follows third molar extractions [2]. Administration of analgesics preoperatively termed “pre-emptive analgesia” is one strategy to reduce postoperative pain [3].

Piroxicam is an oxicam-type NSAID that inhibits prostaglandin-mediated pain and inflammation. Piroxicam is not addictive and it does not cause decreased sensitization of peripheral receptors or cognitive impairment. Its plasma half-life is estimated as approximately 57 h. Piroxicam is used for postoperative pain relief, and its use as a pre-emptive analgesic

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medication has been well documented in the literature [4, 5].

Conversely, tramadol is a centrally acting opioid analgesic and weak agonist that is effective in controlling moderate to severe pain. It modifies the transmission of pain, acts on the opioid receptors, and inhibits the reuptake of serotonin and noradrenaline [6]. Tramadol is extensively used as a premedication because of its therapeutic safety. Furthermore, Tramadol does not cause respiratory depression [2,7–10]. It has low dependence and abuse potential and is effective against acute pain conditions, including postsurgical pain. These properties make tramadol ideal for the management of postoperative pain. It was first synthesized in 1965 and introduced in the US in 1995 as a non-scheduled drug due to its low abuse potential [11,12]. However, tramadol abuse is high in Western Asian and African nations. It is the most commonly abused opioid in these areas. In addition, the misuse, abuse, and addiction of tramadol is increasing globally [13,14].

The purpose of this study was to evaluate the pre-emptive analgesic efficacy of piroxicam, a non-opiod, compared to that in tramadol, an opiod, in decreasing postoperative oral pain. The results of this study may decrease opioid prescriptions to control post-operative pain after dental surgeries and thereby decrease opioid dependence.

METHODS

Seventy-eight patients who required surgical extraction of impacted mandibular third molars in an outpatient setting were enrolled in this double-blind, randomized controlled trial. The priori sample size of 26 in each group was selected based on a fixed-effects ANOVA sample size test with a power of 0.7 and a type 1 error of 5%. The study was conducted in accordance with the ethical principles of the current amended version of the 1975 Declaration of Helsinki (revised 2018) and approved by the Institutional Ethics Committee of SVS University (IRB number: SVSIDS/OSURG/1/2015). Informed consent was obtained from all patients. Demographic data (age, sex) were collected. The inclusion criteria were as follows: men and women aged 18 years and older, those who were free from any systemic conditions, and those who had a clinical and radiographic diagnosis of impacted mandibular third molar (any grade in the Pederson difficulty index). The Pederson difficulty score is the classification of impacted third molars based on their angulation, relation to the ramus, and depth [15]. Exclusion criteria were: 1) hypersensitivity to study medications and 2) subjects classified as other than ASA-1 according to the American Society of Anesthesiologists (ASA) Classification of Physical Status.

Randomization and masking/procedures and medications

Patients were randomly allocated to three groups using Microsoft Excel and the CHOOSE and RANDBETWEEN commands. Only two researchers (TM and RR) had access to the Excel documents and group coding. Preoperative analgesia was disbursed to the oral surgery team by the two researchers in a single-use generic luer-lock syringe. Patients and surgeons involved in the operative procedures and follow-up examinations were blinded to the patient group allocation. Group I patients were administered 100 mg (2 ml) of tramadol, group II received 20 mg (2 ml) of piroxicam, and group III received 2 ml of normal saline. All medications were administered intramuscularly in the deltoid region 30 min prior to surgical extraction of the impacted mandibular third molar. One milliliter of piroxicam was diluted to 2 ml (by TM) using normal saline to ensure double-blinding of the study. Impacted third molars were extracted following the standard soft and hard tissue surgical techniques. Bone troughing and sectioning of the tooth were performed using a slow-speed electric handpiece drill and surgical carbide burs under a continuous external saline spray. The time required for the entire surgical extraction procedure was recorded. All

Table 1. Patient and surgical characteristics among the study groups

Variable	Group I (Tramadol)	Group II (Piroxicam)	Group III (Placebo)
No. of subjects	25	26	26
Gender(M: F)*	12/13	8/18	21/5
Mean age(years)†	28.31 ± 9.12	26.27 ± 7.12	27.18±10.27
Distribution based on the type of impaction‡			
Mesio-angular	12	14	12
Disto-angular	5	4	5
Horizontal	5	4	6
Vertical	3	4	3
Pederson surgical difficulty no of cases (Mild/ Moderate/ Severe)§			
Mild	13	15	8
Moderate	8	10	11
Severe	4	1	7
Time taken in minutes for the surgical procedure			
10 to 20 mins	7	6	8
21 to 40 mins	12	12	9
41 to 60 mins	6	6	9
61 to 90 mins	0	2	0

*Fisher's exact- P-value = 0.009
†Anova- P-value = 0.71
‡Fisher's exact = 0.989
§Fisher's exact- P-value = 0.125

patients received detailed postoperative instructions and pain medication in an unmarked plastic case (aceclofenac-100 mg and paracetamol- 325 mg; Tablet Zerodol-P™ manufactured by IPCA Labs) as rescue medication.

Preoperative maximal interincisal opening and facial measurements were recorded. Patients were subsequently recalled for follow up and assessed on the second and seventh postoperative days for pain intensity using the Visual Analog Scale (VAS), time to first analgesic administration, total analgesic consumption, facial edema, and trismus. The VAS score was recorded by the oral surgeon using a VAS 100 mm laminated color card given to the patient to select current pain levels. The card had a numerical scale and facial expression images on a 100 mm unidirectional scale. The time to the first analgesia and total analgesic medication were recorded by the patient in a personal diary. The patients were asked to record the time when they consumed the analgesic medication and to present the diary to the study team member on the subsequent follow-up visit. The leftover pain medications given to the patients were collected during the second or third week of the follow-up visits. Using the leftover pain medication count assisted in correlating the total analgesic medication consumption recorded in the patient diary. The maximal interincisal opening was measured between the upper and lower central incisors on a metallic scale. Facial edema was measured using standard landmarks with a measuring tape for two variables: 1) tragus and outer corner of the mouth and 2) angle of the mandible and lateral canthus of the eye. This value was recorded. Throughout the study period, an oral surgery resident doctor (RR) monitored the patients and recorded any adverse events (AEs). Intraoperative and postoperative complications were also recorded.

The data were subjected to statistical analysis using SPSS version 23 software. Descriptive statistics, paired t-tests for intragroup comparisons, one-way ANOVA, and Kruskal-Wallis test for intergroup comparisons were applied. A P value of $\leq$ 0.05 was considered as statistically significant.

Table 2. Indicators of analgesic effectiveness

Variable	Group I (Tramadol)	Group II (Piroxicam)	Group III (Placebo)	P value
Time to first analgesic in hours- (mean± standard deviation)	4.84 ± 4.2	10.17 ± 7.12	3.85 ± 2.3	≤0.0001*
Total analgesic consumption (mean± standard deviation)	6.4 ± 2.9	5.5 ± 3.8	6.6 ± 4.3	0.559†
VAS Score for pain intensity‡				
Preoperative	1.8 ± 1.9	1.65 ± 2.0	1.8 ± 1.8	0.852
Postoperative day 2	2.44 ± 1.2	1.62 ± 1.5	2.19 ± 1.7	0.115
Postoperative day 7	0.92 ± 1.0	0.54 ± 1.3	1.08 ± 1.4	0.034‡

*Kruskal-Wallis test was used to test variance between the three groups for the variable "time to first analgesic" as it was not normally distributed. Post Hoc- Group 1 vs 2 and Group 2 vs 3 were significant (P = 0.0008 & P = 0.0001 respectively).
†Anova test- nonsignificant
‡To compare the VAS scores, we used the Kruskal-Wallis test as the data is ordinal. The Post-hoc Dunn's test using a Bonferroni corrected alpha of 0.017 indicated that the mean ranks of the following pairs are significantly different- The piroxicam group vs tramadol group (P-value = 0.016) and Piroxicam group vs the placebo group (P-value = 0.011). Tramadol and placebo group were statistically not different.
VAS, visual analog scale

RESULTS

The patient and surgical characteristics and variables are presented in Table 1. Of the 78 patients enrolled in the study, 42 were male and 36 were female. There was no statistically significant difference in mean age between the groups (P = 0.71). No subject in the piroxicam or placebo groups experienced gastric discomfort or other AEs during the study period. One of the 26 subjects in the tramadol group complained of nausea, and the study trial was aborted for that patient. There was no statistically significant difference in pain medication distribution based on the angulation of the impacted tooth (P = 0.98). The entire surgical extraction time was also recorded; there was no significant difference between the groups in extraction time.

VAS scores for pain intensity were comparatively low in the piroxicam group on the second and seventh postoperative days compared with those in the tramadol and placebo groups. The Kruskal-Wallis test revealed a significant difference in the VAS pain intensity scores between the three groups on the seventh postoperative day. The post hoc Dunn's test revealed a significant difference in the VAS pain intensity scores between the piroxicam and tramadol groups (P = 0.016) and between the piroxicam and placebo groups (P = 0.011).

All patients in the three groups received rescue analgesics except for one patient in the piroxicam group. The time to consumption of the first rescue analgesic medication was significantly longer in the piroxicam group than that in the other groups. The mean time to consumption of the first rescue analgesic medication in the piroxicam and tramadol groups showed a longer pain-free interval than that of the placebo group (mean time 4.8, 10.1, and 3.8 h, respectively). Comparisons among the study groups significantly favored piroxicam over tramadol in terms of time to first rescue analgesic medication (P < 0.001) (Table 2).

Total analgesic consumption differed among the three groups. Patients in the placebo group consumed the most post-operative rescue analgesics of all groups during the seven postoperative days. The piroxicam group consumed fewer rescue analgesics than the tramadol group; however, the difference was not statistically significant (P = 0.559) (Table 2).

Table 3 shows the pre- and postoperative interincisal opening and facial measurements. All groups had an evident increase in facial edema on the second postoperative day and minimal facial edema on the seventh postoperative day. There was no statistically significant difference between the groups. There was a greater decrease in facial edema (change in facial measurement) in the piroxicam group preoperatively to

Table 3. Facial edema and maximum interincisal opening comparison between the groups

Variable	Group I (Tramadol)	Group II (Piroxicam)	Group III (Placebo)	P value
Tragus and outer corner of mouth (in mm)				
Preoperative	101.5 ± 6.6	103.1 ± 8.6	103.9 ± 7.5	0.512
Postoperative day 2	106.2 ± 6.9	107.6 ± 7.0	108.2 ± 9.1	0.837
Postoperative day 7	104.2 ± 7.2	103.5 ± 6.9	104.1 ± 8.3	0.950
Difference of Postoperative day 7 & Preoperative values	2.72 ± 4.22	0.38 ± 4.21	0.15 ± 3.81	0.053
Angle of mandible and lateral canthus of eye (in mm)				
Preoperative	101.3 ± 5.9	100.8 ± 8.2	104.1 ± 8.6	0.262
Postoperative day 2	105.9 ± 6.0	104.7 ± 7.6	107.1 ± 7.5	0.489
Postoperative day 7	102.2 ± 5.9	101.2 ± 7.9	105.3 ± 8.6	0.145
Difference of Postoperative day 7 & Preoperative values	0.92 ± 2.7	0.46 ± 4.2	1.19 ± 2.7	0.729
Maximum inter-incisal opening (in mm) (mean &SD)				
Preoperative	50.6 ± 4.2	51.3 ± 4.9	50.5 ± 5.5	0.848
Postoperative day 2	39.0 ± 9.5	42.0 ± 10.6	40.0 ± 8.2	0.528
Postoperative day 7	46.5 ± 7.6	47.5 ± 7.0	46.0 ± 6.4	0.740
Difference of Pre and 7^{th} day postoperative interincisal openings	-4.12 ± 5.7	-4.58 ± 6.7	-3.81 ± 6.7	0.911

The values are expressed as mean ± standard deviation. Anova tests was used for all the above.

postoperative day seven (0.38 mm; P = 0.053, 0.46 mm; P = 0.72, respectively) compared to that in the tramadol and control groups (2.72 mm, 0.92 mm; 3.15 mm, 1.9 mm, respectively). The second postoperative day maximum interincisal opening was lowest among all three groups compared to that preoperatively. Nevertheless, this difference was not statistically significant (P = 0.528). All patients showed an increase in interincisal mouth opening by the seventh postoperative day (P = 0.740). The difference between the preoperative and seventh postoperative day mouth opening between the groups was not significant (Table 3).

DISCUSSION

The beginning of the 20th century witnessed great advances in pain management, one of which was the introduction of pre-emptive analgesia. Crile first presented the concept of pre-emptive analgesia, which is based on the philosophy of minimizing postoperative morbidity by blocking pain transmission prior to the initial surgical incision [16]. Impacted third molar surgical extraction can induce acute pain of moderate to severe intensity. Thus, this diagnosis and procedure has been studied in many clinical trial models for pain studies [17].

In this study, the efficacy of piroxicam and tramadol for pre-emptive analgesic was compared. Considering their systemic bioavailability, piroxicam and tramadol were administered intramuscularly. Age and surgical factors were similar between the groups; this implies that the significant difference in pain intensity can be attributed to drug use. We measured and recorded pain intensity using the VAS, a commonly used scale for pain assessment [9]. An important observation from our study was that the piroxicam group had lower pain intensity (VAS) than that in the tramadol and placebo groups throughout the evaluation period.

The progression of postoperative pain was higher on the second day and gradually decreased thereafter. As expected, the VAS scores for pain were significantly lowest in the piroxicam group and highest in the placebo group than those in the other two groups. These results imply that piroxicam is more effective in controlling pain. Ong and Tan reported significantly lower pain in a ketorolac (NSAID)-treated group than that in a tramadol group for preemptive analgesia [7].

The edema after surgical extraction was evaluated and compared among and between the three groups in our study [18]. Postoperative edema peaked on the second

postoperative day and then gradually decreased by the seventh day across all groups. Patients in the piroxicam group had less facial edema than that in the other two groups. Postoperative edema was defined and calculated as the difference in facial measurements between the seventh postoperative day and preoperatively. To our knowledge, this has not been performed in previous pre-emptive studies measuring edema. Our results showed that the difference in facial measurements pre and postoperatively was comparatively smaller in the piroxicam group. Patients in the piroxicam group were closer to their baseline facial measurements within 7 days. The differences between postoperative day seven and preoperative facial measurements between groups was not statistically significant; however, the piroxicam group exhibited less edema than that in the other two groups. This can be attributed to the anti-inflammatory role of piroxicam in reducing facial edema throughout the evaluation period. As there were no significant differences in facial edema between the groups in our study, we cannot rule out the possibility that the reduction in edema was simply due to the natural healing processes. A previous study by Isiordia-Espinoza et al. evaluated the effect of meloxicam and tramadol on postoperative edema after third molar surgery and observed no difference in edema even after drug administration [19].

In our study, postoperative trismus was measured as the decrease in maximal interincisal opening after surgical extraction of mandibular third molars. Decreased mouth opening is partly due to associated pain. We found a significant decrease in interincisal opening on the second postoperative day. By the seventh postoperative day, mouth opening returned to almost baseline. These results are consistent with those of previous studies that measured and recorded mouth opening between similar groups [20–23].

The median time to the consumption of the first rescue analgesia was 4.5 h in the piroxicam group, 3.5 h in the tramadol group, and 3 h in the placebo group, a statistically significant difference ($P < 0.0001$). Pain was most severe between 6 and 8 h after surgical extraction [24,25]. Shah et al. found that preoperative tramadol produced postoperative analgesic effect for 7.4 h, which varies from our results [8]. The results of the present study showed that the piroxicam group had a longer period of time prior to the first consumption of analgesic tablets postoperatively than that in the tramadol group. This suggests that preoperative intramuscular piroxicam is more effective than tramadol for reducing pain following third molar surgery. Similar to our study results, Isiordia Espinoza et al. reported that the time to the first analgesic was higher in a meloxicam group than that in a tramadol group after lower third molar extraction [19].

Analgesic consumption is used to assess drug efficacy as patients self-administer rescue analgesic drugs to avoid unpleasant pain sensations. A comparison between the quantities of rescue medication (Zerodol-P^{TM}) consumed among the three groups in our study showed that those patients who received placebo medication consumed more rescue drugs than the other groups during the evaluation period. Between group comparison revealed a lower consumption of analgesia in the piroxicam group. Higher consumption of rescue medication by the placebo group implies higher pain levels experienced in this group. Isiordia-Espinoza et al. found that the total analgesic consumption was higher in a tramadol group than that in a meloxicam group. These results contradict our results when using piroxicam [19].

The superior analgesic properties of piroxicam compared to tramadol can be explained by the inflammatory pathogenesis of dental pain. This type of pain is better managed using NSAID's rather than opioids [8]. Evidence-based medicine has shown that NSAIDs are superior analgesics for the treatment of dental pain [26]. A meta-analysis by Isiordia-Espinoza et al. demonstrated that NSAIDs were superior to tramadol in terms of efficacy and safety profile in oral surgery [27].

Limitations of this study include the statistically adequate but small sample size, which may have contributed to group differences in sex proportions. However, larger randomized studies may not address this concern. Future studies may also benefit from considering

a greater variety of oral surgical procedures in addition to impacted mandibular third molar extraction. The strengths of our study include the novel use of pre-post facial measurements to define edema, the use of validated measurements (VAS) for pain, and double-blinding of participants and surgeons in a randomized controlled experimental design.

In conclusion, to our knowledge, this is the first study comparing piroxicam with an opioid analgesic for pain control following oral surgical procedures. The use of piroxicam resulted in significantly lower pain intensity, increased time to first analgesic, and reduced edema from preoperative to postoperative day seven than those in tramadol and placebo. Our study shows that a single preoperative dose of piroxicam (20 mg IM) can offer the advantages of delayed postoperative pain, increased pain threshold, and decreased edema compared to those in tramadol for patients who undergo surgical procedures. Our study also suggests an adequate safety profile with no adverse reactions with the exception of one nausea event. Pre-emptive analgesic administration of piroxicam should be considered routinely as a rational strategy to reduce pain following oral surgical procedures.

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Ritesh Rajan: Investigation
Viveka V. Reddy: Investigation, Methodology, Project administration, Writing - original draft
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CONFLICTS OF INTEREST:

The authors declare no conflicts of interest.

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