Original Research Article

TITLE

Efficacy of Piroxicam and Tramadol as a Pre-Emptive Analgesic Agent for Mandibular Third Molar Surgery

ABSTRACT

Objectives: The aim of the present clinical trial study is to compare the pre-emptive analgesic effectiveness of 20 mg of piroxicam and 50 mg of tramadol for mandibular third molar surgery.

Methods: This prospective study included 30 patients who had been referred to the Department of Oral and Maxillofacial Surgery, Chennai for surgical removal of impacted mandibular third molars of similar difficulty index under local anesthesia. The patients were randomly assigned to 2 groups: Group A was administered 20 mg of piroxicam intramuscularly (IM) 50 minutes before the surgery and Group B was given 50 mg of tramadol IM 50 minutes before the surgery. The time to analgesic re-medication, Pain intensity (VAS Scores) at 1st, 2nd, 12th, 24th hour, total analgesic consumption was evaluated.

Results: The group receiving 20 mg of piroxicam IM showed differences in pain intensity evaluated by the visual analogue scale and total analgesic consumption [Lesser values] when compared with the group receiving 50 mg of tramadol IM and the results were statistically significant ($p<0.05$). However, the time to first rescue analgesic medication, number of patients requiring the rescue analgesic procedure (10 mg of oral ketorolac), and number of patients without the need for analgesic during the period of evaluation did not show statistically significant differences between the two groups ($P >0 .05$).

Conclusion: Within the limitations of the present study, the patients receiving 20 mg of preoperative piroxicam had less pain intensity and total analgesic consumption than those receiving 50 mg of preoperative tramadol. Therefore, piroxicam given preoperatively showed

superior analgesic properties for intermediate surgical procedures in comparison to pre-emptively administered tramadol.

Keywords: third molar; pre-emptive analgesia; impacted, mandibular molar; postsurgical pain; piroxicam; tramadol

INTRODUCTION

Removal of the impacted third molar teeth is one of the most common oral surgical procedures performed in dentistry and invariably gives rise to a number of postoperative sequelae, among which pain is almost always present [1]. The onset of pain usually begins as the effects of the local anesthetic agent subside. The concept of pre-emptive analgesia involves the administration of an analgesic before a painful stimulus is initiated. It consists of antinociceptive treatment that prevents central neural sensitization which amplifies postoperative pain [2]. Analgesics given before surgical trauma are thought to have a pre-emptive effect; implying that analgesia will start before the surgical stimulus, leading to a reduction of CNS input and, hence, reducing pain [2].

Tramadol is an opioid analgesic clinically effective in treating moderate to moderately severe pain, and it has low addiction potential. In acute therapeutic use, it produces analgesia against multiple pain conditions, including postsurgical pain, obstetric pain, terminal cancer pain, and pain of coronary origin. The analgesic acts at the opioid receptors and appears to modify the transmission of pain impulses by inhibiting monoamine reuptake [3]. Several nonsteroidal anti-inflammatory drugs (NSAIDs) have been used for pain, swelling, and trismus control after mandibular third molar surgery [4]. These medications achieve their therapeutic effect through the inhibition of cyclooxygenase (COX), which determines the inhibition of prostaglandin (PG) production [5].

Piroxicam is an NSAID of the acidic enolic class that preferentially inhibits the inducible Cox-2 enzyme and shows a weaker influence on the constitutive Cox-1 enzyme [6, 7]. Thus, it is largely used for the treatment of acute and chronic pain and inflammatory and degenerative disorders [7]. There also has shown to be an antinociceptive synergism between intraperitoneal piroxicam and morphine [8]. Postoperative analgesia comparable with that of opioids has been demonstrated with the non-steroidal anti-inflammatory drugs (NSAIDS) [9, 10]. An opioid-sparing effect has also been observed with NSAIDs, as well as a reduction in opioid-induced nausea, vomiting, and respiratory depression. This reduction in opioid requirement and side effects may benefit the patient by producing increased postoperative analgesia and, even, reducing hospital stay [11].

Previously our team has rich experience in working on various research projects across multiple disciplines [12–26]. Now the growing trend in this area motivated us to pursue this project. Based on this inspiration, we aim to compare the pre-emptive analgesic effectiveness of 20 mg of piroxicam and 50 mg of tramadol for mandibular third molar surgery.

MATERIALS AND METHODS

Study Setup:

This randomized prospective controlled clinical study was conducted among patients reporting to the outpatient dental department of the oral surgery clinic during the period between June 2020- March 2021. The study population included 30 adult patients who were randomly selected and allocated by simple lottery method and had been referred to the department of oral and maxillofacial surgery for surgical removal of impacted mandibular molar. The sample size was divided mainly into two groups, each with 15 patients, namely: Group A was administered 20 mg of piroxicam intramuscularly 50 minutes before the surgery, and Group B was administered 50 mg of tramadol intramuscularly 50 minutes before the surgery.

Inclusion Criteria:

- Patients between 18 years-50 years of age
- Both genders
- Clinical and radiographic diagnosis of a partially bony impacted mandibular third molar
- No pain associated with the subject third molar up to the day of surgery

Exclusion Criteria:

- Patients with incomplete clinical and radiological records.
- Patients with severe systemic conditions like diabetes and hypertension.
- Use of analgesics 3 days before the procedure, history of seizure disorder, pregnancy or lactation, oral contraceptive use, and known hypersensitivity to the study medications.

Procedure:

All the surgical procedures were carried out at the Department of Oral and Maxillofacial Surgery by the same surgeon, and evaluations were made by a single independent investigator. Anesthesia was achieved through a block of the lingual, buccal, and inferior alveolar nerves by use of two 1.8-mL capsules of 2% lidocaine–containing 1:100,000 epinephrine. Once anesthesia was given, surgery was started. A mucoperiosteal flap was prepared by making an incision distal to the mandibular second molar along the anterior edge of the ascending ramus of the mandible. This flap was used to close the surgical wound. Suturing was done with No. 4-0 silk. In each patient, a partial bony impacted mandibular third molar was extracted. The time to analgesic re-medication was registered. The patients were given four 10-mg oral ketorolac pills and were instructed to take 1 pill as rescue medication at least 6 hours apart, according to their requirements. At the end of the evaluation period (24 hours), the patients returned the unused ketorolac. The pills were counted to determine the number of consumed pills, as well as the number of patients in each group who did not need any pills. The total analgesic consumption was also evaluated.

Diagnostic Criteria

Post Operative Pain Evaluation by Visual Analogue Scale:

A 100-mm visual analog scale (VAS) was used to assess the pain. The VAS consisted of an interval scale ranging from 0, representing no pain or discomfort, to 100, representing maximum pain or discomfort. The VAS report was recorded each at 1st, 2nd, 12 hours after completion of the surgery, and the last evaluation was done at 24 hours.

Study Parameters:

The following data were extracted for the purpose of the study:

- Age of the patient
- Gender of the patient
- Postoperative VAS pain Scores
- Time to analgesic re-medication (ie, the time from the end of the surgery until the intake of the first rescue analgesic medication became necessary for the patient)
- Number of patients in each group who did not need any pill
- Number of patients requiring the rescue analgesic procedure (10 mg of oral ketorolac)
- Total analgesic consumption

The subjects were divided into four age groups- Group 1: 11-20 years, Group 2: 21-30 years, Group 3: 31-40 years, Group 4: 41-50 years.

Data Collection:

The data relating to the study parameters were obtained from among patients who reported to the Outpatient Department from June 2020- to March 2021. Approval for the study was obtained from the Institutional Ethical Committee. Institutional Ethical Committee(SDC/SIHEC/2020/DIASDATA/0619-0320) All assessments were done by a single examiner and the findings were reviewed and recorded by two investigators. All the subjects were informed of the possible risks of oral surgery and experimental treatments, and they signed an institutionally approved written consent form.

Statistical Analysis:

The data were tabulated and analyzed using IBM SPSS version 23.0 software. Descriptive statistics were expressed by frequency and percentage. Student's t-test was used to compare variables (Time to analgesic re-medication, number of patients in each group who did not need any pill, number of patients requiring the rescue analgesic procedure, total analgesic consumption) between Piroxicam and Tramadol Groups. The effects over time of the pre-emptive analgesics on pain intensity were evaluated by Mann-Whitney U-Test. The significance level was set at $P<0.05$ with a confidence interval of 95%.

RESULTS

A total of 30 patients participated in this study, with an overall 100% participation.

Age Distribution:

The youngest and oldest patients were aged 18 and 50 years, respectively. The distribution of study subjects based on age revealed that most patients belonged to 31-40 years of age group (67.50%).

Gender Distribution:

The distribution of study subjects based on gender, over a ten-month period, revealed that 20 patients (75%) women and 10 patients (25%) men participated in this study.

Post Operative Pain Evaluation by Visual Analogue Scale:

Pain score at 1st and 2nd hours after surgery were different between the two analgesic groups; the mean VAS scores recorded after injection of piroxicam at 1 and 2 hours respectively were significantly lower than after tramadol at 1st and 2 hours, respectively. The

pain intensity was also highest at the end of 2nd hour for the tramadol group (Figure 1). No significant differences in pain scores were observed between the two analgesics at 12 and 24 hours post-surgery (P>0.05) [Mann-Whitney U test].

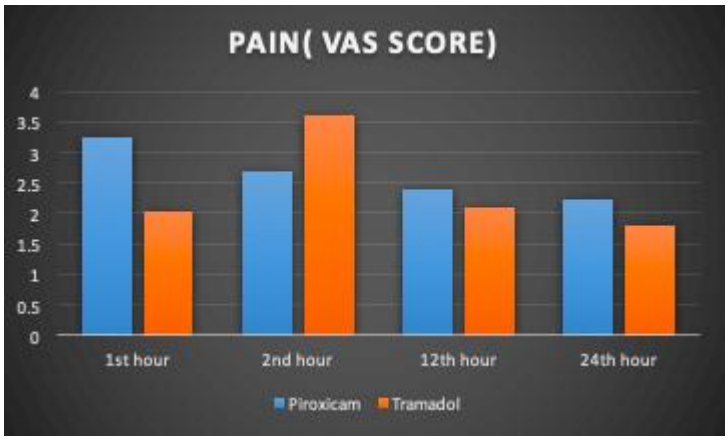

Figure 1: Bar diagram depicting VAS scores of the piroxicam group (blue) and the tramadol group (orange) at the 1st, 2nd, 12th, and 24th-hour post-surgery. The X-Axis depicts the Post extraction hour and Y-Axis represents the VAS Scores. The VAS scores of the tramadol group were higher than the piroxicam group at the 2nd-hour post-surgery.

Time to first rescue analgesic medication, number of patients requiring rescue analgesia, number of patients without the need of analgesia, total analgesic consumption:

The parameters: Time to first rescue analgesic medication, number of patients requiring the rescue analgesic procedure (10 mg of oral ketorolac), number of patients without the need for analgesic during the period of evaluation did not show significant statistical differences (P >.05). However, the difference between total analgesic consumption between the 2 groups was statistically significant (p=0.019) [Table 1].

Table 1 depicts the distribution of variables (time to first rescue analgesic medication, number of patients requiring the rescue analgesic procedure (10 mg of oral ketorolac), number of patients without the need for analgesic during the period of evaluation, and total analgesic consumption) between Piroxicam Group and Tramadol Group.

Parameters	Piroxicam Group (Mean)	Tramadol Group (Mean)	Test Value	P-Value
Time to first rescue analgesic (hr)	1.05	0.95	1.23	0.42
No. of patients (%) requiring rescue analgesic during the period of evaluation (24hr)	6	3	5	0.12
No. of patients (%) not requiring analgesic during the period of evaluation (24 hr)	1	6	-4	0.15
Total analgesic consumption (mg)	12.6	24.2	-34.3	0.019*

***Statistically significant; Independent sample t-test**

On comparison of the parameters between the two groups, there was no statistically significant difference in time to first rescue analgesic medication (p=0.42), number of patients requiring the rescue analgesic procedure (10 mg of oral ketorolac) (p=0.12), number of patients without the need for analgesic during the period of evaluation (0.15). However, the difference between total analgesic consumption between the 2 groups was statistically significant (p=0.019).

DISCUSSION

Analgesia is given immediately before surgical stimulus has been described as "pre-emptive analgesia". It prevents or reduces central hyperexcitability, leading to improved postoperative analgesia and reduced postoperative analgesic requirement [27]. Pre-emptive analgesia usage is controversial in oral surgery, with reports in favor of it as well as against it [28]. Therefore, some guidelines and protocols have been developed to assess the quality of reports of randomized clinical trials in pain research. It has been reported that blind assessments produce significantly lower and more consistent scores than open assessments [29].

A meta-analysis by Ong et al [30] assessing the ability of pre-emptive analgesia interventions to attenuate and alleviate postoperative pain scores, decrease postoperative analgesic requirements, and prolong the time to first rescue analgesia showed an overall beneficial effect in selected analgesic regimens that were most pronounced after epidural analgesia, local wound infiltrations, and systemic NSAID administration. Recent studies by Richmond et al [31] using opioids have shown that preoperative morphine reduced pain scores and postoperative analgesic requirements in patients undergoing abdominal hysterectomy. Another study showed that administration of 30 mg of ketorolac IV produces better pre-emptive analgesic efficacy in comparison to 50 mg of tramadol IV preoperatively in third molar surgery [32].

A study by Isiordia et al [28] showed that patients receiving 15 mg of preoperative meloxicam had less pain intensity and total analgesic consumption than those receiving 50 mg of preoperative tramadol. All of these results were in accordance with the results of our study. However, a study performed by Nekoofar et al [7] showed no significant differences in the analgesic efficacy of meloxicam, piroxicam, and placebo but showed a significant effect of the time factor on reducing postoperative pain after endodontic treatment.
In this study, 50 mg of tramadol was administered because this dose has been used widely in the treatment of postoperative pain after third molar surgery and has been shown to be effective and safe [32–34]. Tramadol is an effective postoperative analgesic and can be used for a much longer time than morphine. Unfortunately, the widespread use of tramadol is hindered by its major adverse effects of nausea and vomiting [35]. In this study, the major side effects were not evident because it was a single-dose study.

The main action mechanism of piroxicam is the inhibition of COX, which determines the inhibition of PG. The PGs are released from the damaged tissues and directly sensitize the peripheral nociceptors, and they also play a role in primary and secondary hyperalgesia and these are important in the modulation of pain [36]. The inhibition of the peroxidase enzyme by piroxicam provides the advantage of a better gastrointestinal tolerance in comparison to other NSAIDs. Moreover, piroxicam with its long half-life and when given preoperatively may provide a longer effect that is clinically relevant [37].

This is the first study comparing piroxicam with an opioid analgesic both as pre-emptive analgesics for pain control after third molar surgery, and few studies have reported on its analgesic efficacy in this acute pain clinical model in comparison to other NSAIDs [38–40]. These studies have shown that piroxicam can be a good alternative in pain treatment after the extraction of a mandibular third molar. It is possible that higher doses of tramadol (100 or 200 mg) may have a better analgesic effect in comparison to meloxicam. However, the incidence of side effects, particularly nausea and vomiting, may be high. Dental pain is largely inflammatory, and evidence-based medicine has shown that NSAIDs are the best analgesic for dental pain [41, 42]. Our institution is passionate about high-quality evidence based-research and has excelled in various fields [16, 43–62].

Limitations

As the VAS Scores were based on patients' perception, a subjective opinion regarding the results was obtained, hence it would be a limitation of our study. Also, the pain threshold for different patients would not be similar.

Future Scope

Although the literature provides a number of studies on the pre-emptive analgesic efficacy of piroxicam and tramadol, there are limited studies related to comparing piroxicam with an opioid analgesic both as pre-emptive analgesics for pain control after third molar surgery.

CONCLUSION

Within the limits of this study, it can be concluded that the patients receiving 20 mg of preoperative piroxicam had less pain intensity and total analgesic consumption than those receiving 50 mg of preoperative tramadol. Therefore, piroxicam given preoperatively showed

superior analgesic properties for intermediate surgical procedures in comparison to pre-emptively administered tramadol.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly used products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by the personal efforts of the authors.

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