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ORIGINAL ARTICLE

A Comparative Study Of Oral Analgesics: Etoricoxib With Tramadol In Acute Postoperative Pain: A Randomised Double Blind Study

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ABSTRACT

Background: Etoricoxib is known to be a selective inhibitor of the cox-2 enzyme. It is an effective analgesic, associated with a reduced risk of bleeding due to platelet dysfunction, gastrointestinal bleeds and ulcers. Studies on etoricoxib in the dental extraction pain model have proved the superior efficacy of etoricoxib with fewer adverse effects as compared to oxycodone/acetaminophen.

Aims: The aim of this study was to compare the efficacy and tolerability of oral etoricoxib 120mg with oral tramadol 100 mg in postoperative pain. This comparison will help to determine the rapidity and sustained efficacy of these agents in pain relief and the possible side effects attributable to the medications.

Settings and Design: The study was conducted among 60 patients with one or more impacted third molar teeth, posted for extraction at the oral surgery department of the Vinayaka Missions Kirupananda Variyar Medical College and Hospitals, Salem, Tamil Nadu. Patients selected for the study were randomized by a computer generated list using random allocation software and were given a sequentially-numbered sealed opaque envelope containing the study drugs by the blinded investigator.

Methods and Material: Pain assessment was done by assessing the following: mean pain scores using a 10 point VAS scale, investigator assessment of ancillary clinical outcomes, inflammation, opening of the mouth, global assessment of study medications and the incidence of adverse effects.

Statistical Analysis used: The statistical analysis was done by using the paired preference test. Unpaired t test was used to compare the mean VAS score values from day 0 to day 5.

Results and Conclusions: The frequency of the inflamed condition at day 0 to the uninflammed condition at day 5 was 86.67% and 70% respectively for etoricoxib and tramadol. Statistically, etoricoxib was preferred to tramadol by a T score of 0.667 (50% confidence). The frequency of lack of pain was found to be predominant in etoricoxib as compared to tramadol (93.34% versus 60%). Preferential analysis showed a clear preference for etoricoxib, with a T score of 1.219, significant at a 77% confidence level. Etoricoxib had a superior effect over tramadol in terms of anti-inflammatory and analgesic properties. Patients receiving cox-2 inhibitors had a lower incidence of gastritis and drowsiness as compared to patients receiving tramadol.

Key Words: etoricoxib, anti-inflammatory and analgesic, dental pain, tramadol, etoricoxib efficacy

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Key Messages

- Etoricoxib had a superior effect over tramadol in terms of anti-inflammatory and analgesic properties.
- The efficacy and tolerance of etoricoxib 120mg OD was almost equivalent to that of tramadol 100mg OD.
- Subjects in the study preferred etoricoxib to a greater extent than tramadol.
- Cox-2 inhibitors have a lower incidence of gastritis and drowsiness as compared to tramadol.
- Newer Cox- inhibitors like etoricoxib might prove to be superior analgesics than other drugs in the market.

Introduction

Acute pain serves as an important biological function as it warns about the extent of injury or its potential for worsening. It is a rapid response to a noxious stimulus that does not produce long term sequela [1]. On the other hand, it can have adverse psychological and emotional effects. Therefore, attention is being focused on the aggressive prevention and treatment of acute pain to reduce complications and progression to chronic pain states.

Dental pain is a painful sensation which can be evoked by a specific dental treatment. Removal of the third molar teeth is widely used as an experimental pain model in pharmacological studies on the effect of analgesic drugs [2].

The post operative period is characterised by pain, trismus and inflammation frequently [3] [3] It can cause significant suffering, anxiety, fear, anger and depression. An ideal drug administered after the surgical removal of impacted third molar should alleviate pain and associated symptoms, facilitate healing and cause no undesirable side effects [4].

Pain is assessed using the Visual Analog Scale (VAS) and four and five point categorical scales to assess the efficacy variables [5],[6]. The Visual Analog Scale is an easy method that is simple to understand and interpret by the population that is under study. It is a ten point scale with increasing severity. Pain parameters are graded numerically and pictorially. They are easy, inexpensive and are frequently used.

The selection of analgesics is based on previous studies on safety and tolerability. Cox-2 NSAIDs which selectively inhibit the cox-2 isoenzyme were developed to limit the NSAID adverse effects. Etoricoxib is known to be a selective inhibitor of the cox-2 enzyme. It is an effective analgesic which is associated with a reduced risk of bleeding due to platelet dysfunction, gastrointestinal bleeds and ulcers [7], [8].

Etoricoxib has been tried in the management of several conditions including pain, osteoarthritis, and rheumatoid arthritis. It was noted that Etoricoxib had a similar efficacy when compared with the traditional NSAIDs (including naproxen, diclofenac and ibuprofen) in these conditions. Etoricoxib was chosen since it was found to have equipotent efficacy to the traditional NSAIDs and opioids and shows a prolonged action with lesser adverse effects like gastric irritation [9]. [10].

Reviews of published studies have noted that at least 50% pain relief was reported by 64% users of etoricoxib 120 mg. Also, significantly fewer participants opted for rescue medication when on etoricoxib 120 mg than those taking placebo. The 120 mg dose of etoricoxib was reported to be as effective as, or better than other commonly used analgesics [11].

Studies on etoricoxib in the dental extraction pain model have proved the superior efficacy of etoricoxib with fewer adverse effects as compared to oxycodone/acetaminophen [12].

Tramadol hydrochloride is an oral narcotic analgesic whose effects are brought about through its influence on the central nervous system. It relieves moderate to severe pain by combining synergistically weak opioid and monoaminogerically mediated anti-nociceptive mechanisms [13].

Tramadol, a nonscheduled drug is marketed as an effective and safe analgesic for moderate to moderately severe pain. McQuay and Moor reviewed 18 studies which demonstrated that all doses of tramadol were superior to placebo in relieving postsurgical and dental pain and showed a dose-response effect [14]. Studies have claimed that it has a low potential for abuse and psychological dependence and also as an effective analgesic that is well tolerated by both the adult and the paediatric patient population [15],[16].

Adverse effects such as nausea, vomiting and dizziness may occur with the use of tramadol. It should be used with caution in patients with a history of seizure disorder. Tramadol is contraindicated in patients with a tendency of opioid abuse or dependence [17].

Comparison of the analgesic efficacy of etoricoxib with tramadol is not studied until now. The aim of this study was to compare the efficacy and tolerability of oral etoricoxib 120mg with oral tramadol 100 mg in postoperative pain. The comparison of the analgesic drugs in this study aimed to determine the rapidity and sustained efficacy of these agents in pain relief and the possible side effects attributable to the medications; the efficacy variables considered were pain intensity and the physician assessment of pain and inflammation [18].

Materials And Methods

This was a randomized, double blind parallel group comparator – controlled trial, conducted at the oral surgery department of Vinayaka Missions Kirupananda Variyar Medical College and Hospitals, Salem, Tamil Nadu, between August 2006 and June 2007.

Patients posted for the surgical extraction of one or more impacted third molar tooth, partially or fully impacted or in the germinal phase, were included in the study. The study population included men and women with ages ranging from 18 – 60 years, who were eligible for standard intervention and specifically anterior discharge cutting, followed by suture of the cut. It was also made sure that the subjects included had no acute ongoing inflammation of the oral cavity at the time of surgery. Further, good general health and patient self-assessment, with particular emphasis on the reports of past or current gastric or duodenal ulcers and anaemia were also considered in the inclusion criteria.

Patients above 60 years, children below 18 years and women who were pregnant or lactating, were not included in the study. Patients with a history of conditions such as: infective caries, peptic ulcer, bronchospasm, angio-oedema, urticaria, renal and hepatic disease, seizures, recent angina, hypertension, myocardial infarction, fluid retention and oedema were excluded from the study. Further, smokers/alcoholics and those on steroids or other analgesics were also excluded.

The study was conducted among 60 patients with one or more impacted third molar teeth, posted for extraction at the oral surgery department of the study centre.

The Institutional Ethics Committee approved the study protocol and the informed consent form. All the eligible patients were informed about the purpose and requirements of the study, details of the drugs, efficacy and safety points. Patients were informed about their freedom to withdraw from the study without giving any reason at any given time and they were informed that while doing so, they would not be denied the option of continuing quality medical care in the same institute. Written informed consent was obtained in the local language – Tamil from each patient. Case record forms were prepared for each of the patients and were kept with the investigator. Drugs were given free of cost to the patients. Patients were advised to take the medication as prescribed and to come for a follow up. They

were advised to report any adverse event to the investigator immediately over phone.

Details of the patient's demographical profiles, medical history, dental and allergic history, concomitant medication, physical examination and dental examination and the type of extraction procedure were recorded. Patients who were selected for the study were randomized by a computer generated list using random allocation software and were given a sequentially-numbered sealed opaque envelope containing the study drugs by the blinded investigator.

Local anaesthesia was administered during all interventions; intravenous sedation was not used on the patients in the study. After the extractions were completed, the patients were supplied with a neatly packaged course of their study analgesics. Patients were allowed to use rescue medication if the study drug was not effective in controlling the pain.

The study drugs used were T.Etoricoxib 120mg OD and T.Tramadol 100mg OD. All the drugs were prescribed for a period of five days and the first dose was given one hour after completion of the surgery and was continued until suture removal on day 5. All patients received postoperative prophylactic antibiotics Cap.Amoxicillin (1g every 12h for 5 days) and T. Metronidazole 400mg TID.

Pain scores using Visual Analog Scales were evaluated at 1 hour after surgery and after 8 hrs at the time of discharge by a blinded observer. All patients were provided VAS sheets in which they were instructed to record pain intensity over 5 consecutive days, starting with the day of surgery. These VAS scales were collected on the 5^{th} day after surgery, when the sutures were removed. The investigator evaluated the outcome of surgery in each patient by using a proforma data collection form that included questions about the appearance of the tissues and ease / pain associated with the opening of the mouth.

All data thus accrued were incorporated into a database and were used by a statistician for analysis.

Pain assessment was done by:

i) Mean pain scores using a 10 point VAS scale. (0-indicates no pain, 1-mild pain, 2- discomforting pain, 3- distressing pain, 4-intense pain, 5-excruciating pain)

ii) Investigator assessment of ancillary clinical outcomes:
   a. Inflammation (A – No inflammation, B- Mild inflammation, C- Severe inflammation) and
   b. Opening of the mouth (A – Restriction with pain, B – Not restricted with pain, C- Not restricted without pain)

iii) Global assessment of study medications: (1-Poor, 2-Fair, 3-Good, 4-Excellent)

iv) Incidence of adverse effects

Statistical Analysis

The statistical analysis was done by using the paired preference test. A paired preference test determines whether there is a statistically significant preference between two products for a given population of respondents. Paired preference testing can address the overall preference or preference for a specified sensory attribute. Unpaired t test was used to compare the mean VAS score values from day 0 to day 5. P values less than 0.05 were considered to be significant.

Results

A total of 100 eligible patients were screened and gave their informed consent for participation in this trial. However, 15 of these patients did not meet the inclusion criteria. Therefore, 85 patients were eventually included. Among these 85 patients, 40 were randomized to the Tramadol group and 45 patients were assigned to the Etoricoxib group.

8 patients did not turn up for the follow-up. 5 patients did not return the case report form and 2 patients violated the study protocol by taking the rescue drug less than 2 hours after study drug intake in all the treatment groups. These patients

were excluded from the treatment effect analysis. Finally, 30 patients in each group completed the study successfully on day 5.

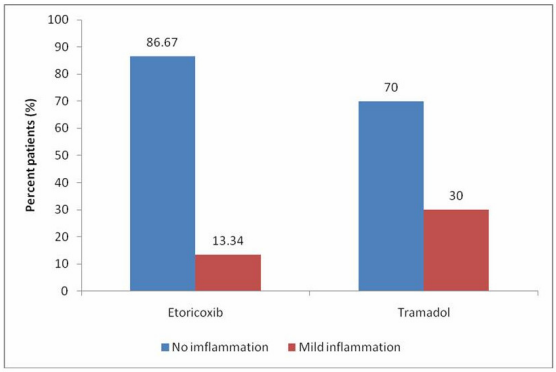
(Table/Fig 1) shows the demographic profiles and clinical features of these 60 patients. All 60 patients underwent upper and lower impacted molar tooth extraction by our technique. The baseline characteristics among the treatment groups were statistically similar with respect to age and sex and baseline pain intensity.

(Table/Fig 1) Baseline demographic profiles and clinical features

	TRAMADOL N=30	ETORICOXIB N=30
WOMEN	15	13
MEN	15	17
MEAN AGE	28.6	29.6
RANGE	20-48	18-47
WEIGHT(KG)	63±8	62±11
LENGTH OF SURGERY (MIN)	27±11	31±13
LOCAL ANESTHETIC (ML)	4±1	4±1

Physicians' Assessment

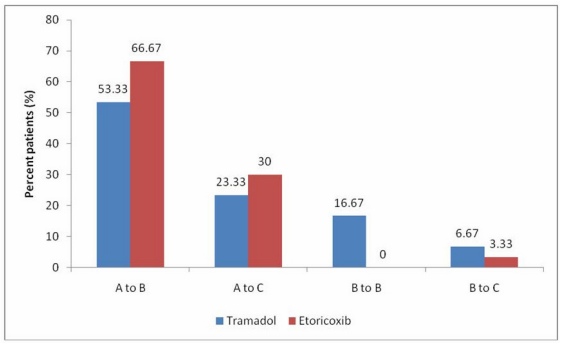
The reduction of inflammation caused by etoricoxib and tramadol were compared in this study. The frequency of the inflamed condition at day 0 to the uninflammed condition at day 5 was 86.67% and 70% respectively for etoricoxib and tramadol. The statistical analysis showed a preference for etoricoxib, with a T-score of 0.667, significant at a 50% confidence level. The complete comparison is given in (Table/Fig 2).



(Table/Fig 2) Comparison of the anti-inflammatory effects of Etoricoxib and Tramadol at day 5

Pain On Opening Mouth

Four sets of observations were seen in the patients studied. However, only three types of observations were seen in the etoricoxib group. No restriction and no pain from a restricted opening was a predominant frequency in both the groups, implying good analgesic effects by the drugs (66.67% *versus* 53.33% respectively for etoricoxib and tramadol). Therefore, this effect was used as a parameter for the comparison in the preference test. Statistically, etoricoxib was preferred to tramadol by a T score of 0.667, which was significant at a 50% confidence level. The complete analysis of the study is depicted in [Table/Fig 3].



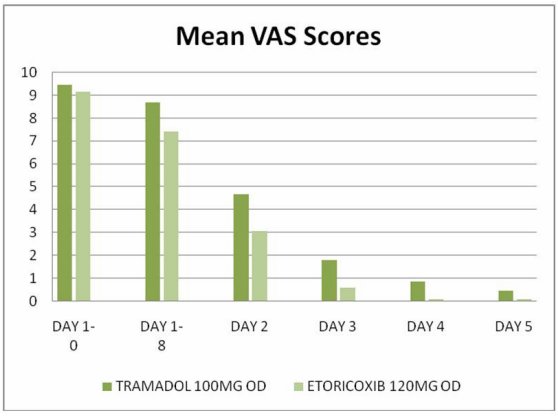
(Table/Fig 3) Effects of Etoricoxib and Tramadol at various stages of mouth opening with pain or no pain

Patient's Assessment

Diminished/reduced pain was assessed by patients themselves on day 0 and day 5. The frequency of lack of pain was found to be

predominant in the etoricoxib group as compared to the tramadol group (93.34% versus 60%). Etoricoxib was statistically preferred over tramadol due to the comparative analysis of the T score of 1.475, which was significant at an 85% confidence level.

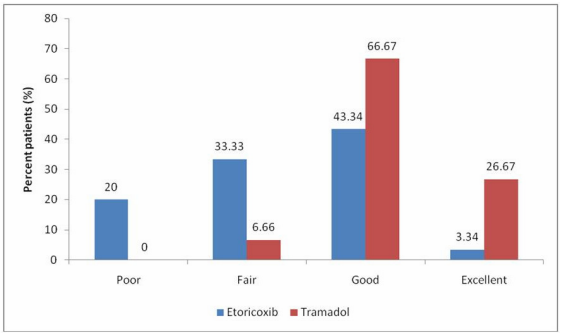
The unpaired t test demonstrated clear significance rates with the use of etoricoxib. The mean VAS scores were almost equal at 0 hours while significant differences were noted in the subsequent recordings [Table/Fig 4]. A significant difference was noted at 8 hours (p=0.0423), while the difference was extremely significant on days 2 and 4 (p <0.0001). Further, the difference was also highly significant on days 3 and 5 (p=0.0423 and 0.0043 respectively).



(Table/Fig 4) Mean VAS scores at different intervals.

Global Assessment

Global assessments were carried out to categorize the treatments as poor, fair, good, and excellent. The Etoricoxib treatment showed no patients with poor clinical outcome, while six patients in the tramadol group were categorized as poor. Etoricoxib was assessed as excellent in 26.67% patients. Both treatments had high frequency of 'good' as categorization (66.67 versus 43.33 for etoricoxib and tramadol respectively). Preferential analysis of this data showed a clear preference for etoricoxib, with a T score of 1.219, significant at a 77% confidence level. The complete global analysis of the treatments is given in (Table/Fig 5).



(Table/Fig 5) Global assessment of Etoricoxib and Tramadol treatments

Side Effects

The total number of side effects reported were 33, among which 27 were reported in the tramadol group. The incidence of the side effects such as dizziness or sedation was reported in a considerably higher number of people (19 vs 2) who took tramadol. Nausea and vomiting were comparatively higher with tramadol treatment than with the treatment with etoricoxib in appropriate doses. No serious adverse events occurred [Table/Fig 6].

ADVERSE EVENTS	TRAMADOL N=30	ETORICOXIB N=30	TOTAL N=60
HEADACHE	1	0	1
NAUSEA	3	1	4
VOMITING	3	0	3
DIZZINESS/SEDATION	19	2	21
EPIGASTRIC PAIN	0	0	0
HYPERSENSITIVITY REACTIONS	0	3	3
SWEATING	1	0	1
	27	6	33

(Table/Fig 6) Safety assessment

Discussion

Mean pain scores following surgical extraction of impacted third molars are comparable to the maximum pain scores from a number of painful conditions like back pain and cancer. Thus, the present study has the power to predict the analgesic efficacy of orally administered Etoricoxib and Tramadol in pain states of

moderate to severe intensity, as in more extensive surgical procedures.

This study reconfirms the analgesic efficacy of the two drugs used in this study, with significant reduction in the pain intensity during the postoperative period following extraction of the impacted third molars.

Ancillary clinical endpoints such as inflammation, swelling and jaw movement improved satisfactorily among the two drugs. T.Etoricoxib had significant anti-inflammatory efficacy and beneficial effect on local postoperative trauma than tramadol. The reduction of inflammation caused by etoricoxib and tramadol on day 5 was considerably higher (86.67% and 70% respectively). The presence of mild inflammation even on day 5 on the other hand, was reported by only about 13% of the subjects treated with etoricoxib, while 30% of those treated with tramadol showed the presence of mild inflammation on day 5.

A higher percentage of subjects who took etoricoxib (30%) reported both reduction in pain and unrestricted mouth opening as compared to those who took tramadol (23%). The results of the unpaired t test revealed the difference in effects of etoricoxib over tramadol. The difference was extremely significant on days 2 and 4, while a significant difference existed on all other days.

A prolonged analgesic effect was observed with the treatment of etoricoxib. The patient assessment scores denoted statistically significant difference in pain reduction with respect to etoricoxib (93.34% reported lack of pain) versus tramadol (60% had no pain) at the end of 5 days.

Preferential analysis of the global assessment data denoted a clear preference for etoricoxib (T score of 1.219 significant at 77% confidence level) over tramadol.

Safety assessment showed that the two drugs used in the study were generally well tolerated. Gastrointestinal side effects like vomiting and nausea were greater in the Tramadol group as compared to the cox-2 inhibitor, Etoricoxib.

Pharmacodynamically, the selective cox-2 inhibitors are as effective as the older generation of non selective NSAIDs like Ibuprofen and diclofenac sodium. Cox-2 inhibitors have a longer duration of action and a rapid onset of action as compared to the various 1st generation NSAIDs [19]. Etoricoxib has been authorized in all European Union member states and 60 other countries around the world for a number of years and its benefits have outweighed the risks for the treatment of conditions like Rheumatoid arthritis and Ankylosing spondylitis [20].

However, the long term use of cox-2 inhibitors has been found to increase the cardiovascular and cerebrovascular adverse effects. The adverse events were attributed to the action of these drugs which affect the balance between the prothrombotic and antithrombotic processes. Cox-2 inhibitors decrease PGI_2 production which has antithrombotic properties; so these agents are found to increase the likelihood of thrombotic events and hypertension. In addition, Cox-2 inhibitors have antiatherogenic effects, as they inhibit inflammation. They do not have any significant effect on platelet function as cox-1 inhibitors [21].

Tramadol being a centrally acting narcotic with a significant analgesic effect as compared to the NSAIDs can be preferred in cases of hypersensitive reactions to NSAIDs. It is also preferable in patients with severe anxiety associated with surgery, since it produces significant sedation. Further studies are needed to find out the analgesic efficacy and tolerability of Tramadol in doses above 100mg in postoperative pain and to study the combined effect of tramadol with newer cox- inhibitors like Etoricoxib in pain. Etoricoxib might prove to be a superior analgesic than other drugs in the market.

Conclusion

In this clinical study, the drugs under evaluation, Tramadol 100mg OD and Etoricoxib 120mg OD were almost equivalent in efficacy and tolerance. Etoricoxib however, had a superior effect over

tramadol in terms of anti-inflammatory and analgesic properties. The patients preferred etoricoxib to a greater extent than tramadol. Patients receiving cox-2 inhibitors had lower incidence of gastritis and drowsiness as compared to patients receiving tramadol.

Declarations

No funding for the paper
No conflicts of interest

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