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Comparative Evaluation of Two Doses of Etoricoxib (90 mg and 120 mg) as Pre-Emptive Analgesic for Post-Operative Pain Relief in Mandibular Fracture Surgery Under General Anaesthesia: A Prospective, Randomised, Double-Blinded, Placebo-Controlled Trial

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Abstract

Objective: This trial investigated the post operative analgesic efficacy of oarl etoricoxib 90 mg and 120 mg and a placebo in mandibular fracture pain model.

Methods: A total of 63 adult patients with mandibular fractures who were scheduled to undergo maxillofacial surgery were randomly allocated to receive etoricoxib 90 mg, etoricoxib 120 mg and a placebo 1 hour before the surgery. Patients were followed-up till 24 hours after the surgery. Duration of analgesia, intra-operative and post-operative analgesic requirement, pain score, post-operative patient satisfaction and adverse effects were measured.

Results: The baseline demographic parameters were similar in all the groups. Duration of analgesia was longer in both the E120 (6.00±0.816 hours) and E90 (4.37±1.008 hours) groups ($p<0.05$) as compared to the placebo group (2.60±0.821 hours). Mean difference of duration of analgesia between E120 and E90 was 1.62 (95% confidence interval: 0.234–3.484; $p>0.05$). Post-operative pain intensity was significantly lower in both the E120 and E90 groups as compared to the C group. Both the etoricoxib groups required less intra-operative ($p=0.002$) and post-operative ($p=0.001$) analgesic supplementation as compared to the placebo group. The patient satisfaction score and rate of occurrence of significant adverse effects were similar among all the three groups.

Conclusion: Etoricoxib 90 mg is equally efficacious to etoricoxib120 mg with a similar side effect profile in a severely acute setting.

Keywords: Analgesia, etoricoxib, mandibular fracture

Introduction

Pre-emptive analgesia has been defined as a treatment that starts before the surgery and prevents the establishment of central sensitisation caused by incisional and inflammatory injuries (1). It not only provides intra-operative analgesia but also reduces post-operative analgesic consumption and development of chronic post-operative pain (2-4). Traditionally, opioids have been used for intra-operative and post-operative pain management. However, opioids have potential side effects such as nausea, vomiting, respiratory depression, urinary retention, pruritus etc.

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Non-steroidal anti-inflammatory drugs (NSAIDs) may be used as a substitute and can help in reducing the intake of opioids, thereby decreasing the side effects (5). NSAIDs mediate their action on pain pathways by preventing the production of prostaglandins by inhibiting the action of the cyclooxygenase (COX) enzyme. The COX enzyme has two distinct subunits, namely, COX-1 and COX-2 (6). COX-2 mainly mediates pain and COX-1 is responsible for inhibiting deleterious side effects such as gastrointestinal bleeding, platelet dysfunction, bleeding disorders, etc. Selective COX 2 inhibitors have the advantage of blocking pain pathways without producing any serious adverse effects.

Etoricoxib has a greater COX-2 selectivity than COX-1 as compared to other COX-2 inhibitors, such as rofecoxib, valdecoxib and celecoxib (7, 8). Etoricoxib has been used in multiple studies to reduce peri-operative pain. However, these are mostly orthopaedic surgeries, laparoscopic surgeries and less severe pain models such as impacted third molar extractions (9-13).

At present, in the literature, there is no data on the role of etoricoxib as a pre-emptive analgesic in a pain model of maxillofacial surgery. Therefore, we performed a prospective randomised study to examine the pre-emptive and post-operative analgesic effect of etoricoxib in mandibular fracture patients who were undergoing open reduction and internal fixation.

Methods

The study was conducted in the Department of Anaesthesiology, Pain Medicine and Critical Care and the Department of Oral and Maxillo-Facial Surgery, All India Institute of Medical Sciences, New Delhi. The institutional ethical clearance was obtained (IEC/NP-361/08,10.2014,RP-15/2014) before commencement of the study and registered with the Clinical Trial Registry-India (ctri.nic.in), Registration number: CTRI/2008/17/009272.

This was a randomised, double-blinded, prospective and placebo-controlled trial that compared two doses of etoricoxib (90 mg and 120 mg) as pre-emptive analgesics to a placebo to assess the control of pain in the post-operative period. Written and informed consent was obtained from all the participants before enrolling them in the study.

The primary aim of this study was to assess and compare the efficacy of oral etoricoxib 90 mg, etoricoxib 120 mg and a placebo as pre-emptive analgesics for providing post-operative analgesia in a mandibular fracture pain model. The duration of analgesia, intra-operative and post-operative analgesic requirement, pain scores, post-operative patient satisfaction and adverse effects between the groups were the secondary outcomes of the study.

Sample size

To identify a difference of 20% with 90% power and a type I error of 5%, 13 subjects were required per group. To accommodate for dropouts and to increase the precision of the study, 20 subjects per group were included (Stata 13).

Out of the 79 patients who were screened, randomisation was done for 63 eligible patients based on a computer-generated random number sequence. Allocation concealment was done using the sequentially numbered, sealed opaque envelope technique. Each group received premedication 1 hour prior to the anticipated time of induction. Study tablets were prepared by crushing and filling empty capsules with one of the following: etoricoxib 90 mg (E90), etoricoxib 120 mg (E120) or crushed sugar (C), which served as the placebo. Capsules were prepared with the help of a pharmaceutical company. All the capsules were identical so that the participating anaesthesiologist and the patient were not aware of the group allocated.

The study drugs were placed in specific boxes according to the groups allocated by a nurse who did not participate in the study beyond this point. All the patients were explained about the 0–10 cm Visual Analogue Scale (VAS) for pre- and post-operative assessment of pain (0 indicated no pain and 10 indicated maximum imaginable pain). All the patients were followed-up in the pre-operative, intra-operative and post-operative period up to 24 hours. A blinded investigator recorded the data.

The study was conducted on adult patients meeting the following inclusion criteria:

- Patients aged 18–50 years,
- American society of Anesthesiologists classification grade I-II,
- Patient scheduled for mandibular fracture surgery.

The following patients were excluded from the study*:*

- Known allergy, sensitivity, contraindication to etoricoxib/NSAIDs,
- Patients with known hypertension, asthma, bleeding disorders,
- Patients on anticoagulants,
- History of dyspepsia, abdominal pain, peptic ulcer,
- Patients with coronary artery disease, peripheral vascular disease and cerebrovascular disorder,
- Patients with hepatic and renal impairment,
- Patients already on analgesics for control of pain for some other ailment.

Anaesthesia technique

After premedication, patients were observed in the pre-anaesthesia room with standard monitoring devices. Before shifting

the patient to the operation theatre (OT), baseline pain was assessed by using the VAS score. After shifting the patient to the OT, standard monitoring devices were attached and baseline vitals were noted (heart rate: HR, blood pressure: BP, SpO_2 and respiratory rate: RR). Anaesthesia was induced with intravenous (IV) fentanyl 2 mcg kg^{-1} followed by propofol (2–2.5 mg kg^{-1}) and atracurium (0.5 mg kg^{-1}) for neuromuscular blockade. Airway patency was managed with endotracheal tubes (ETT) of appropriate sizes. Anaesthesia was maintained with O_2: Air (50:50), isoflurane (minimum alveolar concentration=1–1.5 mg kg^{-1}) and controlled ventilation to maintain the end tidal CO_2 within normal limits. Boluses of IV fentanyl 0.5 µg kg^{-1} were given as a rescue analgesic when there was a >20% rise in HR or BP. Intra-operative analgesic supplementation was recorded. In a similar previous study that assessed the efficacy of ketorolac on mandibular fracture surgery, the time to the first dose of rescue analgesic in the control/placebo group averaged 28 minutes, with a SD of 4.5 (14).

At the end of the surgery, ondansetron 4 mg was given as an antiemetic and ETT was removed after reversing the patient with neostigmine (50 mcg kg^{-1}) and glycopyrrolate (10 mcg kg^{-1}). Intra-operative vitals were noted every 5 minutes. Post-operatively, the patient was monitored at 15-minute intervals for pain, vitals and side effects of the drug, if any. The data were recorded at 2, 4, 6, 8, 12 and 24 hours. The patients were given paracetamol 1 gm every 8 hours. The post-operative pain was noted by VAS score, and if VAS score was more than 4 at or in between the time of recording, IV fentanyl 0.5 mcg kg^{-1} was given and repeated every 15 minutes till the score was less than or equal to 4. An anaesthesiologist, who was blinded to the group allocation, assessed the post-operative pain and recorded the amount of analgesic consumption.

The duration of analgesia was noted as the time of first requirement of post-operative analgesia after shifting the patients to the post-anaesthesia care unit. Patients were observed for common side effects during this period. Patient satisfaction was assessed by asking them to rate their overall satisfaction on a five-point Likert scale where 1, 2, 3, 4, 5 represents very satisfied, satisfied, neutral, dissatisfied and very dissatisfied, respectively (15).

Statistical analysis

Descriptive analysis (mean, standard deviation, frequency, significance) was done for all parameters of our study population. Chi-square test was used to determine the categorical outcome. Inter-group comparison for continuous variables was assessed by analysis of variance test and post hoc analysis was performed by the Bonferroni test. All data were analysed by IBM Statistical Package for the Social Sciences for Windows® version 21.0 (IBM SPSS Corp.; Armonk, NY, USA) software. A p value of 0.05 was considered significant.

Results

A total of 79 patients were screened for eligibility to participate in the study, out of which 16 patients were excluded from the study either because they did not meet the inclusion criteria (10 patients) or refused to provide consent (6 patients). The remaining 63 patients were randomised into 3 groups. Post-randomisation, 3 patients were excluded because of the following reasons: (1) need for re-exploration surgery, (2) intake of additional analgesics in the pre-operative period and (3) failure to receive the study drug due to a communication error. Finally, the clinical data of 60 patients, with 20 patients in each group were analysed (Figure 1).

The baseline demographic parameters were similar among all three groups. Mean pain score before surgery, duration of surgery and drain output for 24 hours post-surgery were similar in all the three groups (Table 1). Time to first dose of analgesic medication (Table 2) was longer in both the E120 (6.00±0.816 hours) and E90 (4.37±1.008 hours) groups and this was statistically significant (p=0.001) as compared to the C group (2.60±0.821 hours). An inter-group comparison with post hoc Bonferroni analysis (Table 3) showed the mean difference between E90 group versus C group to be 1.77 (95% confidence interval [CI]: 0.012–3.538), between E120 group versus C group to be 3.40 (95% C: 1.367–5.163) and between E120 group versus E90 group to be 1.62 (95% CI: 0.234–3.484).

Although the E120 group had a longer duration of analgesia than the E90 group, this was not statistically significant (p>0.05). The pre-operative baseline VAS scores were comparable in all groups (p=0.739) (Table 1). The post-operative pain intensity (VAS) was significantly lower in both the E120 and E90 groups as compared to C group, however there was no difference in pain scores between the E90 and E120 groups at all time points (Figure 2). The mean intra-operative fentanyl rescue boluses were 2.6±0.548 for C group, 1.0±0.816 for E90 group and 0.5±0.577 for E120 group. Similarly, post-operative mean fentanyl consumption was 4.6±0.546 boluses for C group, 3.0±0.816 boluses for E90 group and 2.0±0.816 boluses for E120 group. Both the E90 and E120 groups required less intra-operative (p value 0.002) and post-operative (p value 0.001) analgesic supplementation as compared to the C group.

Patient satisfaction score was similar in all three groups (Table 2). Gastrointestinal adverse effects such as nausea, vomiting and constipation were the most commonly observed adverse effects in all the three groups, but none of the patients required any additional treatment. One patient in each group had post-operative dizziness and one patient in E120 group was abnormally sleepy, but he promptly recovered without any complications. Two patients in the C and E90 groups

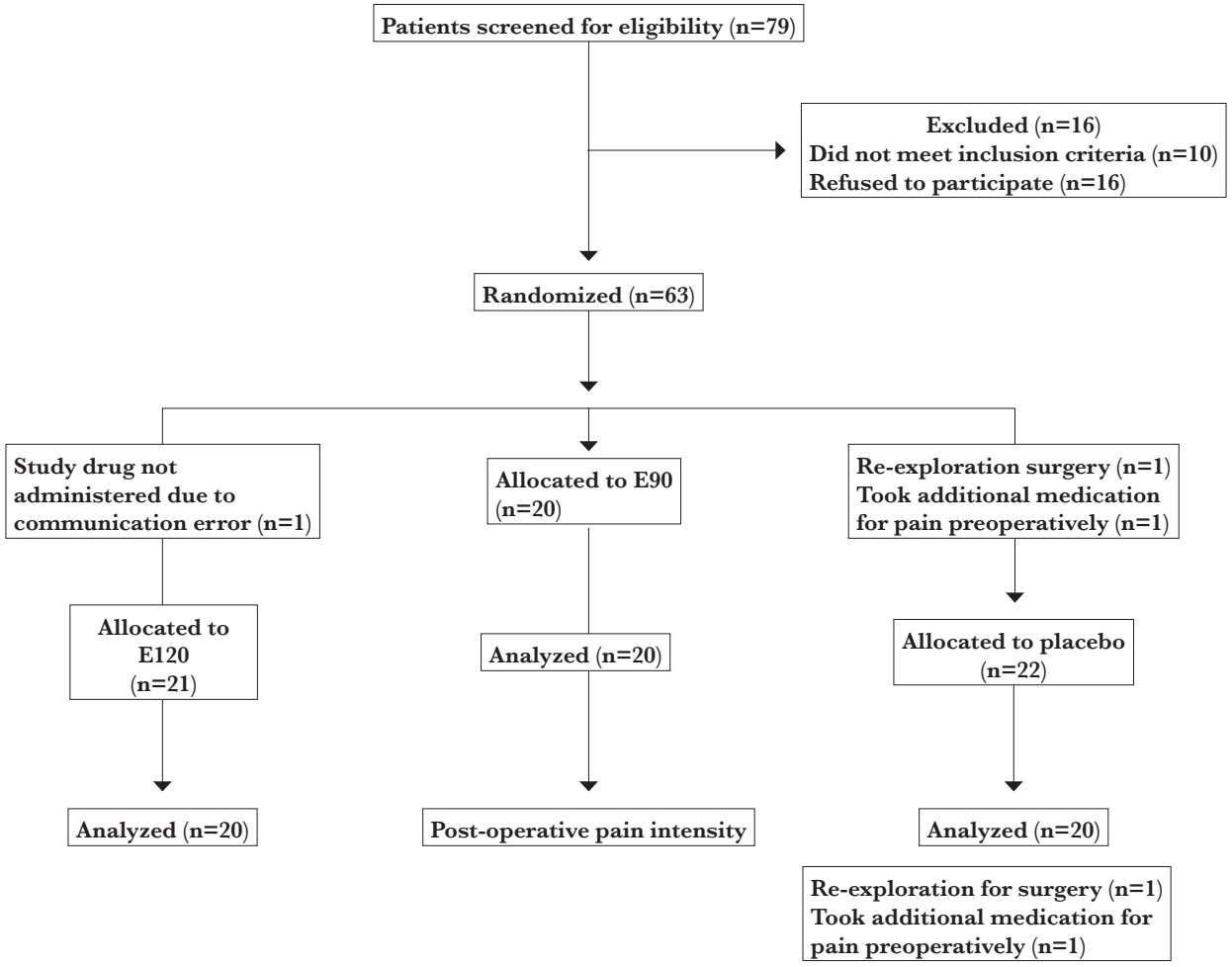

Figure 1. CONSORT flowchart
***E120 = etoricoxib 120 mg, E90 = etoricoxib 90 mg**

Table 1. Patient characteristics

Characteristics	Control	Etoxib90	Etoxib120	p
Age	29.20	34.50	28.25	0.366
Weight	74.00	69.25	63.25	0.266
Sex				
(Male/Female)	12/8	13/7	11/9	
Mean pain score before surgery (VAS)	6	5.25	4.75	0.739
Duration of surgery (hours)	1.75±0.288	1.37±0.478	1.50±0.677	0.586
Drain output (ml)	212.50±103.078	243.75±87.500	280.00±90.458	0.594

Table 2. Medication usage and patient satisfaction among the groups

Characteristics	Control	Etoxib90	Etoxib120	p
Intra-op rescue fentanyl boluses	2.6±0.548	1.0±0.816	0.5±0.577	0.002
Duration of analgesia (hours)	2.60±0.821	4.37±1.008	6.00±0.816	0.001
Patient satisfaction score (mean)	3.00±1.150	3.50±1.291	4.00±1.414	0.472
Post-op rescue fentanyl boluses	4.6±0.546	3.0±0.816	2.0±0.816	0.001

Table 3. Inter-group comparison of duration of analgesia

	Mean difference (hours)	95% confidence interval	p
Etoxib90 vs control	1.77	0.012–3.538	0.048
Etoxib120 vs control	3.40	1.367–5.163	0.001
Etoxib120 vs etoxib90	1.62	−0.234–3.484	0.093

Table 4. Adverse events among groups

	Control, n (%)	Etoxib90, n (%)	Etoxib120, n (%)	p
Gastrointestinal (dyspepsia, flatulence, nausea, vomiting, constipation)	3 (15)	2 (10)	3 (15)	0.866
Neurological (dizziness, headache, somnolence)	1 (5)	1 (5)	2 (10)	0.765
Cardiovascular (tachycardia, hypertension)	1 (5)	0 (0)	1 (5)	0.596
Fever	2 (10)	2 (10)	1 (5)	0.804
Renal (oliguria)	0 (0)	0 (0)	0 (0)	0.000

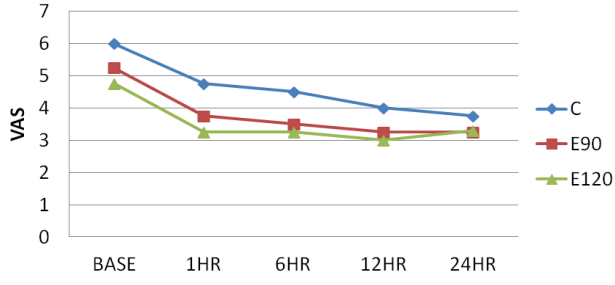

Figure 2. Pain intensity among the groups

each and one patient in the E120 group had post-operative fever. There was no incidence of oliguria or acute renal failure in any of the patients. Post-operative bleeding as measured by drain output and the incidence of adverse effects were similar in all the three groups (Table 4).

Discussion

The primary objective of this study was to evaluate the efficacy of 90 mg and 120 mg etoricoxib as compared to a placebo in terms of post-operative pain relief, when administered as a pre-emptive analgesic in a mandibular fracture surgery pain model. Our study found that both 90 mg and 120 mg doses of etoricoxib were efficacious in prolonging the duration of analgesia and had a similar incidence of side effects as compared to the placebo. Intra-operative and post-operative consumption of rescue fentanyl was significantly less in both the etoricoxib groups as compared to the placebo group. Post-operative pain as measured by the VAS score at all time points was higher in the placebo group as compared to 90 mg and 120 mg etoricoxib groups, but this was not statistically significant. The overall patient satisfaction score was similar across all the groups.

There is no universally accepted definition of pre-emptive analgesia. The explanatory concept indicates that pre-emptive analgesia is an analgesic intervention that is performed before the initiation of noxious stimuli and has the potential to reduce post-operative pain (16).

Etoricoxib is a COX 2 inhibitor with an onset of action at 20–30 minutes, with a duration of action of ≥ 24 hours. The relative activity of COX 2/COX 1 is 106 (5). The COX 2 enzyme is generally absent in healthy tissues but its concentration increases significantly following inflammation (6). In addition to the peripheral mechanism, etoricoxib has also been shown to have a central mode of action for alleviating pain (17). Post-operative pain is generally more severe in the first 24 hours, with the highest intensity being in the initial 6–8 hours (18). Pain of maxillofacial surgery is considered to be mild to moderate (14). However, mandibular fractures are associated with greater soft tissue injury and have more severe pain than dental extractions. Since the mandible is a mobile bone, the associated injuries present with excruciating pain along the fracture site. If not treated properly and in time, it may lead to chronic pain. Infection and malocclusion are considered to be common complications of mandibular fracture (19). A single dose of oral etoricoxib has been shown to produce good quality pain relief after acute post-operative pain in adults (20, 21). Post-operative pain management has been studied extensively in orofacial procedures like orthognathic surgery and third molar extraction, but has not been studied in mandibular fracture cases (22). The Cochrane review on 'Interventions for the management of mandibular fractures' observed very few studies reporting information on post-surgical pain as an outcome (23).

Etoricoxib has been used as a pre-emptive analgesic in orthopaedic surgery, arthroscopy and laparoscopic cholecystecto-

my (8-11), where it has shown its efficacy in reducing post-operative pain. Most of these studies compared the effectiveness of 120 mg etoricoxib with a placebo. However, there have been limited studies in the literature that compared two different doses of etoricoxib (90 mg versus 120 mg), especially in orofacial surgery (12, 24). Low doses may have a similar efficacy but fewer side effects. Malmstrom et al. (24), in their dose-ranging study of etoricoxib used for acute pain associated with dental surgery, compared the analgesic efficacy of a single oral dose of etoricoxib (60 mg, 120 mg, 180 mg and 240 mg) to a placebo. They showed that 60 mg etoricoxib is inferior to 120 mg etoricoxib in reducing pain over an 8-hour period and that 120 mg is the minimum dose that can show maximum efficacy.

The only study that compared 90 mg and 120 mg doses of etoricoxib in a post-operative pain setting was conducted by Daniels et al. (12). They compared two doses of etoricoxib with ibuprofen and acetaminophen/codeine and found both the doses of etoricoxib to be superior to acetaminophen/codeine and not inferior to ibuprofen. The two doses of etoricoxib showed similar efficacy in reducing post-operative pain, which is similar to our study. However, this study was conducted in patients after surgical extractions of ≥ 2 third molars, which may not cause pain severe enough to demonstrate the difference between two doses of etoricoxib. Therefore, we postulated that comparing the same in a different pain model with more extensive tissue trauma and bone injury such as a mandibular fracture, as in our case, might produce a starker difference in the efficacy of two doses of etoricoxib. However, our study also could not produce any difference between the 90 mg and 120 mg doses of etoricoxib, although it is quite possible that more uniformity in the pain model could have produced a difference in our result, because mandibular fracture is a broad term that includes different severities of tissue and bone injury. Apart from that, non-uniformity of surgical intervention by different surgeons and small sample sizes were also some limiting factors. The overall patient satisfaction score at the end of a 24-hour period was higher in both etoricoxib groups as compared to the control group, although this was not statistically significant. Etoricoxib is a long-acting analgesic that dosed once daily and requires a few days to develop a steady plasma level. Hence, a longer follow-up with daily dosing of etoricoxib could have produced better pain relief and a higher satisfaction score in both the etoricoxib groups as compared to the placebo group.

Both the etoricoxib doses were found to be safe and well-tolerated. The overall incidences of adverse side effects of the two doses of etoricoxib were comparable with the control (placebo) dose. Previous studies comparing etoricoxib with either placebo or NSAIDS (9-12) showed increased incidence of nausea, vomiting, constipation, dizziness and somnolence, because of the increased use of the rescue medications. Increased requirement of a post-operative opioid such as hydrocodone might be responsible for the numeric increase in gastrointestinal and neurological side effects. Our study showed a similar incidence in the adverse effects of all the groups, in spite of a significant increase in fentanyl consumption in the control group. Protocolised use of antiemetic medication just before extubation, use of nonopioid analgesics like paracetamol and diclofenac in the post-operative period and the use of shorter-acting opioid fentanyl in place of hydrocodone as a rescue analgesic probably decreased the incidence of adverse effects in the control group. Fever and tachycardia were evenly distributed among all the groups; they were transient, self-limiting and did not require any treatment. These are very commonly observed adverse effects in the post-operative period, which has multiple confounding factors like pain, blood loss, anxiety, etc. Post-operative blood loss as measured by the drain output were similar among all the groups. Derangement of platelet function leading to increased blood loss may have occurred due to COX-1 inhibition by traditional NSAIDs. Etoricoxib being a selective COX-2 inhibitor does not inhibit platelet function and does not increase blood loss.

It is apparent from the above data; 90 mg etoricoxib is equally efficacious to 120 mg etoricoxib, and has a similar side effect profile when treating severe acute pain. Previous data has already proven the effectiveness of 90 mg etoricoxib in less severe pain-inducing procedures, such as in third molar tooth extractions. The validity of the result of this study needs to be evaluated using other, more severe pain models.

Study limitations

Using bispectral index monitoring instead of haemodynamic parameters could have been a better guide for administration of the rescue analgesic.

Conclusion

Etoricoxib 90 mg is as efficacious as etoricoxib 120 mg, as they demonstrate similar pain-relief effects and insignificant side effects in treating severe acute pain.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of All India Institute of Medical Sciences.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – D.G.; Design – D.G., A.S.; Supervision – A.R.C., O.B.; Resources – D.G., A.S., D.K.B., Materials – D.G., A.S., R.Y., Data Collection and/ or Processing – A.S.; Anal-

ysis and/ or Interpretation – D.G., A.S., D.K.B., R.Y.; Literature Search – D.G., A.S., D.K.B., R.Y.; Writing Manuscript – D.G., A.S.; Critical Review – A.R.C., O.B.; Other – D.G., A.S.

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