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COMPARATIVE SAFETY AND EFFICACY EVALUATION OF IBUPROFEN WITH PARACETAMOL VERSUS ETORICOXIB ALONE FOR PAIN AFTER TOOTH EXTRACTION: A RANDOMIZED DOUBLE-BLIND STUDY

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ABSTRACT: Objective: To study the safety and efficacy of ibuprofen with paracetamol versus etoricoxib alone in patients who experienced acute pain after tooth extraction. **Materials and methods:** A total of 80 patients were recruited and randomised to two study groups, IP and E on ibuprofen 400mg with paracetamol325mg and etoricoxib 60 mg alone for three days. The analgesic efficacy was assessed by visual analogue scale, pain relief score, and global evaluation score. Patients were assessed at 0, 6, 24, 48 & 72 hr. Safety was assessed by the Patient's estimation of the severity of adverse drug reaction using a 3-point scale and the type of adverse drug reactions reported by the patients after 72 hrs. **Results:** Mean pain intensity reduction, mean pain relief score, and global evaluation score all showed comparable analgesic efficacy results in group E as compared to group IP. No patient had reported any serious adverse drug reaction in either group. Mild to moderate adverse reactions were reported in both the group; however, the incidence of GIT intolerance was seen only in the IP group. **Conclusion:** Etoricoxib alone is safer alternative of commonly prescribed ibuprofen with paracetamol combination in pain after tooth extraction.

INTRODUCTION: Pain serves as a primary indicator of the inflammatory response [1]. Routine dental extractions, excluding those of third molars, are categorised as minor surgical procedures that typically result in mild to moderate postoperative pain [2]. Traditional non-steroidal anti-inflammatory drugs (tNSAIDs) like ibuprofen with low dose paracetamol are commonly prescribed drugs for the control of pain and inflammation.

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The elevated risk of gastric mucosal damage and bleeding associated with COX-1 inhibition by traditional NSAIDs (tNSAIDs) [3] spurred the development of selective COX-2 inhibitors, such as celecoxib, parecoxib, and etoricoxib *etc* [4]. Paracetamol is an analgesic antipyretic drug with poor anti- inflammatory activity and is devoid of gastric mucosal damage like ibuprofen and thrombotic episode like Rofecoxib [5].

Evidence suggests that etoricoxib have comparable effect with ibuprofen in dental pain [6]. However, vigilant monitoring of its use remains essential due to the inherent thrombotic risks associated with selective COX-2 inhibitors. Further research is required to optimize etoricoxib's analgesic efficacy

while mitigating its potential for pro-thrombotic events and dose-related adverse reactions, specifically fatigue and headache [7]. There is no convincing scientific evidence to compare the analgesic efficacy and safety of etoricoxib over the frequently used fixed dose combination of ibuprofen with low dose paracetamol in acute pain conditions. This study is designed to evaluate the comparative safety and clinical efficacy of etoricoxib versus a commonly prescribed ibuprofen-paracetamol fixed dose combination in the management of acute post-extraction dental pain.

MATERIALS AND METHODS:

Study Design: This was a prospective, randomized, double-blind, comparative interventional study conducted jointly by the Departments of Pharmacology and Dentistry at the Jaya Arogya (J.A.) Group of Hospitals, Gajra Raja Medical College, Gwalior (M.P.). The study was done from February 2020 to August 2021 after obtaining approval from the institutional ethics committee. (No.431/IEC-GRMC/2019). The study was also registered prospectively in the Clinical Trials Registry of India (CTRI number: CTRI/2020/09/027587). The study included 80 participants undergoing dental extractions, who were equally allocated into two groups: Group E and Group IP (n=40 per group) via random assignment. Patients of group E were given etoricoxib 60 mg once a day, while group IP patients received ibuprofen 400 mg and paracetamol 325 mg 8 hourly thrice a day. Informed consent was taken from all the study patients. Randomisation was done using a random number table.

Inclusion Criteria: All patients of both genders between 25-60 years of age & weight between 40 kg to 70 kg having an active mobile number came for tooth extraction except the third molar in the dental OPD.

Exclusion Criteria: Female patients who were pregnant or breastfeeding, patients who were intolerant to any NSAIDs, patient with chronic diseases like diabetes, hypertension, cerebro-vascular disease, hepatic or renal insufficiency, gastric disease, patients with comorbid dental conditions, those on any current pharmacotherapy (excluding antibiotics), and individuals who had ingested analgesics within the 48 hours.

Blinding Procedure: After tooth extraction, each patient was given a coded envelope containing three pink and six white packets of tablets, each packet containing two tablets. 80 such envelopes containing drugs for each of the patients enrolled in two study groups were prepared, and then the third person who had not been part of the study coded them. The investigator noted the code mark on the patient's assigned envelope. Patients were instructed to take the tablets first from the pink packet when the pain starts, and then the tablets from the white packet after 8 hr and 16 hr respectively, daily for three days **Fig. 1.** Throughout the study, all personnel and patients remained blinded to treatment assignments. An independent third party, uninvolved in the study, broke the codes for the final analysis.

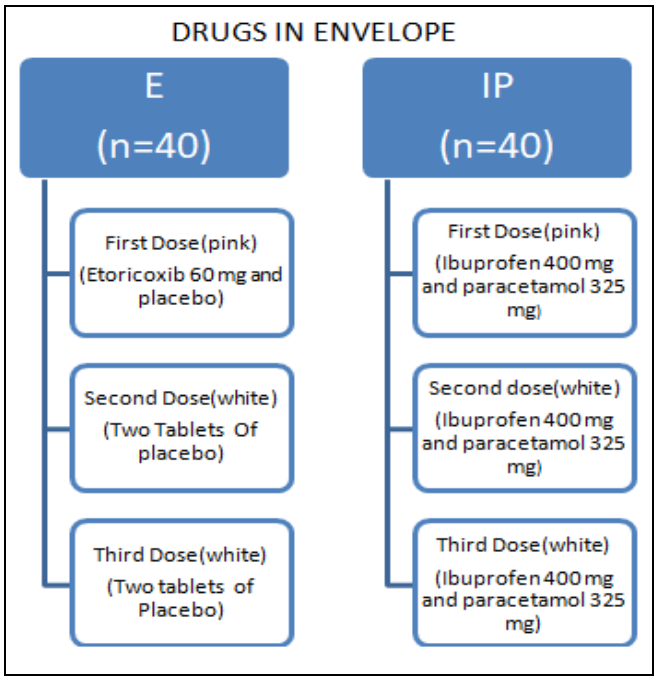

FIG. 1: FLOW DIAGRAM SHOWING PREPARATION OF ENVELOPE CONTAINING PACKETS OF STUDY DRUGS

Questionnaire: Efficacy of the study drugs was evaluated on the basis of a questionnaire, provided to the patient before the start of treatment, having questions framed to collect information on pain intensity and pain relief. Patients were asked to fill this form at home during three days, and data were collected at 0, 6, 24, 48, and 72 hr after taking the drugs.

Efficacy Assessments: Analgesic efficacy of drugs was assessed by using three different scales-

Pain intensity was evaluated by the patients marking in horizontal visual analogue scale **(VAS)** of 10 cm. Patients were asked to mark 'no Pain' at 0 and 'worst possible pain' at 10[8].

Pain relief was measured by the marking done by the patients on a 5-point scale **(PAR)** as follows: 0: no pain relief, 1: some pain relief, 2: medium pain relief, 3: good pain relief, and 4: total pain relief [9].

Overall assessment of medication was judged by Global evaluation score (GES) measured after 72 hrs by asking the patients using a 4-point scale, as follows: 0: poor, 1: Fair, 2: good, and 3: excellent [10].

Safety Assessments: Adverse reactions if any, experienced by patients were recorded after 72 hrs of treatment. Patients were also asked about the severity of estimated adverse drug reactions and were marked on a 3-point scale (1: mild, 2: moderate, 3: severe) [11].

Drugs: Following study drugs were purchased from the market-

1. Paracetamol 325 mg (Glaxo Smith Kline)
2. Ibuprofen 400 mg (Abbott)
3. Etoricoxib 60 mg (Abbott)

Statistical Analysis: All data analysis utilized SPSS version 20 software. Quantitative variables are presented as mean ± standard deviation. Normality assessment was done by Shapiro-wilk test ($p>0.05$). Intra group statistical analysis was conducted using a paired t-test. Intergroup (between-group) statistical analysis was carried out by unpaired t-test. *P*-value <0.05 was considered statistically significant.

RESULTS: The base line demographic details of both the group is shown in **Table 1.**

TABLE 1: BASE LINE CHARACTERISTICS OF STUDY POPULATION

Demographic parameters	Group IP	Group E
Age	44 ± 12	40 ±11
Female: Male	24:16	25:15
Urban: Rural	31:9	29:11
Literate: Illiterate	40:0	39:1

IP-Ibuprofen 400 mg with paracetamol 325 mg, E- Etoricoxib 60 mg

Measures of Efficacy:

Effect on Pain Intensity: The mean pain intensity reduction was seen in 30%, 55%, 73%, and 92% in group E and 33%, 54%, 70%, and 92% in Group IP as compared to baseline at 6, 24, 48 and 72 hr respectively. Reduction in mean pain intensity within both the groups was significant (*P*<0.01) as compared to baseline at 6, 24, 48 & 72 hr. On comparison between the two groups, IP was non-significantly better in reducing pain intensity than the E group (P >0.05) **Fig. 2.**

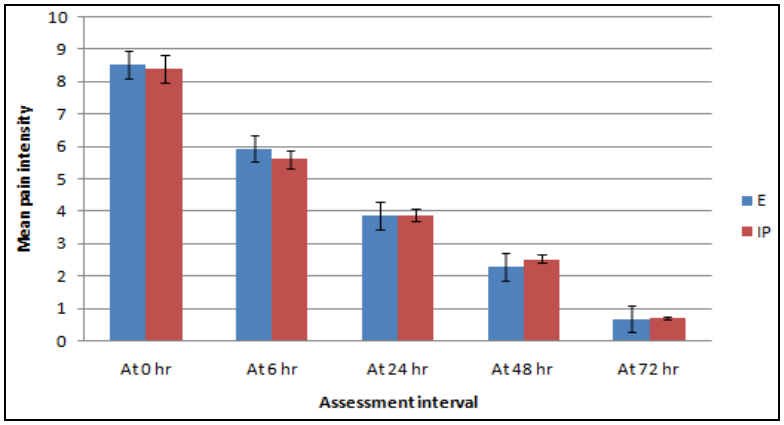

FIG. 2: EFFECT OF ETORICOXIB VERSUS IBUPROFEN WITH PARACETAMOL ON MEAN PAIN INTENSITY (BY VISUAL ANALOGUE SCALE) AT DIFFERENT TIME INTERVALS IN PATIENTS AFTER TOOTH EXTRACTION. Values are expressed as mean ± SD, n=40 in each group, E=Etoricoxib 60 mg once a day, IP = Ibuprofen 400 mg and paracetamol 325 mg thrice a day

Effect on Pain Relief: The baseline score in both the groups at 0 hr is '0' means no relief from pain. In Group E, the mean pain relief score was increased from baseline 0 means no relief from pain to 25%, 53%, 75%, 90% pain relief at 6, 24,48 & 72 hours respectively.

A significant increase of pain relief score was seen within the group as compared to baseline at 6, 24, 48 & 72 hr respectively (P<0.01). In Group IP the mean pain relief score was increased from baseline 0 means no relief from pain to 28, 57%, 75%, 91% pain relief at 6, 24, 48 & 72 hrs respectively.

A significant increase of pain relief score was seen within the group as compared to baseline at 6, 24, 48, & 72 hr (P<0.01). On comparison, IP showed non-significantly better pain relief than the E group (P >0.05) **Table 2.**

TABLE 2: EFFECT OF ETORICOXIB VERSUS IBUPROFEN WITH PARACETAMOL ON MEAN PAIN RELIEF SCORE IN PATIENTS AFTER TOOTH EXTRACTION

Assessment Interval	E	IP
At 0 hr	0	0
At 6 hr	1.00±0.00	1.10±0.30
At 24 hr	2.10±0.30	2.28±0.80
At 48 hr	2.98±0.28	3.00±0.23
At 72 hr	3.60±0.50	3.63±0.49
p-value	P <0.01	P <0.01

Values are expressed as mean ± SD, n=40 in each group, E= etoricoxib 60mg once a day, IP =ibuprofen 400 mg and add on paracetamol 325 mg thrice a day

Effect on Global Evaluation Score: In group E, 2.5% (n=1) patient rated their medication as poor, 20% (n=8) patient rated their medication as fair, 45% (n=18) patients rated it as good while 32.5% (n=13) patient rated their medication as excellent.

Thus, the majority of patients rated their medication as good. In group E, the mean global evaluation score was 2.15±0.73. In group IP, 7.5% (n=3) patients rated their medication as poor, 7.5% (n=3) patients rated it as fair, 50% (n=20) patients rated their medication as good, while 35% (n=14) patients rated it as excellent.

Thus, the majority of patients rated their medication as good; the mean global evaluation score was 2.18±0.98. On intergroup comparison, patients acceptance of drug in group IP was non-significantly better than group E (P>0.05) **Table 3.**

TABLE 3: EFFECT OF ETORICOXIB VERSUS IBUPROFEN WITH PARACETAMOL ON PATIENT'S OVERALL ASSESSMENT OF MEDICATION JUDGED BY GLOBAL EVALUATION SCORE (GES) AFTER 72 HRS OF TOOTH EXTRACTION

4- point scale	E (no. of patients)	IP (no. of patients)
0-Poor	1	3
1-Fair	8	3
2-Good	18	20
3-Excellent	13	14
Mean ± SD	2.25±0.63	2.18±0.98

Values are expressed as mean ± SD, n=40 in each group, E= etoricoxib 60mg once a day, IP =ibuprofen 400 mg and add on paracetamol 325 mg thrice a day

Measures of Safety: Mild to moderate adverse drug reactions were seen in 5 patients in group E and 8 patients in group IP.

Safety of the medication was assessed by report of adverse effects by the patients. In Group E, headache and fatigue were seen in 5% of patients each, whereas dizziness was seen in 2.5% of patients. Thus headache and fatigue were the most common symptom in this group.

In Group IP, dizziness was reported by 2.5% of patients, abdominal pain and vomiting each by 5%, while nausea was shown by 7.5% of patients. Thus, gastrointestinal adverse drug reactions were most common in this group **Table 4.**

TABLE 4: ADVERSE DRUG REACTIONS OBSERVED IN PATIENTS DURING THREE DAYS PERIOD OF TREATMENT WITH ETORICOXIB VERSUS IBUPROFEN WITH PARACETAMOL AFTER TOOTH EXTRACTION

S. no.	Adverse Effects	E	IP
1.	Headache	2(5%)	0
2.	Fever	0	0
3.	Dizziness	1(2.5%)	1(2.5%)
4.	Abdominal pain	0	2(5%)
5.	Nausea	0	3(7.5%)
6.	Vomiting	0	2(5%)
7.	Perspiration	0	0
8.	Shivering	0	0
9.	Fatigue	2(5%)	0

Values are expressed as mean ± SD, n=40 in each group, E= etoricoxib 60mg once a day a, IP =ibuprofen 400 mg and add on paracetamol 325 mg thrice a day

DISCUSSION: Patients experience acute pain in several inflammatory diseases like rheumatoid arthritis, acute gouty arthritis, ankylosing spondylitis, osteoarthritis, bursitis, toothache, and post-operative pain, so management of pain is a primary clinical necessity [12].

Etoricoxibis currently a widely used analgesic and anti-inflammatory drug found to be advantageous in gastroduodenal mucosal protection, but is under supervision for cardiovascular adverse effects. In the present double-blind study, paracetamol in low dose was added 8 hrly (due to short half-life 6-8 hrs) to ibuprofen for treatment of pain in patients after tooth extraction [13]. The two drugs are not used as a fixed-dose combination, which is irrational due to pharmacokinetic differences between the two drugs [14].

Result of the study showed that the etoricoxib showed comparable efficacy with ibuprofen and paracetamol combination in all three parameters used to assess analgesic activity, such as reduction in pain intensity on the visual analogue scale, pain relief score, and overall compliance by global evaluation score, in patients after tooth extraction. Previous comparative studies between etoricoxib 60 mg and ibuprofen 400 mg in pain showed better efficacy in etoricoxib group than ibuprofen [15].

While in our study it is comparable, might be due to addition of paracetamol in low dose with ibuprofen. It suggests that paracetamol could increase analgesic efficacy when added to ibuprofen better than to Etoricoxibalone in patients of tooth extraction. This is in accordance with the earlier study suggesting paracetamol has predominant COX-2 inhibiting activity [16] than COX-1 blocking activity and, COX-2 expression is increased in acute inflammation [17]. Further COX-1 generated prostaglandins also play some role in producing inflammation, and the addition of paracetamol with ibuprofen broadens the efficacy than of therapeutic dose etoricoxib [18].

In this safety comparison study, no severe adverse reactions were reported in either group. Mild to moderate adverse drug reactions were reported in 12.5% of etoricoxib treated group, and 20% of ibuprofen treated group, suggests etoricoxib is the overall safer drug. GIT intolerance was seen in 17.5% of cases in ibuprofen treated group whereas no incidence of GIT intolerance was noticed in etoricoxib treated group, which confirms their gastro-protective nature [19]. Further adverse effects reported in the ibuprofen 400mg and paracetamol 325mg received group were mostly of gastrointestinal intolerance, even in a short treatment period suggest the use of proton pump inhibitors ,especially when we need to continue treatment for a longer period [20].

Thus, etoricoxibis found comparable in analgesic efficacy and better in safety as compared to ibuprofen with paracetamol treated group. It can be used for the treatment of pain as an alternative inpatients not tolerating tNSAIDs. This study is of short duration, small sample size and exclude the patient with chronic diseases. Also we don't assess the use of rescue medicine in this study. These all are the limitations of the study There is a need to conduct several multicentre studies in different pain-producing conditions to validate the efficacy and safety of etoricoxib in different pain conditions.

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CONFLICT OF INTEREST: Nil

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