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Research Article

EFFICACY, SAFETY, AND COST-EFFECTIVE ANALYSIS OF LOW-DOSE ETORICOXIB AND ADD-ON PARACETAMOL VERSUS THERAPEUTIC DOSE ETORICOXIB FOR PAIN IN PATIENTS AFTER TOOTH EXTRACTION: A RANDOMIZED INTERVENTIONAL DOUBLE-BLIND STUDY

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ABSTRACT

Objectives: The objectives of the study were to study the efficacy, safety, and cost-effective analysis of low-dose etoricoxib and add-on paracetamol versus therapeutic dose etoricoxib in patients who experienced pain after tooth extraction.

Methods: Patients were recruited and randomized to two study groups E1P and E2 on etoricoxib 30 mg and add-on paracetamol 500 mg 8 hourly and etoricoxib 60 mg once respectively for 3 days. The efficacy was assessed by visual analog scale, pain relief score, and global evaluation score. Patients were assessed at 0, 6, 24, 48, and 72 h. Safety was assessed by adverse drug reactions reported by the patients after 72 h. Cost-effective analysis was done by calculating the cost of treatment and the cost-effective ratio in both groups.

Results: Eighty patients completed the study having 40 patients in each group**.** Mean pain intensity reduction, mean pain relief score, and global evaluation score all showed significantly better results ($p<0.05$) in Group E1P as compared to Group E2 at 6, 24, 48, and 72 h, respectively. No patient had reported any serious adverse drug reaction in both the groups; however, incidence of headache and fatigue was twice in the etoricoxib only treated group (n=4) than low-dose etoricoxib-treated group (n=2). The treatment cost of Group E1P was lesser than Group E2 and was also cost effective.

Conclusion: Low-dose etoricoxib with add-on paracetamol is a better analgesic than therapeutic dose etoricoxib and is also found to be safer and cost effective.

Keywords: Cost effective, Etoricoxib, Low dose, Pain, Paracetamol.

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INTRODUCTION

Pain is an unpleasant, annoying, and emotional experience related to actual or potential tissue damage. It is not a disease on its own but people recognize pain as a signal of disease [1]. It is the most common symptom which takes the patient to the physicians. Extraction of teeth is a common dental procedure. After tooth extraction, most of the patients experience pain, and there is a varying degree of severity between patients. About 82% of patients experience moderate pain on the evening of extraction day, and up to 16% of patients continued to experience this post-extraction pain after a week [2].

Traditional nonsteroidal anti-inflammatory drugs (tNSAIDs) such as ibuprofen, naproxen, ketorolac, and indomethacin provide greater efficacy and tolerability compared with opioid-based treatments in minor surgical settings such as dental procedures [3]. However, these drugs also have well-documented adverse effects, such as gastric mucosal damage, gastrointestinal bleeding, sodium and water retention, and asthma [4]. Their anti-inflammatory and analgesic actions are related to inhibition of COX-2, while side effects affecting the gastrointestinal tract are mostly a result of their inhibition of the COX-1 enzyme.

Improved knowledge on more selective COX enzymes led to the development of specific COX-2 inhibitors, such as celecoxib, parecoxib, and etoricoxib with analgesic, anti-inflammatory, and gastroprotective properties [5]. Etoricoxib is a second-generation coxib that has the highest COX-2 selectivity in this class of drugs and is widely used as an analgesic. It has a long half-life (~24 h), which makes it suitable for once-daily dosing compared with tNSAIDs that need to be taken 3–4 times per day [6].

Many drugs produce adverse effects when they are used in high doses [7]. Some of the selective COX-2 inhibitors, such as rofecoxib and valdecoxib, are banned due to prothrombotic influence and enhanced cardiovascular risk [8]. Drugs that act synergistically if given together in low doses will have better efficacy than their alone use. This will also reduce the incidence of adverse effects [9]. Paracetamol is known to inhibit the COX-2 enzyme with a low adverse effect profile. No scientific study is available in the literature to know the analgesic efficacy and safety of low-dose etoricoxib and add-on paracetamol in patients suffering from pain. Therefore, the present study is planned to compare the efficacy, safety, and cost-effective analysis between low-dose etoricoxib and add-on paracetamol and therapeutic dose etoricoxib in patients having pain after tooth extraction.

METHODS

Study design

This was a prospective, randomized, interventional double-blind comparative study conducted in the Department of Pharmacology with the Department of Dentistry at J.A. Group of Hospital, 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).

Sample size calculation

The sample size was calculated using the Epi Info software tool by considering the power of 80%, a significance level of 0.05, expected population size, and expected tooth extraction frequency from the previous study. The required sample size to be calculated is 40 patients

in each group, considering the drop-out rate of 10%, a total of 90 patients were enrolled.

Intervention

Patients who underwent tooth extraction were enrolled for the study and were randomly divided into two groups E1P and E2 received etoricoxib 30 mg once a day and paracetamol 500 mg 8 hourly and etoricoxib 60 mg once a day, respectively, for 3 days.

Informed consent was taken from all the study patients. Randomization was done using a random number table.

Inclusion criteria

The following criteria were included in the study:

- All patients of both genders between 25 and 60 years of age and weight between 40 kg and 70 kg.
- Patients who came for tooth extraction except the third molar in dental OPD.
- The patient who has an active mobile number.

Exclusion criteria

The following criteria were excluded from the study:

- Female patients who were pregnant, breastfeeding, child-bearing age, or using contraception.
- Patients who were intolerant to paracetamol, etoricoxib, or other NSAIDs
- Patient with serious comorbidity, diabetes, coronary artery disease, cerebrovascular disease, hepatic insufficiency, renal insufficiency, and gastric disease.
- Patients with other dental problems.
- Patients who gave a history of tooth extraction in the previous year.
- Patients on any ongoing medication except antibiotics.
- Patients who were taking analgesics in the previous 48 h.

Blinding procedure

After tooth extraction, each patient was given a sealed coded envelope containing three pink and six white packets of tablets, each packet containing two tablets.

The code mark on the envelope assigned to the patient was noted by the investigator. Patients were instructed to take first the tablets from the pink packet 2 h after tooth extraction and then tablet from white packet after 6 h and 12 h, respectively, daily for 3 days (Fig. 1).

All study personnel and participating patients were blinded to treatment assignment for the whole duration of the study. The third person who was not part of the study broke the codes for the final calculation.

Questionnaire

All the patients were provided with a questionnaire having a visual analog scale (VAS) and a 5-point pain relief scale before the start of the treatment. Patients were asked to mark on these scales simultaneously at 0, 6, 24, 48, and 72 h after taking drugs. The questionnaire was collected after 3 days and was analyzed.

Efficacy assessment

Analgesic efficacy of drugs was assessed using three different scales –

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

Pain relief was measured by the marking done by the patients on a 5-point scale. (1: Poor, 2: Average, 3: Good; 4: Very good; and 5: Excellent) [11].

Overall assessment of medication was judged by global evaluation score (GES) measured after 72 h by asking the patients using a 4-point scale. (0: Poor, 1: Fair, 2: Good, and 3: Excellent) [12].

Safety assessments

Patients estimated adverse drug reactions on a 3-point scale (1: Mild, 2: Moderate, and 3: Severe) and also reported what kind of adverse effects they had experienced [13].

Assessment of cost-effectiveness

The 3-day cost of each treatment regime was calculated and the cost-effectiveness ratio was calculated by the ratio of total treatment cost divided by the primary endpoint: Percent reduction in pain intensity.

Drugs

Etoricoxib 30 mg was not available in the market, therefore, etoricoxib 60 mg (Abbott) half tablet was used.

Paracetamol 500 mg (Glaxo Smith Kline) was purchased and used.

Statistical analysis

All the data analyses were performed using SPSS version 20 software. Quantitative variables were expressed as the mean and standard deviation. Intragroup (within-group) statistical analysis was carried out by paired t-test. Intergroup (between-group) statistical analysis was carried out by unpaired t-test. $p<0.05$ was considered statistically significant.

RESULTS

In total, 90 patients were recruited and 80 completed the study, 40 in each group. The patient disposal has been depicted in Consolidated Standard for Reporting Trial (CONSORT) style flow diagram in Fig. 2.

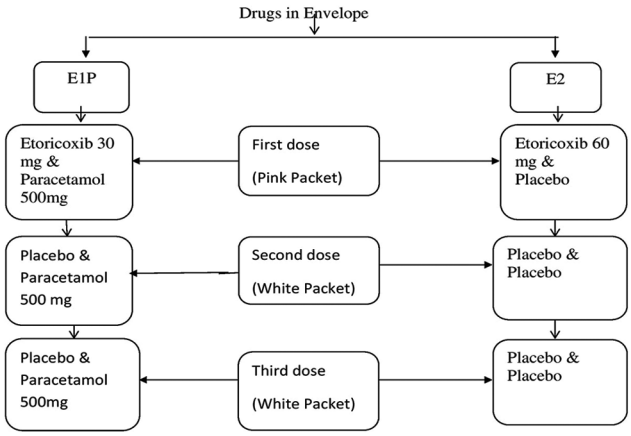

Fig. 1: Flow diagram showing preparation of envelope containing packets of study drugs

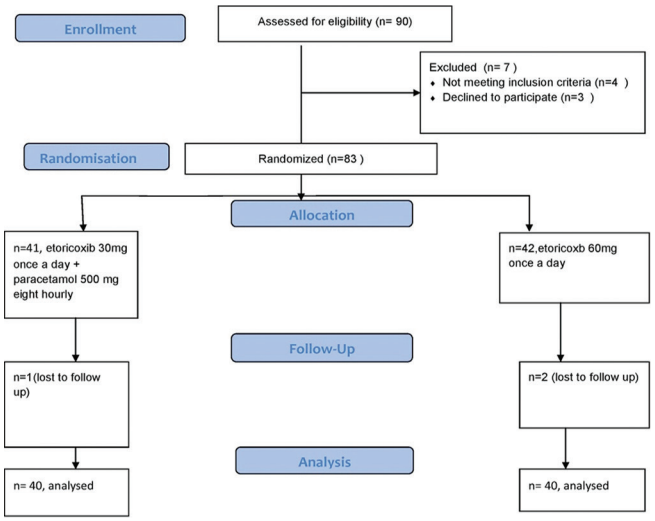

Fig. 2: CONSORT flow diagram

Demographic profile characteristics were comparable in both groups.

Measures of efficacy

Effect on pain intensity

In Group E1P, the mean pain intensity showed a percent reduction of 39%, 64%, 86%, and 98% from baseline at 6, 24, 48, and 72 h, respectively. A significant reduction was seen within the group as compared to baseline at 6, 24, 48, and 72 h (p<0.01). In Group E2, the mean pain intensity showed a percent reduction of 30%, 54%, 73%, and 92% from baseline at 6, 24, 48, and 72 h, respectively. A significant reduction was seen within the group as compared to baseline at 6, 24, 48, and 72 h (p<0.01), respectively. In comparison between the two groups, E1P was significantly better in reducing pain intensity at 6 h (p<0.01), 24 h (p<0.01), 48 h (p<0.01), and 72 h (p<0.05) than E2 group (Table 1).

Effect on pain relief

The baseline score in both the groups at 0 h is "0" means no relief from pain.

In Group E1P, the mean pain relief score was increased from baseline 0 means no relief from pain to 41%, 67%, 86%, and 98% pain relief at 6, 24, 48, and 72 h, respectively. A significant increase of pain relief score was seen within the group as compared to baseline at 6, 24, 48, and 72 h (p<0.01).

In Group E2 the mean pain relief score was increased from baseline 0 means no relief from pain to 25%, 52%, 74%, and 90% pain relief at 6, 24,48, and72 h, respectively. A significant increase of pain relief score was seen within the group as compared to baseline at 6, 24, 48, and 72 h, respectively (p<0.01). In comparison, E1P showed significant pain relief at 6 h (p<0.01), 24 h (p<0.01), 48 h (p<0.01), and 72 h (p<0.01) than E2 group (Fig. 3).

Effect on global evaluation score

In Group E1P, no patient rated their medication as poor, 2.5% (n=1) of patients rated it as fair, 30% (n=12) of patients rated their medication as good, while 67.5% (n=27) of patients rated it as excellent. Thus, the majority of patients rated their medication as excellent; the mean global evaluation score was 2.68±0.53. In Group E2, only 2.5% (n=1) of patients rated their medication as poor, 20% (n=8) of patients rated their medication as fair, 45% (n=18) of patients rated it as good while 32.5% (n=13) of patients rated their medication as excellent. Thus, the majority of patients rated their medication as good. In Group E2, the mean global evaluation score was 2.15±0.70. On intergroup comparison, patients' acceptance of the drug in the Group E_1P was significantly better than Group E2 (*P*<0.01) (Fig. 4).

Measures of safety

The safety of the medication was assessed by the report of adverse effects by the patients.In Group E1P, the headache, dizziness, shivering, and fatigue each were reported by 2.5% of patients only. Thus, all the adverse drug reactions reported were similar in incidence.

Table 1: Effect of low-dose etoricoxib and add-on paracetamol versus therapeutic dose etoricoxib on mean pain intensity (by visual analog scale) at different time intervals in patients after tooth extraction

Assessment interval	E1P	E2
At 0 h	8.44±0.46	8.53±0.42
At 6 h	5.14±0.85*	5.96±0.48
At 24 h	3.03±0.91*	3.88±0.61
At 48 h	1.16±1.07*	2.30±0.69
At 72 h	0.17±0.53*	0.70±0.86
P	<0.01	<0.01

E1P: Etoricoxib 30 mg once and paracetamol 500 mg thrice a day treated group, E2=Etoricoxib 60 mg once a day treated group. Values are expressed as mean±SD, n=40 in each group. *p<0.05 when compared with E2

In Group E2, dizziness was seen in 2.5% of patients only whereas headache and fatigue each were seen in 5% of patients (Table 2). Thus, the incidence of headache and fatigue in Group E2 was more than E1P.

Assessment of cost-effectiveness

The total treatment cost of the E1P group was calculated by adding the cost of one tablet of 30 mg etoricoxib (INR 6) and three tablets of paracetamol 500 mg (INR 3)x 3 days (6+3= 9x3= INR 27). The treatment cost of the E2 group was calculated as the cost of one tablet of 60 mg etoricoxib (INR 12) × 3 days (12×3=INR 36)

In the present study, the cost of treatment per patient in the E1P group is lower than the cost of treatment in the E2 group.

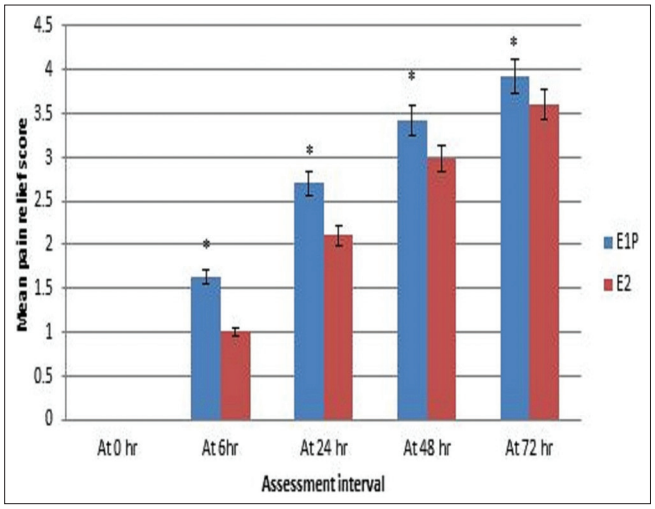

Fig. 3: Effect of low-dose etoricoxib and add-on paracetamol versus therapeutic dose etoricoxib on mean pain relief score in patients after tooth extraction. E1P=Etoricoxib 30 mg once and paracetamol 500 mg thrice a day treated group, E2=Etoricoxib 60 mg once a day treated group. Values are expressed as mean±SD, n=40 in each group,*p<0.05 when compared with E2

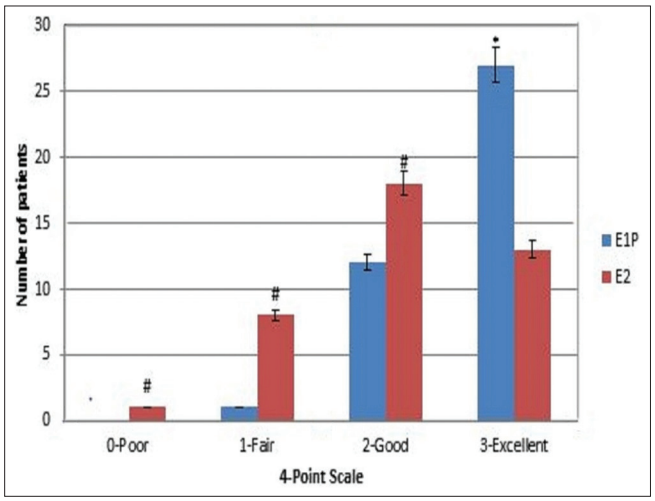

Fig. 4: Effect of low-dose etoricoxib and add-on paracetamol versus therapeutic dose etoricoxib on patient's overall assessment of medication judged by global evaluation score (GES) by the patients after 72 h of tooth extraction. E1P=Etoricoxib 30 mg and paracetamol 500 mg thrice a day treated group, E2=Etoricoxib 60 mg once a day treated group. Values are expressed as mean±SD, n=40 in each group. *p<0.05 when compared with E2, #p<0.05 when compared with E1P

For cost-effective analysis, total cost of the treatment is divided by the percent reduction in mean pain intensity after 3 days in both groups. The cost-effectiveness score is 0.28 in the E1P group and 0.39 in the E2 group. The treatment group having a less cost-effectiveness ratio is considered superior. At the end of the treatment, etoricoxib 30 mg and add-on paracetamol 500 mg thrice are more cost effective (Table 3).

DISCUSSION

The present double-blind study is novel of its kind because no scientific studies are done earlier to compare the analgesic efficacy of low-dose etoricoxib with add-on paracetamol versus therapeutic dose etoricoxib in patients suffering from acute pain. The age of the patients in our study ranged from 25 to 60 years with a mean age of 42.85 years. Out of the total 80 patients of tooth extraction, 39% were male and 61% were female patients. Thus, females were predominant in our study this is similar to another study [14]. Females generally have a low threshold for pain which can explain the female preponderance. In our study, 73% of the patients were from the urban area and 27% were from the rural area, thus, the majority of patients had an urban background.

In the present study, analgesic efficacy of low-dose etoricoxib (30 mg) once with add-on paracetamol thrice a day was significantly better than etoricoxib 60 mg alone in terms of reduction in pain intensity and improvement in pain relief at 6, 24, 48, and 72 h. Reduction in pain intensity was 6% more in the low-dose etoricoxib-treated group and was significant than the etoricoxib 60 mg treated group. Similarly, the pain relief score was significantly greater in the etoricoxib low dose as compared to the etoricoxib alone group. Thus, the results of the present study revealed that etoricoxib 30 mg and paracetamol 500 mg showed significantly better analgesic activity than etoricoxib 60 mg alone. Our results are in accordance with an earlier study where COX-2 inhibitors, rofecoxib (now it is banned) when given as an add-on with paracetamol showed better efficacy than COX-2 inhibitor alone [15]. Results of the present study also confirm that paracetamol when added to low-dose selective COX-2 inhibitor increases the analgesic efficacy [16]. At present in literature paracetamol is classified under non-selective cox inhibitor but it has also shown the features of cox-2 selectivity[17].

Table 2: Adverse drug reactions observed in patients during 3 days period of treatment with low-dose etoricoxib and add-on paracetamol versus therapeutic dose etoricoxib after tooth extraction

Serial number	Adverse reactions	Number of patients (E1P)	Number of patients (E2)
1	Headache	1	2
2	Fever	0	0
3	Dizziness	1	1
4	Abdominal pain	0	0
5	Nausea	0	0
6	Vomiting	0	0
7	Perspiration	0	0
8	Shivering	1	0
9	Fatigue	1	2

E1P: Etoricoxib 30 mg once and paracetamol 500 mg thrice a day treated group, E2=Etoricoxib 60 mg once a day treated group

Table 3: Cost-effectiveness of low-dose etoricoxib with add on paracetamol as compared to therapeutic dose etoricoxib

Study groups	Total cost of treatment (INR)	Percent reduction in mean pain intensity after 72 h (%)	Cost-effectiveness ratio
E1P	27	98	0.28
E2	36	92	0.39

E1P: Etoricoxib 30 mg once and paracetamol 500 mg thrice a day treated group, E2: Etoricoxib 60 mg once a day treated group, INR: Indian national rupee

The apparent COX-2 selectivity of paracetamol is shown by its poor antiplatelet activity and good gastrointestinal tolerance [18]. Recent studies suggest that paracetamol acts by several other mechanism such as inhibition of nitric oxide formation and increased activity of the endocannabinoid system [19] that adds to its analgesic efficacy.

In the present study, we also compared the global evaluation scores given by patients at the end of treatment. This score evaluates the overall experience of treatment by patients. A higher global evaluation score was seen in the group treated with low-dose etoricoxib with the addition of paracetamol. Our results are in accordance with earlier studies [20].

In the present study, no patient had reported any serious adverse drug reaction in both groups. However, the incidence of headache and fatigue was twice in the etoricoxib only treated group than the low-dose etoricoxib-treated group. Our findings were similar to an earlier study [15] showing a greater incidence of fatigue and headache with therapeutic dose etoricoxib-treated group than non-selective NSAIDs. This study also reveals that with the lower dose of etoricoxib, the incidence of fatigue and headache is also lower as compared to the therapeutic dose.

We also did a cost-effective analysis between the study groups. The present study suggests that per day treatment cost of etoricoxib 30 mg once and paracetamol 500 mg thrice a day is INR 9.00 and is cheaper than etoricoxib 60 mg which cost INR 12.00. The mean pain intensity decrease by 98% in the etoricoxib 30 mg and paracetamol 500 mg treated group was higher as compared to 92% in the etoricoxib 60 mg treated group. Thus, it is clear that the addition of paracetamol to low-dose etoricoxib is a cost-effective regime. Our study also suggests that if paracetamol is given, once with etoricoxib 30 mg will produce a significant analgesic effect up to 6 h because of quick action and short half-life of paracetamol. Therefore, paracetamol is given every 8 h as per need for continuous analgesia and etoricoxib has a long half-life given once only and need not be repeated before 24 h. This will save approximately INR 3 per day and INR 90 per month.

In the market, fixed-dose combination of etoricoxib 60 mg with paracetamol 325 mg is available which costs around INR 13 per tablet and is prescribed more than once a day by physicians on account of the short half-life of paracetamol which exposes the patients to increased cost, dose, and adverse effects due to etoricoxib unnecessarily. This fixed-dose combination is irrational because the two drugs having different pharmacokinetic profiles should not be combined [9].

This is a 3-day study conducted on a limited number of patients in one center. The results found are encouraging and a need is felt to conduct several multicenter studies for a long duration including patients of osteoarthritis, rheumatoid arthritis, gouty arthritis, lumbar pain, and chronic pain-producing illnesses to find the efficacy and long-term safety of this regime.

CONCLUSION

This is the first study of its kind that clearly shows that the addition of paracetamol 500 mg is a cost-effective addition to increasing analgesic efficacy of low-dose etoricoxib with no additive adverse effects.

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AUTHORS' CONTRIBUTIONS

All authors have contributed to study design, manuscript writing, and review, data analysis, and article finalization.

CONFLICTS OF INTEREST

None.

AUTHORS' FUNDING OR AUTHORS' SPONSORSHIP

None.

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