

EFFICACY AND SAFETY OF DICLOFENAC SODIUM AND ETORICOXIB IN CONTROLLING POST EXTRACTION DENTAL PAIN – A RANDOMISED OPEN LABEL COMPARATIVE STUDY

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ABSTRACT:

AIM: The aim of this study is to evaluate the efficacy and safety of COX-2 inhibitor Etoricoxib 120mg OD compared to Diclofenac Sodium 50mg BD in post extraction dental pain.

MATERIAL AND METHODS: A total number of 100 patients posted for third molar extraction were recruited for the study. Those who met the inclusion criteria (n = 51) were randomized into two treatment groups A & B. Group A received T. Diclofenac Sodium and Group B received T. Etoricoxib. Written Informed consent was obtained from all the patients. On the day of surgery patients were given the study drugs and visual analog scales (VAS) to assess the pain intensity for 5 days. Baseline pain intensity immediately after surgery and at 8hrs was recorded on the day of surgery. They were asked to report any adverse events over phone during the study period. On day 5 the completed forms were collected and evaluated statistically using one way analysis of variance.

RESULTS: The statistical analysis of pain intensity using VAS showed that 78% of patients showed severe baseline pain intensity and at the end of 8 hours on the first day of surgery, Diclofenac group showed 27% reduction in pain intensity and 39% reduction in Etoricoxib group (P value < 0.05). On day 5 pain reduction was 97% and 100% in Diclofenac and Etoricoxib group respectively. Global assessment and safety assessment showed better gastrointestinal profile for the Etoricoxib than Diclofenac sodium. No major adverse effects were reported in the two study groups.

CONCLUSION: Present study proves that Etoricoxib has a rapid onset and prolonged pain relief and statistically significant analgesic effect in the immediate postoperative period of 8 hrs in comparison to Diclofenac sodium. The traditional

time tested analgesic Diclofenac sodium 50mg b.d and newer Etoricoxib 120mg are equally effective in post extraction dental pain. Safety Profile especially GIT toxicity was comparatively better for Etoricoxib than Diclofenac sodium during the study period.

Key words: Etoricoxib, diclofenac sodium, visual analog scale, pain assessment, safety

INTRODUCTION

The surgical extraction of impacted third molar teeth is a clinically validated, reliable model for acute pain and evaluating the efficacy of analgesics. Patients recruited for this procedure are young, healthy, degree of interpatient variation is less and patients are naive of previous pain experiences. This surgical procedure is clean, uniform, not life threatening, causes predictable moderate to severe pain, with anxiety.¹

Pharmacological management of pain involves the administration of medications which include: opioid analgesics, non steroidal anti inflammatory drugs, local anesthetics, glucocorticoids and alpha₂ agonists. We are still in constant search of an ideal analgesic drug which alleviates pain, anxiety effectively and facilitates wound healing without undesirable side effects like gastritis, bleeding, sedation and hypersensitivity reactions.

Non steroidal anti inflammatory drugs (NSAIDs) are commonly used drugs for the control of postoperative pain of moderate to severe intensity.² The mechanism of action of NSAIDs is inhibition of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes and thereby preventing synthesis of prostaglandins. Prostaglandins are one of the major mediators of pain and inflammation peripherally. COX-1 is protective for gastric mucosa, platelet action and kidney function.³ Inhibition of COX-1 results in gastrointestinal toxicity and peptic

ulcer. Cox-2 is expressed in only a few specialized tissues like brain and kidney. It is induced during inflammation and plays important physiological roles in tissue repair, reproduction and renal function. This enzyme is particularly not involved in mucus production in stomach. COX -2 inhibitors prevent inflammation and sensitization of peripheral nociceptors. In addition they might be safe with significantly lower incidences of gastric injury.⁴

Pain intensity is assessed using pictorial and numerical ten point Visual Analog Scale (VAS). It is designed to present to the patient a rating scale with minimum constraints. It is simple, quick to score and avoids imprecise descriptive terms. VAS scores during treatment and baseline show a Gaussian distribution allowing for the use of parametric statistical analysis. This scale is widely applied in studies on dental pain⁵.

Diclofenac sodium is a time tested commonly used NSAID used in painful conditions including acute postoperative pain. The selection of Diclofenac Sodium is based on the previous studies, as it is proved to offer a good combination of efficacy and tolerance.^{6,7}

The selection of Etoricoxib is to substantiate its analgesic efficacy and safety profile in a short term treatment of 5 days in controlling postoperative pain in Indian population. Pharmacokinetic profile of Etoricoxib compared to diclofenac sodium is favourable with rapid absorption and good bioavailability. Time to peak plasma concentration is quick with elimination half life of 22 hrs in healthy human volunteers with once daily dosing. It is an effective analgesic with good tolerability. Studies on healthy human beings have demonstrated that Etoricoxib does not interfere with platelet aggregation.^{8,9}

The primary objective and aim of the present study is to compare the analgesic efficacy and safety of Cox-2 inhibitor Tab. Etoricoxib 120mg once a day with traditional NSAID Tab. Diclofenac sodium 50mg twice a day in controlling post extraction dental pain in patients undergoing surgery for impacted third molar tooth. The tool used to measure the pain intensity is Visual analog scale.

MATERIALS AND METHODS

The study was conducted among 51 patients with one or more impacted third molar teeth posted for extraction at the oral surgery department of the Dental College, Sri Ramachandra Medical College and Research Institute, Chennai.

The institutional Ethics Committee approved the study protocol, informed consent form and the case report form. The study was a randomized, open-label, comparative, single centre study. Duration of the study period is 5 days with either one of the study drug. Inclusion criteria included both gender aged from 18-60 years, who were posted for surgical extraction of impacted third molar tooth, partially or fully impacted or in germinal phase and all were in good general health, as established by physical, clinical examination and laboratory investigations. Subjects with hypersensitivity to NSAIDs, infective carries, peptic ulcer, cardiovascular abnormalities, diabetes mellitus, hypertension, bronchial asthma, pregnant, lactating women and subjects who had NSAIDs from two days before extraction of teeth were excluded from the study.

The preoperative interviews, the supply of the study medications and visual analog scales recordings and discharge instructions were dealt by an independent observer. Patients who met the inclusion criteria were consequently randomized using a computer generated list using random allocation software, version 1.0 in to two groups A and B.

Group A patients were given T. Diclofenac Sodium 50mg 12th hourly and Group B were provided with T. Etoricoxib 120mg once a day daily. All drugs were prescribed for a period of five days immediately after completion of surgery and continued until suture removal on day 5. Both the groups received postoperative prophylactic antibiotics Cap. Amoxicillin 1g every 12h for 5 days.

All the impacted molars are of equal surgical difficulty and were extracted under local Anesthesia with Lignocaine by the qualified oral surgeons of the study site. Intravenous sedation was never used. After undergoing extraction surgery, patients were supplied with a course of their study analgesic with instructions in the recovery room and were advised

to take the first dose of the medication immediately after surgery. Rescue medication was T.Paracetamol 500mg was provided to the patients if the pain relief is not satisfactory with the study drugs on the first day. Patients were discharged on the day of surgery after 8 hour observation period. All patients were provided using a 10 point Visual analog scale in which they were instructed to record pain intensity over 5 consecutive days at the same time from days 1-5, starting from the day of surgery. Pain intensity was recorded immediately after surgery using VAS and 8 hrs after surgery and discharged. The overall effect of the drug (global assessment of the study medication) on pain and side effects which was assessed by the patients at the end of the trial (fifth day) on a categorical scale with the following categories: 1 – Poor, 2 – Fair, 3 – Good, 4 – Excellent. Patients were advised to report any adverse event immediately over the phone to the independent observer.

On the fifth day of extraction, drug compliance was assessed by counting the remaining tablets. Patients were enquired of any adverse event and they underwent physical examination. Global assessment of the study medications using a categorical scale was recorded from the patients. Visual analog scales were collected back Parameters assessed were Mean pain scores using 10 point VAS, global assessment of study medications and incidence of adverse effects.

One way Analysis of variance test was used to compare the pain intensity (VAS) between the two treatment groups. Intergroup comparison was done using TUKEY'S HSD method. The pain intensity at baseline was included as a covariate in the analysis of pain intensity. The P values below 0.05 were considered to be statistically significant. No adjustment was performed for pair wise comparisons between treatments.

RESULTS

The baseline demographic characteristics were similar among groups. Overall 47 % (24/51) of patients were females and 53 % (27/51) were males. Approximately 78% of patients (38/51) reported severe pain after surgery and 6% (3/51)

reported moderate pain (Table 1). The use of intraoperative anaesthesia was limited to epinephrine administered with lignocaine hydrochloride (Table 1).

The primary efficacy measure was pain intensity. The overall analgesic efficacy of the study drugs over the period of 8 hrs, 24hrs, day 3, day 4 & day 5, were measured by reduction in pain intensity using visual analog scale.

On end of surgery at 1hr the baseline mean pain intensity score \pm SD for the Diclofenac sodium group was 8.76 ± 1.48 and Etoricoxib 120mg group was 8.64 ± 1.58 . At the end of 8 hours of surgery, Diclofenac sodium group showed 6.36 ± 1.63 (CI=8.15-9.37) with 27% reduction in the pain intensity. In case of Etoricoxib group pain score was 5.22 ± 2.01 (CI=7.99-9.29) with 39% reduction in pain intensity which was statistically significant.

On day 2 pain score was 3.64 ± 2.31 (CI=5.69-7.03) with 58% reduction in pain intensity in Diclofenac group, and 3.8 ± 1.78 (CI=4.41-6.07) with 56% reduced pain intensity in Etoricoxib group.

On day 3 pain score was 1.64 ± 1.73 (CI= 2.69-4.59) with 81% reduction in pain intensity in Diclofenac group, and 1.40 ± 1.47 (CI=0.79-2.01) with 83% reduced pain intensity in Etoricoxib group.

On day 4 in Diclofenac group pain score was 0.32 ± 0.63 with 96% reduction in pain intensity, and in Etoricoxib group the pain score was 0.28 ± 0.61 with 96% reduced pain intensity respectively.

On day 5 the pain score was 0.28 ± 0.61 with 96% reduction in pain intensity in Diclofenac sodium group and 0.02 ± 0.20 with 100% reduced pain intensity in Etoricoxib group. Mean daily pain scores in each treatment group over the period of 1 hr of day 1 to the day 5 as well as p values are shown in Table 2.

This analysis including baseline pain intensity as a covariate, shows that the pain intensity is not statistically significant different between groups except for significant pain relief with Etoricoxib 120mg (8hrs) (p value < 0.05). There was no evidence of any statistical difference between drugs for relief of pain on day 2 to day 5. (Fig 1)

The incidence of side effects, especially the epigastric pain and nausea, were significantly higher with treatment of diclofenac sodium than Etoricoxib in appropriate doses. No serious adverse events occurred. One woman reported of vomiting after 6 hours of taking diclofenac sodium as shown in Table 3.

The overall effect of the drug (global assessment of the study medication) on pain and side effects which was assessed by the patients at the end of the trial (day 5) on a categorical scale. All drugs were assessed as good and excellent.

Characteristics	T. Diclofenac sodium n=26	T.Etoricoxib n=25	Total n=51
Sex n (%)Female	14 (53%)	10 (40%)	24 (47%)
Male	12 (47%)	15 (60%)	27 (53%)
Age, yr(mean \pm SEM)	32.5 (1.72)	30 (1.88)	31.3 (1.80)
Weight (kg)	60 \pm 10	62 \pm 11	61 \pm 10.5
Length of surgery (minutes)	28 \pm 12	31 \pm 13	29.5 \pm 12.5
Local anaesthesia (ml)	4 \pm 1	4 \pm 1	4 \pm 1
Baseline pain intensity n (%) Severe:(VAS>8)	15 (58)	23 (92)	38 (78%)
Moderate: (VAS>5)	2 (8)	1 (4)	3 (6%)

Table 1. Baseline Characteristics Between Groups

Study Period	Diclofenac Sodium 50MG BD (mean \pm SD)	sEM	Etoricoxib 120MG OD (mean \pm SD)	sEM	P VALUE
DAY 1-1 hr	8.76 \pm 1.48	0.29	8.64 \pm 1.58	0.31	.748
DAY 1-8 hrs	6.36 \pm 1.63	0.32	5.22 \pm 2.01	0.40	.000
DAY 2	3.64 \pm 2.31	0.45	3.8 \pm 1.78	0.36	.474
DAY 3	1.64 \pm 1.73	0.35	1.40 \pm 1.47	0.29	.276
DAY 4	0.32 \pm 0.63	0.13	0.28 \pm 0.61	0.12	.367
DAY 5	0.28 \pm 0.61	0.12	0.02 \pm 0.20	0.04	.154

Table 2. Mean Pain Scores \pm Sd Using Visual Analog Scale

Fig 1. MEAN VISUAL ANALOG SCORE FOR PAIN INTENSITY

ADVERSE EVENTS	DICLOFENAC SODIUM n=26	ETORICOXIB n=25	TOTAL n=51
NAUSEA, VOMITING	5	1	6
POSTOPERATIVE BLEEDING	5	2	7
DIZZINESS	3	2	5
EPIGASTRIC PAIN	5	0	5
HYPERSENSITIVITY REACTIONS	1	1	2
OTHERS (edema, cough)	1	2	3
TOTAL NO. ADVERSE EFFECTS	20	8	28

Table 3. Adverse events profile of study drugs

DISCUSSION

In a national survey conducted in USA by Jeffrey L. Apfelbaum et al. and published in 2003, it was reported that approximately 80% of all patients experienced acute pain after surgery. Most of the inpatients and outpatients had moderate, severe and extreme pain. Ambulatory patients felt more pain after discharge than when they are in the hospital.¹⁰

With increasing attention being given to successful postoperative pain management in the hospital setting, development of newer analgesics with potency and fewer adverse effects, and use of balanced analgesia plays a prominent role.

The role of the COX-2 inhibitors in the management of other conditions such as osteoarthritis and rheumatoid arthritis has been widely discussed. However, their role in the treatment of postoperative dental pain which is a reliable method for comparing analgesics has been evaluated to a lesser extent in south Indian population. In the present clinical study, approximately 78% reported severe baseline pain intensity following surgical removal of an impacted third molar tooth using visual analog scale. The overall analgesic efficacy and analgesia during the acute postoperative period (8 hrs after surgery) and duration of analgesic effect were evaluated and compared between the study drugs (T. Etoricoxib and T. Diclofenac sodium).

At the end of 8 hrs of postoperative period, the analgesia produced by T. Etoricoxib was statistically significant to the analgesia produced by T. Diclofenac sodium (P value < 0.05). This proves the quick onset of peak analgesic action of Etoricoxib compared to Diclofenac sodium. This result can be extrapolated in a clinical setting to control the acute pain effectively with Etoricoxib on the day of surgery. On the first day of postoperative period the pain relief was almost similar in both groups showing the prolonged action of Etoricoxib in a single daily dose and improved compliance with the use of this drug.

However, on the fourth day of postoperative period of our study the pain relief was almost complete and similar in the both treatment groups. So the overall analgesic efficacy of the single dose of COX-2

inhibitor Etoricoxib 120mg was found to be equal in efficacy to nonselective NSAID, Diclofenac sodium which was given in two divided doses. Patients were overall satisfied with the analgesic efficacy of both the study drugs evaluated by global assessment scale.

The traditional post-surgical analgesia with non-selective NSAIDs and opioids are associated with several side effects such as post-operative bleeding, gastrointestinal problems, nausea, and constipation. The incidence of GI perforations, ulcers, bleeding with Etoricoxib is far less than half that associated with older NSAIDs in a combined analysis of data from ten clinical trials. COX-2 inhibitors are especially useful in patients with a high risk of upper gastrointestinal bleeding or with a history of peptic ulcer.¹¹

Safety assessment showed that both the drugs used in the study were generally well tolerated. No serious adverse event was reported among patients in all treatment groups. Gastrointestinal side effects like epigastric pain and nausea were greater in the diclofenac sodium group compared to Etoricoxib. No episodes of severe gastritis and vomiting were reported in Etoricoxib group confirming the advantage of Etoricoxib over Diclofenac sodium. They do not have any significant effect on platelet function as COX-1 inhibitors.^{12, 13} The use of COX-2 inhibitors has been possibly reported to have increased the cardiovascular and cerebrovascular adverse effects.¹⁴

According to the European Medicines Agency (EMA) when COX-2 inhibitors are prescribed in accordance with contraindications and precautions, the balance of benefit and risk remains positive in target patient population.¹⁵ In India many preparations of Etoricoxib is approved for use for acute pain conditions in the lowest effective dose for a limited time in adults.¹⁶

In the present study being a short term acute pain study, no reports of such serious intolerance and adverse events occurred in the entire treatment groups with Etoricoxib and Diclofenac sodium. To

prove and substantiate the safety and efficacy of Etoricoxib in painful conditions many more clinical trials and studies with good sample size and sound methodologies are needed in Indian population.

CONCLUSION

In this clinical study, Diclofenac sodium 50mg BD and Etoricoxib 120mg OD were overall similar in analgesic efficacy and safety. While both NSAIDs provide a better pain relief in patients following impacted third molar extractions, Etoricoxib has a rapid onset of pain relief and prolonged duration of action in comparison to diclofenac sodium in the immediate postoperative period and can be especially useful in individuals with gastritis and acid peptic disease. Diclofenac sodium is preferably cost effective. Nevertheless, the risk vs. benefit and other cardiovascular, renal adverse effects must be considered while selecting particular NSAIDs for the treatment of dental pain.

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REFERENCES

- Forbes JA. Oral surgery, advances in pain research and therapy: the design of analgesic clinical trials. Max MB, Portenoy R, Laska EM, eds. New York: Raven Press, Ltd, 1991:347-74.
- Mehlisch DR, Markenson J, Schnitzer TJ. The efficacy of nonsteroidal anti-inflammatory drugs for acute pain. *Cancer Control* 1999; 6:5-9.
- Kaplan-machlis B, Klostermeyer BS. The cyclooxygenase-2 inhibitors: safety and effectiveness. *Ann Pharmacother* 1999; 33:979-88.
- Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med* 1999; 340:1888-99.
- Vickers ER, Cousins MJ, et al. Pain description and severity of chronic Orofacial pain conditions. *Australian Dental Journal*; 1998; 43: 403-9. (28) in dissertation.
- Breivik EK, Pal Barkvoll, Eva Skovlund. Combining diclofenac with acetaminophen or acetaminophen-codeine after Oral surgery: A randomized, double-blind single-dose study. *Clin Pharmacol Ther* 1999; 66: 625-35.
- Estelle – Martinez V, et al. Analgesic efficacy of diclofenac sodium versus Ibuprofen following surgical extraction of impacted lower third molars. *Med Oral Pathol Oral Cir Buccal* 2004; 9: 444-53.
- Hunt RH, Harper S, Watson DJ, et al. The gastrointestinal safety of the COX-2 selective inhibitor etoricoxib assessed by both endoscopy and analysis of upper gastrointestinal events. *Am J Gastroenterol* 2003; 98:1725-33.
- Dallob A, Hawkey CT, Greenberg H, et al. Characterization of Etoricoxib, a novel, selective COX-2 inhibitor. *J Clin Pharmacol* 2003; 43:573-85.
- Apfelbaum et al. Postoperative Pain Experience: Results from a National survey suggest Postoperative pain continues to be undermanaged. *Anesth Analg* 2003; 97:534-40.
- Moore RA, Derry S, Makinson GT, Mcquay HJ. Tolerability and adverse events in clinical trials of celecoxib in Osteoarthritis and rheumatoid arthritis: systematic review and meta-analysis of information from company clinical trial reports *Arthritis Research & Therapy* 2005; 7(3):R644-65.

12. Mukherjee D et al., COX-2 inhibitors could increase risk of cardio vascular events. *The Pharmaceutical Journal* 2001; 267: 283.
13. Catella – Lawson F, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the Antiplatelet effects of aspirin. *N.Engl. J. Med.*, 2001, 345: 1809-1817.
14. Anne Burke, Emer M.Smyth, and Garret A.FitzGerald. Analgesic-Antipyretic Agents. In: Laurence LB, John SL, Keith LP. (Eds) *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th ed. NY: McGraw Hill; 2005: pp 684-85.
15. European Medicines Agency, 2008. Questions and Answers on the Review of Etoricoxib-containing Medicines. 2008; Doc. Ref. EMEA/329177/2008.
16. Regional Pharmacovigilance Centre (South). Selective COX-2 inhibitors: current status. *Drug Alert*. 2005; 1(1): 1-4

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