



Journal of
**Pharmacology and
Toxicology**

ISSN 1816-496X



Academic
Journals Inc.

www.academicjournals.com

Efficacy and Safety of Diclofenac Sodium and Aceclofenac in Controlling Post Extraction Dental Pain: A Randomised Open Label Comparative Study

Kudaravalli Jyothisna, Narayan Deshpande and Gali Vijayalakshmi

Department of Pharmacology, Bhaskar Medical College, Yenkapally, RR District, Andhra Pradesh, 500075, India

Corresponding Author: Kudaravalli Jyothisna, Department of Pharmacology, Bhaskar Medical College, Yenkapally, RR District, Andhra Pradesh, 500075, India

ABSTRACT

The aim of this study was to evaluate the efficacy and safety of newer drug Aceclofenac 100 mg BD compared to Diclofenac Sodium 50 mg three times daily tid in post extraction dental pain. 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 and B. Group A received T. Diclofenac Sodium and Group B received T. Aceclofenac. 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 8 h was recorded on the day of surgery. On day 5 evaluated statistically using one way analysis of variance. The statistical analysis of pain intensity using VAS showed that 78% of patients showed severe baseline pain intensity and at the end of 8 h on the first day of surgery, Diclofenac group showed 27% reduction in pain intensity and 40% reduction in Aceclofenac group ($p < 0.05$). On day 5 pain reduction was 95% and 100% in Diclofenac and Aceclofenac group, respectively. Global assessment and safety assessment showed better gastrointestinal profile for the Aceclofenac than Diclofenac sodium. It proves that Aceclofenac has a rapid onset and prolonged pain relief and statistically significant analgesic effect in the immediate postoperative period of 8 h in comparison to Diclofenac sodium.

Key words: Aceclofenac, diclofenac sodium, visual analog scale, pain assessment, gastrointestinal side effects

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 (Forbes, 1991).

Non Steroidal Anti Inflammatory Drugs (NSAIDs) are commonly used drugs for the control of postoperative pain of moderate to severe intensity (Mehlich *et al.*, 1999). 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 (Kaplan-Machlis and Klostermeyer, 1999). 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 (Gill *et al.*, 2011). This enzyme is particularly not involved in mucus production in stomach. COX -2 inhibitors prevent inflammation and sensitization of peripheral nociceptors (Gusdinar *et al.*, 2011). In addition they might be safe with significantly lower incidences of gastric injury (Wolfe *et al.*, 1999).

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 pain (Vickers *et al.*, 1998).

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 (Breivik *et al.*, 1999; Estelle-Martinez *et al.*, 2004).

The selection of Aceclofenac 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 Aceclofenac compared to diclofenac sodium is favourable with rapid absorption and good bioavailability. Time to peak plasma concentration is quick with elimination half life of 4 h in healthy human volunteers with twice daily dosing. It is an effective analgesic with good tolerability (Asmawi *et al.*, 2011). Studies on healthy human beings have demonstrated that Aceclofenac does not interfere with platelet aggregation (Ward *et al.*, 1995; Pasero *et al.*, 1995).

Pharmacological management of pain involves the administration of medications which include: opioid analgesics, non steroidal anti inflammatory drugs, local anesthetics, glucocorticoids and alpha₂ agonists. Thus 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 (Vijayakumar *et al.*, 2011).

The primary objective and aim of the present study was to compare the analgesic efficacy and safety preferable Cox-2 inhibitor Tab. Aceclofenac 100 mg twice daily with traditional NSAID Tab.

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 Bhaskar Medical College andhra Pradesh.

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. Study was conducted from June 2010 to December 2010. 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 (Danquah *et al.*, 2011).

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 50 mg 8th hourly and Group B were provided with T. Aceclofenac 100 twice 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 1 g every 12 h 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 500 mg 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 h 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 h 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 and 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 with 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 49% (49/100) of patients were females and 51% (51/100) were males. Approximately 75% of patients (75/100) reported severe pain after surgery and 9% (9/100) reported moderate pain. 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 h, 24 h, 3, 4 and day 5, were measured by reduction in pain intensity using visual analog scale (Table 2).

On end of surgery at 1 h the baseline mean pain intensity score \pm SD for the Diclofenac sodium group was 8.80 \pm 1.49 and Aceclofenac group was 8.62 \pm 1.56. At the end of 8 hours of surgery, Diclofenac sodium group showed 6.41 \pm 1.64 (CI = 8.15-9.37) with 27% reduction in the pain intensity. In case of Aceclofenac group pain score was 5.25 \pm 2.02 (CI = 7.99-9.29) with 39% reduction in pain intensity which was statistically significant.

Table 1: Baseline characteristics between groups

Characteristics	T. Diclofenac sodium (n = 26)	T. Aceclofenac (n = 25)	Total (n = 51)
Sex n (%)			
Female	15 (58%)	10 (40%)	25 (49%)
Male	11 (42%)	15 (60%)	26 (51%)
Age year (Mean±SEM)	32.5 (1.72)	30 (1.88)	31.3 (1.80)
Weight (kg)	28±13	30±12	28.5±11.5
Length of surgery (min)	5±1	5±1	5±1
Local anaesthesia (mL)	13 (50)	23 (92)	36 (71%)
Baseline pain intensity n (%) severe: (VAS>8)	2 (8)	1 (4)	3 (6%)

Table 2: Mean pain scores±SD using visual analog scale

Study period	Diclofenac sodium		Aceclofenac		p value
	50 MG BD (Mean±SD)	SEM	100 MG BD (Mean±SD)	SEM	
Day 1-1 h	8.80±1.49	0.30	8.62±1.56	0.32	0.745
Day 1-8 h	6.41±1.64	0.33	5.25±2.02	0.40	0.001
Day 2	3.65±2.41	0.46	3.70±1.76	0.38	0.458
Day 3	1.66±1.63	0.36	1.41±1.46	0.28	0.281
Day 4	0.33±0.62	0.15	0.26±0.63	0.13	0.374
Day 5	0.27±0.51	0.14	0.01±0.15	0.03	0.144

Table 3: Adverse events profile of study drugs

Adverse events	Diclofenac sodium (n = 26)	Aceclofenac (n = 25)	Total (n = 51)
Nausea, vomiting	5	1	6
Postoperative bleeding	6	1	7
Dizziness	2	2	4
Epigastric pain	5	1	6
Hypersensitivity reactions	1	1	2
Others (edema, cough)	1	2	3
Total No. Adverse effects	20	8	28

On day 2 pain score was 3.65±2.41 (CI = 5.69-7.03) with 58% reduction in pain intensity in Diclofenac group and 3.7±1.76 (CI = 4.41-6.07) with 56% reduced pain intensity in Aceclofenac group.

On day 3 pain score was 1.66±1.63 (CI = 2.69-4.59) with 81% reduction in pain intensity in Diclofenac group and 1.41±1.46 (CI = 0.79-2.01) with 83% reduced pain intensity in Aceclofenac group.

On day 4 in Diclofenac group pain score was 0.33±0.62 with 96% reduction in pain intensity and in Aceclofenac group the pain score was 0.26±0.63 with 96% reduced pain intensity, respectively.

On day 5 the pain score was 0.27±0.51 with 96% reduction in pain intensity in Diclofenac sodium group and 0.01±0.15 with 100% reduced pain intensity in Aceclofenac group. Mean daily pain scores in each treatment group over the period of 1 h 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 Aceclofenac 100 mg (8 h) (p<0.05). There was no evidence of any statistical difference between drugs for relief of pain on day 2 to day 5.

The incidence of side effects, especially the epigastric pain and nausea, were significantly higher with treatment of Diclofenac sodium than Aceclofenac in appropriate doses. No serious adverse events occurred. One woman reported of vomiting after 6 h 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.

DISCUSSION

In a national survey conducted in USA by Apfelbaum *et al.* (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.

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 preferable COX-2 inhibitors of this group 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 h after surgery) and duration of analgesic effect were evaluated and compared between the study drugs (T. Aceclofenac and T. Diclofenac sodium).

At the end of 8 h of postoperative period, the analgesia produced by T. Aceclofenac was statistically significant to the analgesia produced by T. Diclofenac sodium ($p < 0.05$). This proves the quick onset of peak analgesic action of Aceclofenac compared to Diclofenac sodium. This result can be extrapolated in a clinical setting to control the acute pain effectively with Aceclofenac 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 Aceclofenac 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 predominantly COX-2 inhibitor Aceclofenac 100 mg OD 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 Aceclofenac is far less than half that associated with older NSAIDs in a combined analysis of data from ten clinical trials. Predominantly, COX-2 inhibitors are especially useful in patients with a high risk of upper gastrointestinal bleeding or with a history of peptic ulcer (Moore *et al.*, 2005).

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 aceclofenac group. No episodes of severe gastritis and vomiting were reported in Aceclofenac group confirming the advantage of Aceclofenac over Diclofenac sodium. They do not have any significant effect on platelet function as COX-1 and 2 inhibitors (Mukherjee, 2001; Catella-Lawson *et al.*, 2001). The use of predominant COX-2 inhibitors has not been possibly reported to have increased the cardiovascular and cerebrovascular adverse effects unlike, selective COX-2 inhibitors (Burke *et al.*, 2005).

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 Aceclofenac and Diclofenac sodium (Gusdinar *et al.*, 2011). To prove and substantiate the safety and efficacy of Aceclofenac in painful conditions many more clinical trials and studies with good sample size and sound methodologies are needed in Indian population.

In this clinical study, Diclofenac sodium 50 mg tid and Aceclofenac 100 mg BD were overall similar in analgesic efficacy and safety (Ward *et al.*, 1995). While both NSAIDs provide a better pain relief in patients following impacted third molar extractions, Aceclofenac 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.

CONCLUSION

The study proved that Aceclofenac has a rapid onset and prolonged pain relief and statistically significant analgesic effect in the immediate postoperative period of 8 h in comparison to Diclofenac sodium. Aceclofenac has a better gastrointestinal profile than Diclofenac sodium.

ACKNOWLEDGMENT

Our sincere thanks to Dental surgery department of Bhaskar Medical College.

REFERENCES

- Apfelbaum, J.L., C. Chen, S.S. Mehta and T.J. Gan, 2003. Postoperative pain experience: Results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth. Analg.*, 97: 534-540.
- Asmawi, M.Z., O.M. Arafat, S. Amirin and I.M. Eldeen, 2011. *In vivo* Antinociceptive Activity of Leaf Extract of *Crinum asiaticum* and Phytochemical Analysis of the Bioactive Fractions. *Int. J. Pharmacol.*, 7: 125-129.
- Breivik, E.K., P. Barkvoll and E. Skovlund, 1999. Combining diclofenac with acetaminophen or acetaminophen-codeine after oral surgery: A randomized, double-blind single-dose study. *Clin. Pharmacol. Ther.*, 66: 625-635.
- Burke, A., E.M. Smyth and G.A.F. Gerald, 2005. Analgesic-Antipyretic Agents. In: Goodman and Gilman's The Pharmacological Basis of Therapeutics, Laurence, L.B., S.L. John and L.P. Keith (Eds.). 11th Edn. McGraw Hill, New York, USA., pp: 684-685.
- Catella-Lawson, F., M.P. Reilly, S.C. Kapoor, A.J. Cucchiara and S. Demarco *et al.*, 2001. Cyclooxygenase inhibitors and the Antiplatelet effects of aspirin. *N. Engl. J. Med.*, 345: 1809-1817.

- Danquah, C.A., E. Woode and E. Boakye-Gyasi, 2011. Anti-arthritic effects of an ethanolic extract of *Capparis erythrocarpos* isert roots in freund's adjuvant-induced arthritis in rats. *J. Pharmacol. Toxicol.*, 6: 201-217.
- Estelle-Martinez, V., J. Paredes-Garcia, E. Valmaseda-Castellon, L. Berini-Aytes and C. Gay-Escoda, 2004. Analgesic efficacy of diclofenac sodium versus ibuprofen following surgical extraction of impacted lower third molars. *Med. Oral Pathol. Oral Cir. Buccal.*, 9: 448-453.
- Forbes, J.A., 1991. Oral Surgery, Advances in Pain Research and Therapy. In: The Design of Analgesic Clinical Trials, Max, M.B., R. Portenoy and E.M. Laska (Eds.). Raven Press Ltd., New York, USA., pp: 347-74.
- Gill, N.S., J. Bajwa, P. Sharma, K. Dhiman and S. Sood *et al.*, 2011. Evaluation of antioxidant and antiulcer activity of traditionally consumed *Cucumis melo* seeds. *J. Pharmacol. Toxicol.*, 6: 82-89.
- Gusdinar, T., R. Herowati, R.E. Kartasasmita and I.K. Adnyana, 2011. Anti-inflammatory and antioxidant activity of quercetin-3, 3', 4'-triacetate. *J. Pharmacol. Toxicol.*, 6: 182-188.
- Kaplan-Machlis, B. and B.S. Klostermeyer, 1999. The cyclooxygenase-2 inhibitors: Safety and effectiveness. *Ann. Pharmacother.*, 33: 979-988.
- Mehlisch, D.R., J. Markenson and T.J. Schnitzer, 1999. The efficacy of nonsteroidal anti-inflammatory drugs for acute pain. *Cancer Control*, 6: 5-9.
- Moore, R.A., S. Derry, G.T. Makinson and H.J. Mcquay, 2005. 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 Res. Ther.*, 7: R644-R665.
- Mukherjee, D., 2001. COX-2 inhibitors could increase risk of cardio vascular events. *Pharm. J.*, 267: 283-283.
- Pasero, G., R. Marcolongo, U. Serni, M.J. Parnham and F. Ferrer, 1995. A multi-centre, double-blind comparative study of the efficacy and safety of aceclofenac and diclofenac in the treatment of rheumatoid arthritis. *Curr. Med. Res. Opin.*, 13: 305-315.
- Vickers, E.R., M.J. Cousins and A. Woodhouse, 1998. Pain description and severity of chronic orofacial pain conditions. *Aust. Dent. J.*, 43: 403-409.
- Vijayakumar, T.M., D. Sathyavati, T. Subhashini, S. Grandhi and M.D. Dhanaraju, 2011. Assessment of prescribing trends and rationality of drug prescribing. *Int. J. Pharmacol.*, 7: 140-143.
- Ward, D.E., E.M. Veys, J.M. Bowdler and J. Roma, 1995. Comparison of aceclofenac with diclofenac in the treatment of osteoarthritis. *Clin. Rhematol.*, 14: 656-662.
- Wolfe, M.M., D.R. Lichtenstein and G. Singh, 1999. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N. Engl. J. Med.*, 340: 1888-1899.