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ORIGINAL RESEARCH

Effectiveness of Prophylactic use of Etoricoxib in Comparison with Ibuprofen on Postendodontic Pain-randomized Double-Blind, Placebo-controlled Study: An *in vivo* Study

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ABSTRACT

Aim: To determine if prophylactic etoricoxib significantly reduce postendodontic pain when compared with prophylactic ibuprofen and to establish if any relationship exists between pulpal and periapical diagnosis and the need for additional medication after completion of pulpectomy.

Materials and methods: Sixty patients consented to a double-blind, single-dose oral administration of 120 mg of etoricoxib or ibuprofen 600 mg or placebo before conventional root canal therapy. The patients were discharged with a VAS to fill out the intensity of pain initially first four hours every hour and then in 8, 12, 24, 48, and 72 hours after initial therapy. Each patient was given an escape envelope containing 650 mg of paracetamol in case of continued pain after taking the test medication in question. The patients were instructed to indicate in the VAS form if this additional medication was required and record the time it was taken.

Results: The result of the study showed that etoricoxib provided significantly better pain relief than placebo and ibuprofen. There was no statistically significant difference between placebo and ibuprofen. No difference in drug groups with respect to pulpal and periapical status was observed.

Conclusion: Prophylactic etoricoxib administration provides effective reduction of postendodontic pain. Furthermore, studies are required to know the pulpal and periapical status and need for additional medication.

Keywords: Prophylactic, Etoricoxib, Postoperative, Pain control.

INTRODUCTION

Alleviating pain is of utmost importance when treating dental patients. O'Keefe (1976) showed a significant relationship in endodontic patient between preoperative, operative, and postoperative pain levels. Patients presenting with extreme preoperative discomfort were more likely to have the same degree of discomfort both operatively and postoperatively. However, postoperative pain was more likely to occur in these patients within the first 24 hours period following root canal treatment.[1]

Although pulpectomy eliminates endodontic pain, postoperative pain and discomfort are fairly common side effects of endodontic treatment, a problem for 25 to 40% of all endodontic patients.[2] Many endogenous chemical mediators, particularly prostaglandins, have been associated with inflammation and its related pain.[3] If the inflammatory reaction of the periapical tissue is the major contributor to the post-treatment pain, then the use of a nonsteroidal anti-inflammatory drug (NSAID) may be useful in its management.[4,10]

More recent evidence also demonstrates a significant role for both prostaglandins and cyclooxygenases within the central nervous system, in addition to their role in the peripheral nervous system. Since postoperative pain is a predictable event in most cases, steps should be taken to minimize the pain and discomfort to the patient. NSAIDs inhibit inflammation and induce analgesia by inhibiting the activity of cyclooxygenase enzyme COX. Two forms of COX enzymes have been identified, COX-1 and COX-2. The COX-1 enzymes are present in tissue at all times and responsible for synthesizing prostanoids that have cytoprotective function. COX-1 enzymes regulate normal cell activities in the stomach, kidneys, and platelets. COX-2 enzymes normally are not present in tissue (other than in kidneys) and come into play when tissue injury and inflammation occur.[5]

One such drug commonly used in managing pain in a patient with endodontic origin is ibuprofen.[6-8] Studies using postextraction model have shown preoperative administration of ibuprofen inhibits postoperative pain more effectively than a placebo. Ibuprofen and some of the other NSAIDs have known to inhibit both COX enzymes. The prolonged use of these drugs will cause gastrointestinal tract damage causing gastric erosions, ulcers and bleeding.[5,11]

Drugs which specifically inhibit COX-2 enzymes may provide analgesia, anti-inflammatory and antipyretic activities with long duration of action while avoiding deleterious side effects associated with nonselective COX-1 and COX-2 inhibitors. Newer COX-2 inhibitors have been studied very little for preoperative use. Etoricoxib is a COX-2-specific NSAID having a long duration of action of 24 hrs. It is known to be potent and highly selective COX-2 inhibitor.[5,9]

An important possible advancement in the improvement of postoperative pain was provided by the finding that the central sensitization of intrinsic dorsal neurons seen in animal pain models could be minimized if medications were given before the injury occurs. The reduction of alterations in these neurons that is seen when medications are given before the injury occurs led to the concept of prophylactic analgesia.[10] Even though pre-emptive analgesia has been demonstrated repeatedly in animal models of pain, the clinical evidence that supports the concept of prophylactic analgesia in human pain studies has been more variable.[5,10]

Hence, the purpose of this study was to determine if prophylactic etoricoxib significantly reduces postendodontic pain when compared with prophylactic ibuprofen administration and also to establish if any relationship exists between pulpal and periapical diagnosis and the need for additional medication after completion of pulpectomy.

MATERIALS AND METHODS

This was a single-dose, double-blind study with three randomized parallel treatment groups. Patients who presented to the dental college postgraduate endodontic clinic were evaluated for this study. A diagnosis was determined on the basis of history, clinical and radiological features.

Inclusion Criteria

1. Patient reports spontaneous pain of at least 30 (0-100) in visual analog scale before root canal therapy.
2. Literate patients.

Exclusion Criteria

1. Younger than 18 years or older than 50 years.
2. Analgesic not taken within the last 4 hours prior to the procedure.
3. History of allergy to NSAIDs or local anesthesia.
4. Pregnant or nursing patients.
5. Patients previously medicated with antibiotics or are on antibiotics.
6. History of opioid addiction or abuse.
7. Patients undergoing any type of medical treatment.
8. History of systemic disease.

Preparation of Capsules

Identical gelatin capsules of ibuprofen, lactose and etoricoxib were prepared, stored in separate airtight bottles and named randomly as A, B and C.

If a patient met the above criteria, he/she was informed about the nature of study and invited to participate. Sixty patients signed a consent form outlining the procedure and its possible risk. Patients consented to a double-blind, single-dose oral administration of 120 mg of etoricoxib or 600 mg of ibuprofen or a placebo before conventional root canal therapy. Before administration of any medication, the patients were asked to evaluate their pretreatment pain to determine if any relationship would be found to exist between pretreatment and post-treatment pain. Intensity was measured using a 100 mm visual analog scale. The scale was from 0 to 100, with 0 being "none" and 100 being "pain so severe that cannot be beared".

The root canal treatment was performed in two appointments. The first appointment consisted of cleaning and shaping of the canal using standard aseptic technique. After local anesthesia was achieved under rubber dam access, cavity was prepared and pulp extirpation was done. Cleaning and shaping was conducted utilizing a crown down technique, RC prep was used as a lubricant and 3% sodium hypochloride and saline as irrigants. After access, occlusion was evaluated and reduced if necessary. Then the working length was determined with Root ZX apex locator and was confirmed with intraoral periapical radiographs. The canals were enlarged depending on the size of the canal using protaper endodontic files. After complete cleaning and shaping, the canals were dried and access cavity was closed with a sterile cotton pellet and Cavit G as an intermediate restorative material.

The patients were discharged with a VAS to fill out the intensity of pain initially, thereafter for every hour for the next four hours, and then in 8, 12, 24, 48 and 72 hours after initial therapy. Each patient was given an escape envelope containing 650 mg of paracetamol in case of continued pain after taking the test medication in question. The patients were instructed to indicate in the VAS form if this additional medication was required and record the time it was taken.

RESULTS

In the present study, a total of 60 patients were included. The subjects were divided into three groups: Group A—ibuprofen, group B—placebo and group C—etoricoxib in a randomized manner. Although the patients were randomly assigned into groups, a similarity between groups, in patient demographics, pulpal and periapical diagnosis as well as teeth treated was found (Tables 1 and 2).

Table 1: Distribution of pulpal diagnosis among the three treatment groups

Groups	Number of patients	Normal	Chronic irreversible pulpitis	Acute irreversible pulpitis	Necrosis
A. Ibuprofen	20	0	5	9	6
B. Placebo	20	0	2	14	4
C. Etoricoxib	20	0	5	7	8
$\chi^2 = 5.433$	DF = 4	p = 2.46			

Table 2: Distribution of periradicular diagnosis among the 3 treatment groups

Groups	Number of patients	Normal	Acute apical periodontitis	Chronic apical periodontitis	Acute apical abscess
A. Ibuprofen	20	0	13	2	5
B. Placebo	20	0	17	1	2
C. Etoricoxib	20	1	10	1	8
$\chi^2 = 4.313$		DF = 2		p = 0.116	

GROUP A

Friedman Test

Chi-square = 92.208
df = 9
p = 0.000

Pain reduction from base to end point was statistically significant in ibuprofen group.

Wilcoxon Signed Rank Test

At all point of time it was statistically significant except at 1 to 2 hrs, 1 to 4 hrs, 1 to 8 hrs, 2 to 3 hrs, 2 to 4 hrs, 2 to 8 hrs, 3 to 4 hrs, 3 to 8 hrs, 3 to 8-12 hrs, 3 to 24 hrs, 4 to 8 hrs, 4 to 12 hrs, 4 to 24 hrs, 12 to 24 hrs, 12 to 48 hrs and 24 to 48 hrs.

GROUP B

Friedman Test

Chi-square = 112.079; df = 9; p = 0.000
Pain reduction from base to end point was statistically significant in placebo group.

Wilcoxon Signed Rank Test

At all point of time it was statistically significant except at 1 to 2 hrs, 1 to 3 hrs, 2 to 3 hrs, 4 to 8 hrs, 4 to 12 hrs, 8 to 12 hrs, 12 to 24 hrs, 12 to 48 hrs, 12 to 72 hrs and 24 to 48 hrs.

GROUP C

Friedman Test

Chi-square = 83.810; df = 9; p = 0.000
Pain reduction from base to end point was statistically significant in etoricoxib group.

Wilcoxon Signed Rank Test

At all point of time it was statistically significant except at 1 to 2 hrs, 1 to 3 hrs, 1 to 4 hrs, 1 to 8 hrs, 1 to 12 hrs, 1 to 24 hrs, 1 to 48 hrs, 2 to 3 hrs, 2 to 4 hrs, 2 to 8 hrs, 2 to 12 hrs, 2 to 24 hrs, 2 to 48 hrs, 3 to 4 hrs, 3 to 8 hrs, 3 to 12 hrs, 3 to 24 hrs, 3 to 48 hrs, 3 to 72 hrs, 4 to 8 hrs, 4 to 12 hrs, 4 to 24 hrs, 8 to 12 hrs, 8 to 24 hrs, 8 to 48 hrs, 12 to 24 hrs, 12 to 48 hrs, 12 to 72 hrs, 24 to 48 hrs, 24 to 72 hrs, 48 to 72 hrs.

All the drugs are equally effective in reducing the pain from base line to end point. Differences between drugs were tested at each time point by means of the Kruskal-Wallis one-way ANOVA, and the Mann-Whitney test was used to show where any significant difference was present.

Comparison of Drugs

Until the first 4 hour, etoricoxib provided significantly better pain relief than placebo or ibuprofen. There was no statistically significant difference between placebo and ibuprofen. After the 4th hour, etoricoxib was more effective in reducing pain than placebo or ibuprofen but was not significantly different.

Median pain VAS scores were plotted in relation to time after administration of drugs (Fig. 1).

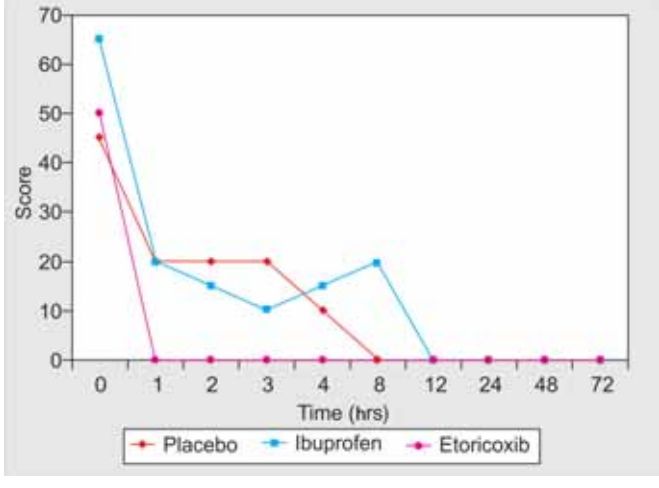

Fig. 1: Median VAS score

Table 3: Diagnosis and additional medication required

Diagnosis	Chronic irreversible pulpitis		Acute irreversible pulpitis		Necrosis	
Pulpal	12	Tablets taken 3 (25%)	30	Tablets taken 7 (23.3%)	18	Tablets taken 5 (27.7%)
	Acute apical periodontitis		Chronic apical periodontitis		Acute abscess	
Periapical	40	Tablets taken 11 (20%)	4	Tablets taken 1 (20%)	15	Tablets taken 3 (20%)

Forty-two reported with pulpitis and 10 required additional medications. Eighteen reported pulpal necrosis and five required additional medications. One patient presented normal periapex and none required additional medication for postendodontic pain. Forty-four patients presented apical periodontitis and 15 needed additional medication. Fifteen presented acute apical abscess and three required additional medication.

There was no statistical significant difference with respect to pulpal and periapical status and need for additional medications (Table 3).

DISCUSSION

Reduction in postendodontic pain after prophylactic administration of NSAIDs has been proved both in oral surgery models[6] and endodontic models.[1,7] Prophylactic administration of NSAIDs before conventional root canal therapy can block the COX pathway and might block the pain sensation before it begins. COX catalyzes the conversion of arachidonic acid to prostaglandins. Prostaglandins represent one of the key chemicals involved in the sensitization of peripheral nociceptors, thereby contributing both to the development of primary hyperalgesia and subsequently to secondary hyperalgesia.[5]

Ibuprofen blocks both COX-1 and COX-2 enzymes, it is a safe, cost-effective with analgesic and anti-inflammatory action. In this study, ibuprofen showed lower pain rating at 1, 2, and 3 hours postoperatively when compared with the placebo but was not statistically significant. This may be for two reasons. First, preoperative ibuprofen was administered half an hour before the start of endodontic therapy and the endodontic therapy went for an average of 100 mins. Pain analysis was started 1 hr after therapy, which was nearly 3 hrs after the administration of the drug. The metabolic half-life of ibuprofen is approximately 2 hours, hence the effective action of the drug is between 4 to 6 hours postadministration.[11]

Second, the action of 2% lidocaine with epinephrine 1:1, 00,000 in the soft tissue is 3 to 4 hrs (Malamide 1986). This may be the reason why placebo group and ibuprofen group had the same pain intensity 3 hrs postoperatively. Similar to this study, Dionne in 1983 compared 800 mg ibuprofen preoperatively and 400 mg of ibuprofen 4 and 8 hrs postoperatively *vs* control group who received either preoperative placebo or postoperative 600 mg of paracetamol with 60 mg codeine or preoperative paracetamol. The ibuprofen group had significantly less pain than either of the control groups. In this study of 107 patients, he concluded that pretreatment with ibuprofen resulted in suppression of postoperative pain when compared with standard therapy without an increase in side effects.[6]

At 4, 8, 12, 24, and 48 hrs, pain rating for ibuprofen was more than placebo group. This could be attributed to the significantly more baseline pain for ibuprofen group than placebo group. This increase in baseline pain for ibuprofen was purely by chance because subjects were administered study drugs in a randomized fashion.

Etoricoxib has been proven to be a highly specific COX-2 inhibitor and COX-2 agents have the advantage of attaining and maintaining therapeutic blood levels rapidly with one or two doses daily. It seems more prudent to administer a drug that will selectively block inflammatory prostanoids that produce pain and inflammation while not interrupting production of cytoprotective prostanoids.[5,15] This study found that prophylactic administration of 120 mg of etoricoxib before root canal therapy was significantly effective than placebo or ibuprofen in reducing postendodontic pain at 1, 2 and 3 hrs postoperatively. At 4, 8, 12 and 24 hrs, the pain reduction was more than placebo or ibuprofen group but was not statistically significant. The result of this study is similar to the study conducted by Gopikrishna in 2003. In his study, the author compared the prophylactic use of Rofecoxib (COX-2 inhibitor) in comparison with ibuprofen on postendodontic pain. He concluded that prophylactic Rofecoxib administration provided effective reduction of postendodontic pain compared with ibuprofen.[7] Similarly, Malstrom K et al studied the analgesic effect of single oral doses of 60, 120, 180, and 240 mg of etoricoxib compared with placebo in the treatment of pain after dental surgery. Ibuprofen was used as an active control. They concluded that 120 mg of etoricoxib was effective in reducing pain in patients with moderate to severe acute pain associated with dental surgery.[12]

After 48 hrs, all the groups showed pain reduction. The significant pain relief at 48 hrs in all groups may be because of pulpectomy alone, whether they received an analgesic or not.[13]

In addition, the technique used to instrument the root canal may be a factor contributing to this result. All cases were done with crown down technique using rotary protaper files. This technique produced less extrusion of necrotic debris during instrumentation and with less extrusion of debris there is less periapical inflammation and hence decrease postoperative pain.[14] This could explain the similarities in pain intensity and relief in all groups. These results strongly suggest that definitive treatment (pulpectomy) allowed for an adequate reduction in pain intensity by 48 hrs after therapy.[13]

The other objective of this study was to establish if any relationship exists between pulpal and periapical diagnosis and need for additional medication after completion of pulpectomy. Of the sixty patients analyzed, one presented with normal periapex, four presented with chronic apical periodontitis. All these clinical entities were not painful on percussion, of these five patients, only one required additional medication for postoperative pain.

The periapical status of the remaining 55 patients of this study was diagnosed as acute apical periodontitis and acute apical abscess characterized by pain on percussion. Of these 55, 14 required additional medication to reduce postoperative endodontic pain. This study also found that significant difference did not exist for the type of pulpal and periapical diagnosis and the need for additional medication after completion of root canal therapy. No difference in drug groups with respect to the pulpal and periapical status was noted.

These findings were in concurrence with study of Gopikrishna, Parameswaran and Jackson et al.[7,10] They found that prophylactic administration of COX-2 inhibitors to patients with severe preoperative pain reduced postoperative pain. It was also found that an association was found between the intensity of pre and postoperative pain, as the intensity of preoperative pain increased, the chances for more severe postoperative pain increased.[16,8]

CONCLUSION

Within the limitations of this *in vivo* study, it is concluded that etoricoxib provided significantly better pain relief than placebo and ibuprofen. There was no statistically significant difference between placebo and ibuprofen.

This study also found that significant difference did not exist for the type of pulpal and periapical diagnosis and the need for additional medication after completion of root canal therapy. No difference in drug groups with respect to pulpal and periapical status was observed.

REFERENCES

1. Menhinick KA, Gutmann JL, Regan JD, Taylor SE, Buschang PH. The efficacy of pain control following nonsurgical root canal treatment using ibuprofen or a combination of ibuprofen and acetaminophen in a randomized double-blind study. Int Endo Journal, Aug 2004;37:531-41.
2. Krasner P, Jackson E. Management of post-treatment endodontic patients with oral dexamethasone: A double-blind study. Oral Surg Oral Med Oral Pathol 1986;62:187-90.
3. Laurence DR, Bennett PN. Clinical pharmacology (6th ed), UK, Churchill Livingstone 1987;279.
4. Negm MM, Cairo. Effect of intracanal use of nonsteroidal anti-inflammatory agents on post-endodontic pain. Oral Surg Oral Med Oral Pathol 1994;77(5):507-12.
5. Crofford LJ. Cox-1 and Cox-2 tissue expression implication and predictions. J Rhenmatol 1997;24(Suppl 49):15-19.
6. Dionne RA, Canpbell RA, Coooper SA, Hall DL, Buchinghan B. Suppression of postoperative pain by the preoperative administration of ibuprofen in comparison to placebo, acetaminophen and acetaminophen plus codeine. J of Pharmacol 1983;23:37-43.
7. Gopikrishna V, Parameshwaran A. Effectiveness of prophylactic use of rofecoxib in comparison with ibuprofen on post endodontic pain. J of Endodo 2003;29(1):62-64.
8. Collins SL, Moore RA, McQuay HJ, Wiffen PJ, Edwards JE. Single dose oral ibuprofen and diclofenac for postoperative pain. Cochrane Database Syst Rev 2000;2:CD001548.
9. Khan Asma A, Dionne Raymond A. The Cox-2 inhibitor: New analgesic and anti-inflammatory drugs DCNA. 2002;46:679-90.
10. Jackson DL, Moore PA, Hargreaves KM. Preoperative nonsteroidal anti-inflammatory medication for the prevention of postoperative dental pain. J Am Dent Assoc 1989;119(5): 641-47.
11. Tripathi KD. Essential of medical pharmacology (5th ed), New Delhi, Jaypee Publishers 2003;177.
12. Etoricoxib in acute pain associated with dental surgery: A randomized, double-blind, placebo and active comparator-controlled dose-ranging study. Clin Ther 2004;26(5):667-79.
13. Oguntebi BR, Deschepper EJ, Taylor TJ, White CL, Pink FE. Postoperative pain incidence related to the type of emergency treatment of symptomatic pulpitis. Oral Surg, Oral Med, Oral Path.
14. Peters Ove E, Koka Ravi S. Preparation of coronal and radicular space. In: Ingle John I, Bakland Leif K, Baumgartner J Craig. Endodontics (6th ed). Hamilton: BC Deker Inc 2008;939.
15. Misra Debasish. Review on etoricoxib. Indian J of Clinical Practice 2005;15(12).
16. Michael SG, Michael HA, Denver, Colo. Preoperative nonsteroidal anti-inflammatory agents review of literature. Oral Surg Oral Med Oral Pathol Oral Radio and Endo 2004; 98(2):146-52.