Analgesic Effect of Etoricoxib Compared to Ibuprofen on Post Endodontic Pain

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Abstract

Aims: Etoricoxib is a second-generation selective COX-2 inhibitor. There are a few researches investigating analgesic effect of Etoricoxib in dentistry.

Methods: This randomized, double-blind, active-control study included sixty patients with clinical pulpal diagnosis of necrosis of the first mandibular molar and an associated periapical radiolucency who experienced severe pain (more than 60 out of 100 in scale of Visual Analog Scale (VAS). The patients were equally randomized into four groups, who received 60 mg etoricoxib (group 1), 90 mg etoricoxib (group 2), 120 mg etoricoxib (group 3), and 400 mg ibuprofen (group 4). All patients randomly received a single dose of the drug after the first session of the root canal therapy. Using VAS, the severity of pain was recorded 2, 4, 6, 12, 24, 48, and 72 hours after the drug was administered.

Results: Changing trends of pain over the time was significant for all groups (P=0.003). In addition, there was not a significant difference between various study arms (P=0.146).

Conclusion: The results showed that ibuprofen had a comparable effect with various dosage of etoricoxib and may remain as the choice analgesic for dental pulpal pain..

Key Words: Analgesic, Etoricoxib, Ibuprofen, Pain, Dentistry

Introduction

Agents such as non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase (COX)-2–selective inhibitors, and opioids are available for the treatment of acute pain [1]. Patients with acute dental pain often require analgesic therapy for a short period of time, usually 2 to 4 days [2,3]. Non-selective NSAIDs deliver anti-inflammatory and analgesic effects through inhibition of the COX-1 and COX-2 isozymes [1]. After long-term use, non-selective NSAIDs increase the risk of developing peptic ulcer disease, GI bleeding and renal toxicity [4]. The primary purported safety advantages of COX-2 inhibitors over non-selective NSAIDs are related to their theoretical lack of associated gastropathy [2-6].

It is well established that non-selective NSAIDs impair platelet function by blocking thromboxane A_2 biosynthesis [6-11]. Non-selective NSAIDs also block the synthesis of prostacyclin, but the net effect of these events is a relatively weak inhibition of platelet function in the great majority of patients [12]. Studies of COX-2–selective inhibitors such as rofecoxib and celecoxib have demonstrated efficacy in the treatment of acute pain [13-15]. The analgesic benefit of these agents within the therapeutic range is attributable mainly to their inhibition of COX-2 without affecting COX-1.

As high as 80% of referral patients with preoperative pain, experience pain after endodontic treatment. About one-fifth of patients report moderate to severe pain after endodontic therapies. It is not uncommon that a patient avoids attending a dental office because of previous annoying experience of post-op pain. Hence, a deep and long standing analgesia after orodental procedure is necessary [16,17].

In addition to the pulpal disease type, gender, pre-operative pain, anxiety, previous painful experience of endodontic treatment, and procedural errors affect the degree of post operative pain [18-20].

Regarding orodental surgeries, various methods including nitrous oxide inhalation, intra nasal sniffing and sublingual administration of analgesics in addition to oral prescription of various combinations and dosages are investigated to enhance the analgesia [21-23].

Etoricoxib is a methylsulfyl second generation coxib. It has a considerable half-life of 22 hours with remarkable COX2/COX1 inhibition ratio of 106 as compared to 7, 1.78, 3.12 and 1.78 for celecoxib, ibuprofen, aspirin and indomethacin, respectively. It is a good substitute for intolerant patients to non-selective NSAIDs with long lasting duration, comparable renal effects and the lower chance of gastrointestinal upset; hence it may be an acceptable alternative for whom ibuprofen is contraindicated [2].

A few studies exist in the literature which assessed the analgesic effect of etoricoxib for pulpal pain. The aim of this study was to compare the analgesic efficacy of different doses of etoricoxib with the efficacy of ibuprofen, the choice drug, in the treatment of patients with post endodontic pain.

Materials and Methods

Patients selection

This randomized, double-blind, active-control, parallel-group study was done from October 2008 to October 2009. Sixty patients were included who were 18 to 65 years old. Patients had a clinical pulpal diagnosis of necrosis of first mandibular molar and an associated periapical radiolucency

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who experienced severe pain (more than 60 out of 100 in scale of Visual Analog Scale (VAS)). They had been referred to the endodontic department of Babol University of Medical Sciences. Exclusion criteria were systemic diseases, allergic reactions to NSAIDs, pregnant or lactating women and the use of an analgesic 12 hours prior to the intervention. This study was approved by the ethics committee of Babol University, and all study patients had been fully informed and had provided written consent for the study procedure and its design.

Interventions, measures, randomization, masking

Patients were randomly distributed into four groups. Group 1 received 60 mg of etoricoxib, group 2 received 90 mg of etoricoxib, group 3 received 120 mg of etoricoxib, and group 4 received 400 mg of ibuprofen. Up to 60% of patients with clinical diagnosis of pulpal necrosis may experience severe pain during the first day after the endodontic treatment [24]. Hence the study was ethically approved to be an active-control clinical trial and not to be as a placebo-control one. Blinding was done in double levels (patients, observer and biostatistician), and all drugs were prepared in identical gelatin capsules by the department of pharmacology. Before the root canal treatment had been applied, all patients received lidocaine (2%) and epinephrine (1:80000) for local anesthesia receiving inferior alveolar nerve block, pulpal and periodontal ligament injection with the same dose. All procedures were performed by a single clinician (ZSM) using rotary instrument with the same preparation, cleaning and shaping techniques. All root canals were prepared with Nickel-Titanium protaper rotary instruments, (Dentsply Maillefer) by using X-Smart motor (Dentsply Maillefer) with a 16:1 contra angle. The S1, S2, F1, F2 protaper rotary instruments were used at 250 rpm with the single length technique according to manufactures instruction. After using each instrument canals were irrigated with 2 ml of 5% Naocl solution.

All patients randomly received a single dose of the drug after the first session of the root canal therapy (i.e, all patients underwent 2-visit root canal therapy). The severity of pain was recorded at 2, 4, 6, 12, 24, 48, and 72 hours after the drugs were administered using the Visual Analog Scale (0 = no pain and 10 = highest intolerable pain). Patients were asked to report side effects including severe nausea, vomiting, light-headedness or any unexpected status that could be related to the medication. The randomization was performed via a computer generated list and an external clinician from the ethics committee was in charge to assure the randomization and to monitor the safety of the trial.

Statistics

We estimated that 15 patients would be required to achieve 80% power for a standardized difference of 1.4 between the ibuprofen group and 60 mg etoricoxib in the rate of pain relief recommended by an expert (using Altman's nomogram). Continuous data were expressed as mean (standard deviation). Age and mean alleviation of pain severity calculated for differences between 2 and 72 hours were compared between study groups by means of Analysis of Variance (ANOVA) test applying Levene statistic to test the homogeneity of data. To trace the changing trends of pain, a General Linear Model (GLM) repeated measure ANOVA was built. Sphericity (One of ANOVA presumption) was tested with a Mauchly' test. In the case of violation, data were adjusted with an Epsilon Greenhouse-Geisser statistic. In addition, for Post-hoc multiple, a Bonferroni test was utilized. We used the chi-square test to compare the percent of pain relief between the studied groups.

Results

There were 37 (61.7%) male and 23 (37.3%) male and female patients. Mean age of participants was 25.66 (7.98) years, which was not significantly differed among various study arms ($F(3,59)=0.729$, $P=0.54$). A significant changing trend for pain relief was observed for all groups during 2-72 hours after the first appointment of root canal therapy ($F(2.81, 157.61)=5.014$, $P=0.0003$, observed power= 0.897). These changes were not contrasted by various study arms ($F(8.44, 157.61)=1.53$, $P=0.146$). There were no remarkable differences observed in two-by-two comparisons ($P>0.05$). Moreover, mean degrees for alleviation of pain severity for etoricoxib 60 mg, 90 mg, 120 mg and ibuprofen 400 mg groups were 0.73 (± 2.15), 0.33 (± 1.39), 1.46 (± 2.09) and 1.93 (± 4.06), respectively. However, a non-significant difference existed between these groups ($F(3, 59) =2.13$, $P=0.11$).

Figure 1 shows that the mean pain severity score (according to the VAS) in the ibuprofen group was 2.8 at 2 hours after treatment, and then it decreased by 66.8% at 72 hours after treatment. The high dose (120 mg) etoricoxib group had a mean pain severity score of 2.5 at 2 hours

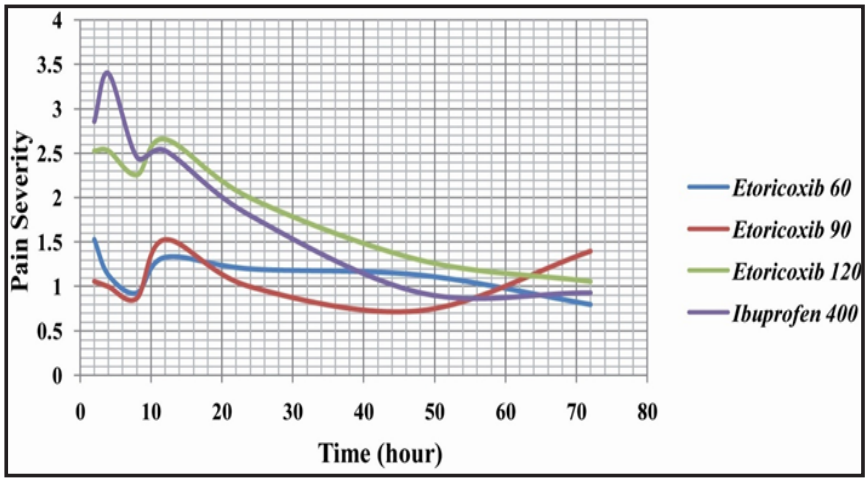

Figure 1. *Changing Trends of Reported Pain Severity in Scale of Visual Analogue Scale (VAS) Displayed for Various Study Arms during 2-72 Hours after Administration of Medications.*

after treatment, which decreased by 59% at 72 hours after treatment. The mean pain severity score of the moderate dose (90 mg) etoricoxib group was 1 at 2 hours after treatment but increased by 49.1% at 72 hours after treatment (this increase was not statistically significant). The mean pain severity score of the low dose (60 mg) etoricoxib group was 1.5 at 2 hours after treatment and decreased by 47% at 72 hours after treatment. Forty-eight hours after receiving medication, pain severity scores were reduced by 67.4%, 55.2%, 31.2% and 26% in the ibuprofen group, high dose (120 mg) etoricoxib group, the moderate dose (90 mg) etoricoxib group and the low dose (60 mg) etoricoxib group, respectively; meanwhile there was no significant difference between groups ($p>0.05$).

Age did not have influence effect neither on mean difference of pain severity for 2-72 hours ($P=0.73$) nor on changing trends of reported pain severity during the study ($F (2.79, 153.69) =0.33$, $P=0.79$), however female patients reported higher pain relief (1.84 (± 0.55)) as compared to male patients (0.40 (± 0.44), $P=0.048$)). Also, gender affected the overall changing trends of reported pain during the study ($F (6,162.97)=2.72$, $P=0.013$, Power=0.87) (*Figure 2*).

All patients tolerated the medications and no remarkable side effect was reported.

Discussion

The results showed that ibuprofen was effective as etoricoxib to alleviate post-endodontic pain. In addition, patients tolerated the analgesics well. Ibuprofen is the prototypical NSAID and currently is considered as the choice drug for post-endodontic pain. Overly, in the absence of particular contraindication, NSAIDs are considered as the drug of choice for treating acute dental pain in ambulatory patients who generally experience a higher incidence of adverse effects after taking opioids analgesics [16]. Many studies have investigated the efficacy of COX-2 inhibitors for the treatment of surgically induced dental pain failed to show any clear therapeutic advantage over ibuprofen [4,25,26]. It is reported that a single dose of 400 mg oral celecoxib mg), as a selective COX-2 inhibitor, had similar efficacy for postoperative pain relief compared to 400 mg ibuprofen [27]. In another study, it has been showed that ibuprofen was as effective as rofecoxib for the relief of acute postoperative pain following third molar surgery when used preemptively [28].

However, in many studies, NSAIDs (selective or non-selective) were better than other analgesics including opioids [29,30]. It is demonstrated that the overall analgesic efficacy over 6 hours of a single dose of etoricoxib (120 mg) was superior to that with a single dose of oxycodone/acetaminophen (10/650 mg) in the treatment of acute postsurgical dental pain. Etoricoxib had a rapid onset of action, and it has a peak analgesic effect similar to that of oxycodone/acetaminophen but with a longer duration. The administration of etoricoxib reduced the need for rescue opioid analgesia compared with the administration of oxycodone/acetaminophen [31].

Previously sex predilection for presentation of painful disorders is been stipulated. The female patients in the present research reported higher pain severity (3(± 3.23)) compared to male participants (1.37(± 1.8)) in the second hour from the onset till the completion of the clinical trial. This may rationale the sex-dependent manner of pain relief and total pain relief over the study period. It is assumed that estrogen may interact with several neuroactive agents involved in inflammatory process. Also, brain response to such stimulants is different in female and male individuals. In addition, perception of pain may be age-dependent, however our study failed to show such predilection [20]. This is primarily due to the almost same mean age of participants in various trial groups

The higher the pre-endodontic pain, the higher the post-endodontic pain [18] Accordingly, patients who reported more than 60 out 100 in scale of VAS were enrolled in the present study, hence post-endodontic pain is adjusted for pre-endodontic pain as a confounding factor. However the exact value is not displayed, as these values are not precisely available at this time.

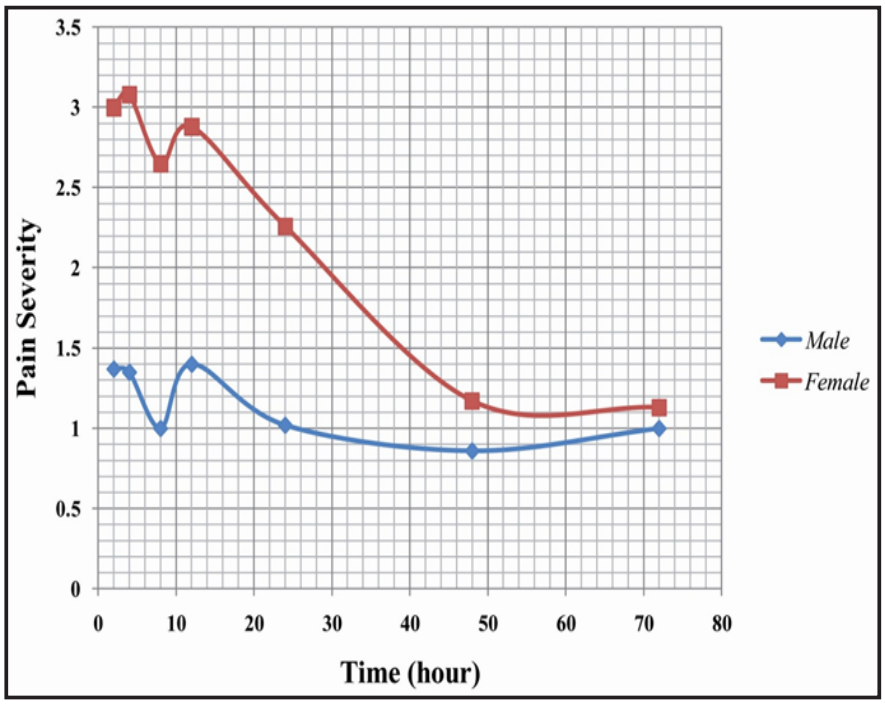

Figure 2. *Sex-dependent Changing trend of Reported Pain Severity in Scale of Visual Analogue Scale (VAS).*

Surprisingly, patients of all group reported increased pain during 6-12 hours which indicates need for additional and escape medication. There was also an insignificant increase of pain severity in 90 mg etoricoxib group for which we did not find a reasonable explanation. This particular phenomenon needs further research.

Our study had some limitations. First, by most recent Cochrane systematic review of randomized clinical trials of preoperative single oral dose of analgesic, 120 mg of Etoricoxib is recommended [32]. Preemptive analgesia would better decrease post operative pain and may inhibit release and expression of inhibitory cytokines more efficiently as compared to post operative prescription of analgesia as we conducted in our research. The preemptive method could also diminish peripheral sensitization as well as central sensitization. However, we believe that in particular cases of pulpal necrosis with radicular cyst formation the disease is in its advanced stage with established cytokine release and peripheral sensitization that pre-emptive vs. post-op prescription of analgesics had lower differential effect when compared to progressing pulpal inflammation in irreversible pulpitis, for which instrumentation can cause more profound release of cytokines. It is stipulated that time for remidication is a reliable tool to assess the efficiency of analgesia. This factor and escape medication were not recorded in present research. As the second limitation, total pain relief (TOTPAR) was not recorded and calculated. Third, low sample size with low achieved power indicate that a large scale study may better elucidate the discernible pattern of analgesia for various medications and dosages. Also, we did not record 0 to 6 hour pain intensity in an hourly manner (i.e., 2, 4, and 6 hour pain intensity was recorded), hence a summed pain intensity difference over six our (SPID6) could not be desirably calculated and taken into account. We did not include a placebo-control arm according to considerable pain after endodontic treatment of necrotic teeth. Gradual and spontaneous relief of pain would inevitably happen, although this was masked by drug prescription. Future research with focus on inflammatory cytokines in rats including placebo arm would be helpful.

There is a controversial body of evidence regarding the effect of NSAIDS on mesencymal differentiation and wound healing. A COX-independent mechanism of action also introdrodcued via suppression of inducible form of nitric oxide synthase (i-NOS II), which is responsible for bone destruction [16]. Further studies are recommended including assessing the gingival crevicular fluid and root canal aspirate content of inflammatory cytokines during remedial sessions. Indeed experimental animal studies with radicular lesion may better reveal the effect of selective and non-selective NSAIDs on bone resroption and healing. Moreover, comparing with dual acting lipoxygenase/COX inhibitors such as tepoxalin and tebufelone [16] is suggested in terms of analgesic, anti inflammatory and bone healing properties.

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References

1. Abramson SB, Weissman G. The mechanisms of action of nonsteroidal anti inflammatory drugs. *Arthritis & Rheumatism* 1989; **32**: 1–9.

2. Cicconetti A, Bartoli A, Ripari F, Ripari A. COX-2 selective inhibitors: a literature review of analgesic efficacy and safety in oral-maxillofacial surgery. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology* 2004; **97**: 139–146.

3. Jeske AH. Selecting new drugs for pain control: evidence-based decision or clinical impressions? *Journal of American Dental Association* 2002; **133**: 1052–1056.

4. Moore PA, Hersh EV. Celecoxib and rofecoxib: the role of COX-2 inhibitors in dental practice. *Journal of American Dental Association* 2001; **132**: 451–456.

5. May N, Epstein J, Osborne B. Selective COX-2 inhibitors: a review of their therapeutic potential and safety in dentistry. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology* 2001; **92**: 399–405.

6. Raskin JB. Gastrointestinal effects of nonsteroidal anti-inflammatory therapy. *American Journal of Medicine* 1999; **106**: 3–12.

7. Chandrasekharan NV, Simmons DL. The cyclooxygenases. *Genome Biology* 2004; **5**: 241.

8. FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *New England Journal of Medicine* 2001; **345**: 433–442.

9. Linton MF, Fazio S. Cyclooxygenase-2 and inflammation in atherosclerosis. *Current Opinion in Pharmacology* 2004; **4**: 116–123.

10. Simon LS. Role and regulation of cyclooxygenase-2 during inflammation. *American Journal of Medicine* 1999; **106**: 37–42.

11. Lipsky PE. The clinical potential of cyclooxygenase-2-specific inhibitors. *American Journal of Medicine* 1999; **106**: 51–57.

12. Schafer AI. Effects of nonsteroidal anti-inflammatory therapy on platelets. *American Journal of Medicine* 1999; **106**: 25–36.

13. Morrison BW, Christensen S, Yuan W, et al. Analgesic efficacy of the cyclooxygenase-2–specific inhibitor rofecoxib in post–dental surgery pain: A randomized, controlled trial. *Clinical Therapeutics* 1999; **21**: 943–953.

14. Chang DJ, Desjardins PJ, Chen E et al. Comparison of the analgesic efficacy of rofecoxib and enteric-coated diclofenac sodium in the treatment of postoperative dental pain: A randomized, placebo-controlled clinical trial. *Clinical Therapeutics* 2002; **24**: 490–503.

15. Clemett D, Goa KL. Celecoxib: A review of its use in osteoarthritis, rheumatoid arthritis and acute pain. *Drugs* 2000; **59**: 957–980.

16. Khan AA, Dionne RA. COX-2 inhibitors for endodontic pain. *Endodontic Topics* 2002; **3**: 31-40.

17. Mohammadi Z, Farhad A, Khalesi M. Pharmacologic Strategies to control Post-operative Endodontic Pain. *Dental Research Journal* 2007; **4**: 61-68.

18. Genet JM, Hart AA, Wesselink PR, Thoden V. Preoperative and operative factors associated with pain after the first endodontic visit. *International Endodontics Journal* 1987; **20**: 53-54.

19. Van Wijik AJ, Hoogstraten J. Reducing fear of pain associated with endodontic therapy. *International Endodontics Journal* 2006; **39**: 384-388.

20. Doa T. Sex Differences in pain. *Journal of the American Dental Association* 2012; **143**: 764-765.

21. Turner CL, Eggleston GW, Lunos S, Johnson N, Wiedmann

TS, Bowles WR. Sniffing out endodontic pain: use of an intranasal analgesic in a randomized clinical trial. *Journal of Endodontics* 2011; **37**: 439-444.

22. Stanley W, Drum M, Nusstein J, Reader A, Beck M. Effect of nitrous oxide on the efficacy of the inferior alveolar nerve block in patients with symptomatic irreversible pulpitis. *Journal of Endodontics* 2012; **38**: 565-569.

23. Trindade PAK, Giglio FPM, Colombini-Ishikiriama BL, et al. Comparison of oral versus sublingual piroxicam during postoperative pain. *International Journal of Oral and Maxillofacial Surgery* 2011; **40**: 292-297.

24. Nist E, Reader A, Beck M. Effect of apical trephination on post operative pain and swelling in symptomatic necrotic teeth. *Journal of Endodontics* 2011; **27**: 415-420.

25. Dionne RA, Berthold CW. Therapeutic uses of non-steroidal anti-inflammatory drugs in dentistry. *Critical Reviews in Oral Biology & Medicine* 2001; **12**: 315–330.

26. Zelenakas K, Fricke JR Jr, Jaywardene S, Kellstein D. Analgesic effect of single oral doses of lumiracoxib and ibuprofen in patients with postoperative dental pain. *International Journal of Clinical Practice* 2004; **58**: 251–256.

27. Derry S, Barden J, McQuay HJ, Moore RA. Single dose oral celecoxib for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2008; **4**: CD004233.

28. Morse Z, Tump A, Kevelham E. Ibuprofen as a pre-emptive analgesic is as effective as rofecoxib for mandibular third molar surgery. Odontology 2006; **94**: 59-63.

29. Squires DJ, Masson EL. A double blind comparison f ibuprofen, ASA-codeine-caffeine compound and placebo in the treatment of dental surgery pain. *Journal of International Medical Research* 1981; **9**: 257-260.

30. Modaresi J, Dianat O, Mozayeni MA. The efficacy comparison of ibuprofen, acetaminophen-codeine, and placebo premedication therapy on the depth of anesthesia during treatment of inflamed teeth. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology* 2006; **102**: 399-403.

31. Chang DJ, Desjardins PJ, King TR, Erb T, Geba GP. The Analgesic Efficacy of Etoricoxib Compared with Oxycodone/Acetaminophen in an Acute Postoperative Pain Model: A Randomized, Double-Blind Clinical Trial. *Anesthesia & Analgesia* 2004; **99**: 807-815.

32. Clarke R, Derry S, Moore RA. Single dose oral etoricoxib for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2012; **4**: CD004309.