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Evaluation of Meloxicam (A Cox-2 Inhibitor) for Management of Postoperative Endodontic Pain: A Double-blind Placebo-controlled Study

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Successful management of endodontic pain represents a continuing challenge. The purpose of this randomized, double-blind, placebo-controlled, parallel-group trial was to compare the pain reducing effect of oral preparations of meloxicam, piroxicam, and placebo in endodontic emergency patients. A total of 51 patients who presented to the Tehran University endodontic clinic and one private dental clinic were invited to participate. Patients were asked to evaluate their pretreatment pain with a visual-analog scale. After root canal therapy they were randomly assigned to one of three groups: meloxicam, piroxicam, or placebo. Each patient was sent home with a visual-analog scale to fill out at 8 and 24 h after completion of therapy. The results of this study showed no significant differences between efficacy of meloxicam, piroxicam, and placebo, but a significant effect of the time factor in reducing postoperative pain in all treatment groups was observed.

Postoperative pain after root canal therapy is of concern for endodontists, dental staff, and patients. Posttreatment pain in endodontics has been reported to occur in 25% to 40% of all endodontic patients (1). Most investigators have found that there is a strong relationship between preoperative and postoperative pain (2–4). Irritation of periradicular tissues during root canal therapy causes an acute inflammatory reaction and its consequences, such as pain and/or swelling (5). Many endogenous chemical mediators, particularly prostaglandins, have been associated with inflammation and its related pain (6).

Prostaglandins (PGs), mainly of the E series (PGE_2), have been linked to several aspects of the inflammatory process, including vascular dilation, vascular stasis, bone resorption, and pain (7). Prostaglandins are a family of lipids derived from arachidonic acid that are enzymatically released from cell membrane phospholipids (6).

Cyclooxygenase (COX) is the first enzyme along the pathway in which arachidonic acid is converted to prostacyclin and PGs. It is now clear that it exists in at least two distinct isoforms: a largely constitutive form termed COX-1 and a largely inducible isoform termed COX-2, which has been associated with the production of inflammation and pain (8, 9).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed analgesics in endodontics. Their therapeutic benefits and their toxicity are attributable to inhibition of PG synthesis; thus they have been regarded as a double-edged sword (9). The discovery of a second isoform (COX-2), being the primary isoform at sites of inflammation, led to suggestions that inhibition of this isoform accounts for the therapeutic benefits of NSAIDs, whereas inhibition of COX-1 results in their shared adverse effects (9). Therefore, selective nonsteroidal COX-2 inhibitors retained anti-inflammatory action, but minimized the harmful side effects of these drugs (8).

Nonetheless, meloxicam is actually one of the most commonly used COX-2 inhibitors in the world. Endodontic literature is replete with investigation on these selective COX-2 inhibitors. The purpose of this study was to compare the effectiveness of meloxicam—a relative selective COX-2 inhibitor—with piroxicam and placebo in controlling posttreatment endodontic pain.

MATERIALS AND METHODS

The subjects were selected from emergency patients presenting to the Dental School of Tehran University and one private dental clinic. Patients were examined at entry for the etiology of their pain. If pain originated from a posterior tooth with no regard to pulpal status or periapical pathosis, patients were screened according to the degree of their baseline pain, which was determined with the use of a visual analog scale (VAS). The VAS (3) consisted of a line of 9-cm length with 0 (0 cm) signifying no pain and 9 cm representing the worst pain imaginable. Patients were asked to mark a score on the line to indicate the most severe pain they had experienced in past 24 h. If a mark was placed at the 5 cm or above level they participated in the study. A complete medical history of all patients was taken. Only those patients who had no significant medical problems (ASA class I) and met the following criteria were considered for the study: (a) over the age of 15 yr; (b) patient

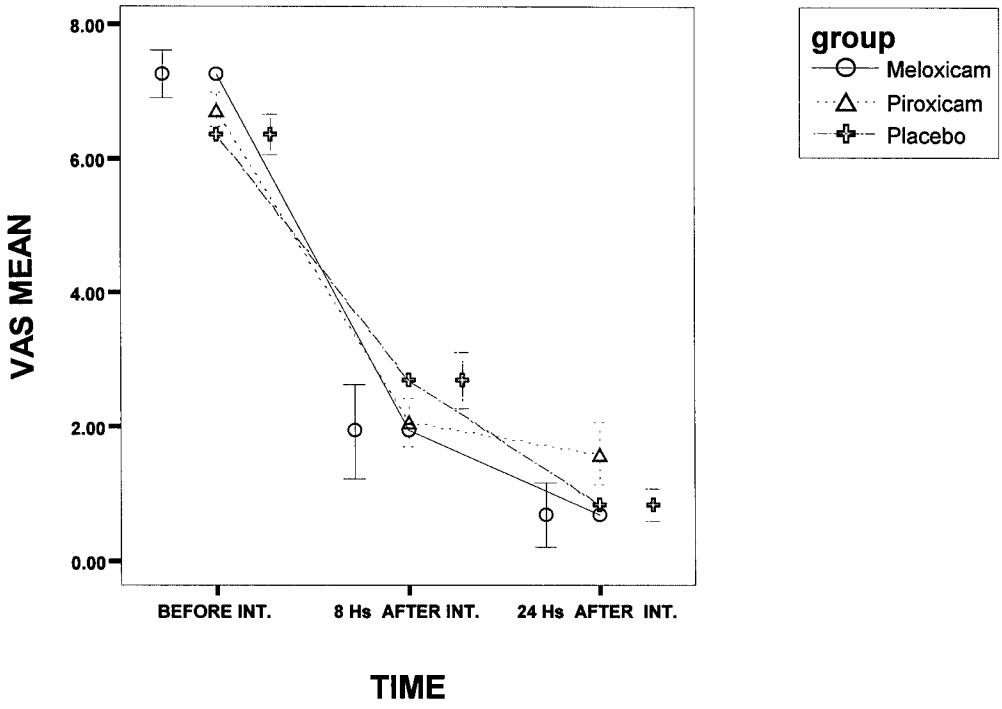

FIG 1. Pain of patients during F/U in different experimental groups.

was able to read and understand VAS; (c) patient provided informed consent. Patients were excluded if they fell into any of the following categories: (a) teeth had had previous endodontic treatment; (b) analgesic ingestion within the last 4 h; (c) history of any allergic reaction to NSAIDs; (d) history of peptic ulcers or GI bleeding; (e) history of renal or hepatic disease; (f) hemorrhagic disorders; (g) pregnancy and lactation; (h) currently taking anti-inflammatory agents, anticoagulants, diuretics, oral antidiabetics, lithium, cyclosporine, and methotrexate; (i) using intrauterine contraceptive device.

The investigation was a randomized, double-blind, placebo-controlled study. Each tablet of meloxicam (15 mg, Bohringer Ingelheim Pharms, Germany) and contents of two piroxicam capsules ($2 \times 10 = 20$ mg, Zahravi, Iran) were placed into identical gelatin capsules. The inert powder (lactose) also was encapsulated and used as placebo.

Treatment in all cases was completed in one visit by one graduate endodontic resident. After anesthetizing each patient with local anesthetic solution (lidocaine + epinephrine 1/80,000, Daroupakhsh, Iran) access was achieved and the rubber dam was placed. The working lengths were determined and confirmed by radiographs. Canal preparation was conducted using a passive step-back technique. Normal saline was used as an irrigant, and the cleaning and shaping were conducted in the presence of RC-Prep® (Premier Dental Products Company, King of Prussia, PA). The working lengths were remeasured after complete instrumentation and necessary adjustments were made. Finally complete obturation of the canals was performed with gutta-percha (Ariadent, Iran) and AH 26® sealer (Dentsply DeTrey, GmbH, Germany) using the lateral-compaction technique. After placing a cotton pellet in the pulp chamber, the access cavity was closed with Coltosol® (Coltene, Swiss).

The patients were randomly given a single dose of oral preparations of meloxicam (15 mg), piroxicam (20 mg), or placebo (according to the manufacturers' instructions). On completion of the procedure, each patient was dismissed with a VAS to fill out at 8 and 24 h after drug administration. If unbearable pain occurred, the patients were asked to call and were allowed to take over-the-counter (OTC) medication. The data from these patients' VAS were analyzed up to the time that they dropped from the study and took another medication. The subjects were asked to return their VAS on the next day. When they returned, they also were evaluated for possible side effects.

On completion of the study, data from VAS scores were statistically analyzed using Sigma Stat2 with a two-way repeated measures ANOVA (drug $\times$ time) to determine if there was a difference in pain-reducing effects of our treatment modalities. Frequency data was analyzed by the Chi-square or Fisher's exact test. All statistical tests were performed at the 5% significance level. The sample size estimation was performed under the assumption of $a = 0.05$ and $b = 0.20$ using Queryadvisor software.

RESULTS

The similarity of the treatment groups was evaluated by comparing patients' age, gender, preoperative pain level, pulpal status, and periapical radiolucency. Treatment groups were similar for distribution of mentioned variables. The effect of the treatment allocation on pain reduction as measured on the VAS is presented in Fig. 1. As shown, two-way ANOVA for repeated measures (drug $\times$ time) indicates a significant effect on the time factor with all groups ($p < 0.001$). Further analysis focused on effects attributable to individual drug treatment.

As shown in Figs. 2 and 3, the mean reduction from baseline pain to the 8 h after intervention was -5.25 cm with meloxicam, -4.8 cm with piroxicam, and -3.5 cm with placebo. The mean reduction from baseline pain to the end of the trial (24 h) was -6.46 cm with meloxicam, -5.3 cm with piroxicam, and -5.1 cm with placebo. Based on the two-way repeated measures ANOVA

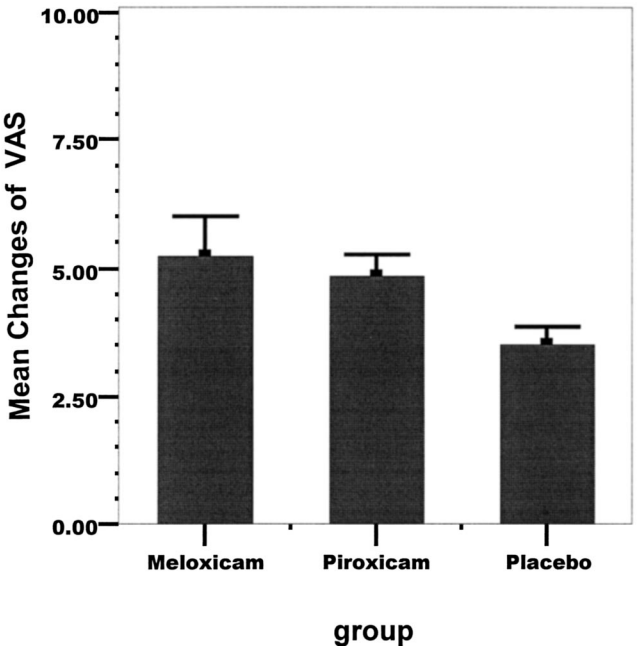

FIG 2. Changes of pain from before to 8 h after experiment.

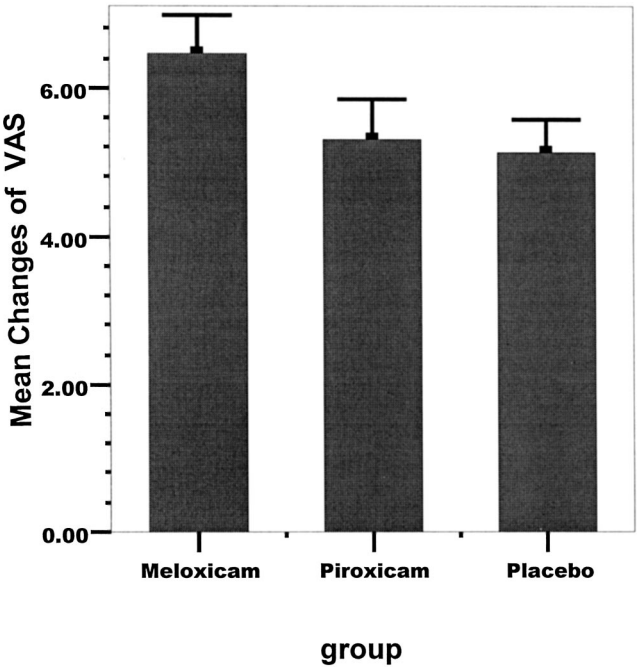

FIG 3. Changes of pain from before to 24 h after experiment).

the reduction of pain with meloxicam, piroxicam, and placebo was not significantly different ($p = 0.058$), although the mean change of pain was greater with meloxicam over the piroxicam and greater with piroxicam than placebo. Nine patients (five in placebo, two in meloxicam, and two in piroxicam) dropped out of the study because of ineffectiveness of the treatment medications and taking OTC medication.

For patients excluded from the study, Fisher's exact test was used to compare the frequency of these patients between treatment groups. There was a higher frequency of withdrawals because of ineffectiveness of medication with placebo than meloxicam and piroxicam, but fell short of statistical significance (29% versus 11%; $p = 0.296$).

Analysis of regression showed that any of the variables involving in the study had role of a confounder variable in the efficacy of treatment drugs in reduction of pain. No side effects were reported by patients in any experimental group.

DISCUSSION

Meloxicam is a new NSAID. In contrast to other NSAIDs currently available, it seems to have greater inhibitory activity against COX-2 than COX-1 (10). Overall, meloxicam has been shown to have potent anti-inflammatory, antipyretic, and analgesic effects with low gastrointestinal toxicity (11). It is used in the treatment of acute and chronic painful, inflammatory, and degenerative disorders such as osteoarthritis, rheumatoid arthritis, lower back pain, dental pain, and postoperative pain (12). The recommended dose is 7.5 mg or 15 mg once daily, depending on the severity of the case (12). Postoperative pain after root canal therapy is a major problem for most endodontic patients. Most clinical studies have shown that the presence of preoperative pain can be an indicator of potential flare-ups after treatment (2–4).

It seems that the presence of inflamed periapical tissues causes postoperative pain or discomfort. This provides the rationale for the efficacy of meloxicam as an analgesic for the relief of postendodontic pain (13). Periapical inflammation is usually induced by the presence of infected root canals or extrusion of debris and microorganisms and their interactions with the host cells in periapical tissues (3). Although several treatment regimens have been advocated for management of inflammation and its associated pain, it should be recognized that they are based primarily on randomized clinical trials conducted in acute postsurgical pain patients. It is likely that both the composition of peripheral inflammatory mediators and the central and peripheral mechanisms of hyperalgesia are distinct in odontalgia compared with models of acute surgical pain (14). These considerations suggest that evaluation of medications directed to the management of postoperative endodontic pain should be based on randomized clinical trials conducted in these patients. Therefore the selected pain model in this study was the postoperative pain in endodontic patients. However, in some reviewed studies selection of pain model was not suitable for evaluation of the medications (15).

Placebo groups are commonly used in drug-efficacy studies. For ethical reasons, however, when a placebo group is included, all patients are informed about the possibility of receiving a "sham" treatment (16). According to the declaration of Helsinki, at any time during the course of clinical research the subject should be free to withdraw permission for continued research (17). We included a placebo group in our study, with respect to all mentioned essentials, to remove the placebo effect of under-assessment drugs and specify the pure efficacy of them.

Because pain has both a physiologic and psychological component, its perception is strongly influenced by the conditions under which the stimulus is received (16). Therefore the control treatment in a trial should approximate the active treatment as closely as possible (16). In this study, treatment of all patients was completed in one visit by one operator and the treatment allocation conducted in a double-blind nature. This identical double-blind method makes it possible for more proper data collection and more accurate and reliable results. However in many reviewed studies, the route of drug administration was not equal in all treatment

groups and didn't have blindness (13, 16). Clearly, the placebo effect of each drug-administration method for both patient and operator significantly differed. In some studies, various medications with different dose intervals were administered in a similar route (3, 5). It is obvious that efficacy of these various drugs is not comparable in similar interval administration. Furthermore in some studies root canal treatment was performed in one or two appointments depending on time and clinical constraints, and was not equal for all patients (16). Also in some studies, the data from the patients who had taken OTC medication were analyzed along with other patients (13), whereas such a statistical analysis is not accurate and their positive result is questionable.

These inequalities in method involve the study with several confounder variables and can make the results questionable. In this study we controlled the effect of these confounder variables as much as possible. In this study, the VAS was chosen to measure pain at baseline and postoperatively because its accuracy and validity is well established. This scale is widely used and independent of language, easily understood, and reproducible (16).

The results of this study showed no statistically significant difference in the analgesic effect of meloxicam and piroxicam. This finding may be because the data from the patients who dropped out because of severe or unbearable postoperative pain and taking OTC medications were excluded from statistical analysis.

Endodontic literature is replete with investigations on meloxicam. Most present investigations on meloxicam have used models such as osteoarthritis and acute lumbago as a pain model (11, 18, 19). Considering the difference in the pain model with our study, this may not be a proper comparison. Nevertheless, our finding supports the results of those studies.

Furthermore the results of the studies mentioned indicated that there were fewer gastrointestinal adverse events among meloxicam patients than piroxicam (11, 18, 19)—a significant advantage for meloxicam compared with piroxicam. In this study, considering the single-dose administration of drugs, no side effects were found for the two drugs. It may be possible that if the use of meloxicam and piroxicam continues for several days after root canal therapy, the difference between their adverse effects would be detected.

The results obtained from this study clearly showed that the administration of meloxicam or piroxicam did not reduce the postoperative endodontic pain, but definitive dental treatment combined with placebo medication reduced pain by >56% in 24 h after root canal therapy. These results confirm earlier studies demonstrating a reduction of pain symptoms in endodontic emergency patients with pulpectomy or complete canal instrumentation (14, 20). Therefore it is clearly evident that effective treatment strategies for endodontic emergency patients should include definitive dental treatment as an important component in the management of these patients.

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References

1. Negm Maged M. Effect of intracanal use of nonsteroidal anti-inflammatory agents on post treatment endodontic pain. Oral Surg Oral Med Oral Pathol 1994;77:507–12.

2. Harrison JW, Baumgartner JC, Svec TA. Incidence of pain associated with clinical factors during and after root canal therapy. Part 2. Postobturation pain. J Endodon 1983;9:434–8.

3. Torabinejad M, et al. Effectiveness of various medications on postoperative pain following complete Instrumentation. JOE 1994;20:345–54.

4. Genet JM, et al. The incidence of preoperative and postoperative pain in endodontic therapy. Int Endod J 1986;19:221–9.

5. Torabinejad M, Dorn SO, Eleazer PD, et al. Effectiveness of various medications on postoperative pain following root canal obturation. J Endodon 1994;20:427–31.

6. Rang HP, Dale MM, Ritter JM. Pharmacology. 4th ed. London: Churchill Livingstone, 1999:214–5.

7. Seltzer S. Endodontology: biologic considerations in endodontic procedures. 2nd ed. Philadelphia : Lea & Febiger, 1988:489–91.

8. Feldman M, McMahon AT. Do cyclooxygenase-2 inhibitors provide benefits similar to those of traditional nonsteroidal anti-inflammatory drugs, with less gastrointestinal toxicity? Ann Intern Med 2000;132:134–43.

9. Jackson LM, Hawkey CJ. COX-2 selective nonsteroidal anti-inflammatory drugs, do they really offer any advantages? Drugs 2000;59:1207–16.

10. Noble S, Balfour JA. Meloxicam. Drugs 1996;51:424–30.

11. Dequeker J, Hawkey C, Kahan A, et al. Improvement in gastrointestinal tolerability of the selective cyclooxygenase (COX)-2 inhibitor, meloxicam, compared with piroxicam: results of the Safety and Efficacy Large-scale Evaluation of COX-inhibiting Therapies (SELECT) trial in osteoarthritis. Br J Rheumatol 1998;37:946–51.

12. ADWIA, Egyptian company for chemicals & pharmaceuticals. ANTI-COX II (Meloxicam). Products monograph.

13. Rogers MJ, Johnson BR, Remeikis NA, BeGole EA. Comparison of effect of intracanal use of ketorolac tromethamine and dexamethasone with oral ibuprofen on post treatment endodontic pain. J Endodon 1999;25:381–4.

14. Doroschak AM, Bowles WR, Hargreaves KM. Evaluation of the combination of flurbiprofen and tramadol for management of endodontic pain. J Endodon 1999;25:660–3.

15. Sadeghein A, Shahidi N, Dehpour AR. A comparison of ketorolac tromethamine and acetaminophen codeine in the management of acute apical periodontitis. J Endodon 1999;25:257–9.

16. Battrum D, Gutmann J. Efficacy of ketorolac in the management of pain associated with root canal treatment. J Am Dent Assoc 1996;62:36–42.

17. Declaration of Helsinki. Recommendation for conduct of clinical research. Available at: www.bioscience.org/guides/declhels.htm. Accessed month dd, year.

18. Carrabba M, Paresce E, Angelini M, Galanti A, Marini MG, Cigarini P. A comparison of the local tolerability, safety and efficacy of meloxicam and piroxicam suppositories in patients with osteoarthritis: a single-blind, randomized, multicentre study. Curr Med Res Opin 1995;13:343–55.

19. Bosch HC, Sigmund R, Hettich M. Efficacy and tolerability of intramuscular and oral meloxicam in patients with acute lumbago: a comparison with intramuscular and oral piroxicam. Curr Med Res Opin 1997;1:29–38.

20. Penniston SG, Hargreaves KM. Evaluation of periapical injection of ketorolac for management of endodontic pain. J Endodon 1996;22:55–9.