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1-26-02

Dear Dr. G.,

Your work on post-endo pain has been reviewed. It is accepted and will appear in the JOE in about 12 months.

Thank you for sending this well-written paper to the JOE.

H. J. Van Hassel

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Effectiveness of Prophylactic Use of Rofecoxib in Comparison with Ibuprofen on Postendodontic Pain

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The purpose of this study was to determine if prophylactic rofecoxib would significantly reduce postendodontic pain, when compared with ibuprofen or placebo. An additional objective was to establish if any relationship exists between periapical diagnosis and the need for additional medication after completion of pulpectomy. A total of 45 patients consented to a double-blind, single-dose oral administration of 50 mg of rofecoxib, 600 mg of ibuprofen, or a placebo before conventional root canal therapy. The root canal treatment was performed in two appointments. Patient-reported visual analog scale ratings of pain intensity were conducted upon initial clinical presentation and at 4, 8, 12, 24, 48, and 72 h after completion of pulpectomy. Results showed that at the 4- and 8-h periods, both rofecoxib and ibuprofen provided significantly better pain relief than placebo. At the 12- and 24-h periods, rofecoxib demonstrated significantly better pain relief than both ibuprofen and placebo. Patients with a periapical diagnosis of acute apical periodontitis showed a significantly increased need for additional medication after completion of pulpectomy compared with all other periapical diagnoses.

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 (1). The pain is thought to be related, in part, to a periapical inflammatory response produced by the endodontic instrumentation. A significant relationship also exists between preendodontic and postendodontic pain. Patients with severe preoperative pain tend to have more severe postoperative pain than patients with mild or no preoperative pain (2).

Prostaglandins (PGs) are important mediators of inflammation, the synthesis of which is initiated by release of arachidonic acid from damaged cell membranes. PGs probably are the most important hyperalgesic and inflammatory mediators. By sensitizing nerve endings to bradykinins and histamines, PGs increase vascular permeability, raise chemotactic activity, induce fever, and increase sensitivity of pain receptors to other active inflammatory mediators (3).

If the periapical inflammatory reaction is a major contributor to posttreatment pain, then it is possible that a nonsteroidal anti-inflammatory drug (NSAID) may be useful in its management. NSAIDs seem to inhibit inflammation and induce analgesia by inhibiting the activity of cyclooxygenase (COX) enzymes. 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 are responsible for synthesizing prostanoids that have cytoprotective functions. The COX-1 enzymes regulate normal cell activities in the stomach, kidneys, and in platelets. COX-2 enzymes normally are not present in tissue (other than in kidneys) and come into play when tissue injury and inflammation occurs. The COX-2–mediated inflammatory response, therefore, generally is delayed because of activation and release of COX-2 enzymes by macrophages, monocytes, synovial cells, leukocytes, and fibroblasts requiring 1 to 3 h to occur (4).

Ibuprofen, ketoprofen, aspirin, and naproxen are nonselective NSAIDs, inhibiting both cytoprotective COX-1 enzymes and inflammatory COX-2 enzymes. Consequently, the prolonged use of these agents is associated with possible damage of the gastrointestinal tract causing gastric erosions, ulcers, and bleeding (5). Drugs that specifically inhibit COX-2 enzymes and leave the cytoprotective COX-1 enzymes intact may provide analgesia, anti-inflammatory, and antipyretic activities while avoiding adverse effects on the gastrointestinal tract and other tissues, as well as on platelets.

Studies using postextraction models have shown preoperative administration of ibuprofen inhibits postoperative pain more effectively than a placebo (6). Hence, preemptive use of a NSAID before root canal therapy might interfere with the inflammatory process before it begins, thereby potentially reducing postoperative pain. Rofecoxib is a COX-2–specific NSAID that has been proven effective in the management of osteoarthritis, primary dysmenorrhea, and postoperative pain in oral surgery models (7). The ability of rofecoxib to control postendodontic pain when administered prophylactically has not been analyzed. The purpose of this study was to determine if prophylactic rofecoxib could significantly reduce postendodontic pain, when compared with prophylactic ibuprofen, and when compared with a placebo. An additional objective was to establish if any relationship exists between 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 Meenakshi Ammal Dental College postgraduate endodontic clinic were evaluated for this study. A clinical examination was conducted that included thermal and electric pulp testing, percussion and palpation evaluation, periodontal probing, mobility assessment, and a periapical radiograph. All past and present symptoms were noted. A diagnosis was determined on the basis of the history, clinical, and radiographic features.

The inclusion criteria for the study were:

1. Patient elects root canal therapy for pain originating from a molar.
2. Patient reports spontaneous pain of at least 30 (0–100) in the visual analog scale (VAS).
3. Patient reads and understands questionnaires.
4. Patient provides informed consent.

Patients were excluded if they fell into any of the following categories:

1. Younger than 18 yr or older than 65 yr.
2. Analgesic intake within last 12 h.
3. History of allergy to NSAIDs or local anesthetics.
4. History of ulcers, active asthma, decreased renal function, decreased hepatic function, hemorrhagic disorders, or poorly controlled diabetes mellitus.
5. Current use of drugs contraindicated with NSAIDs.
6. Pregnant or nursing.

If a patient met all the above criteria, he/she was informed of the nature of study and invited to participate. Forty-five patients signed a consent form outlining the procedure and its possible risks. Patients consented to a double-blind, single-dose oral administration of 50 mg of rofecoxib, 600 mg of ibuprofen, or 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 posttreatment pain. Pain intensity was measured using a 100-mm VAS. The scale was from 0 to 100, with 0 being "none" and 100 being "pain so severe you cannot bear it."

The root canal treatment was performed in two appointments. The first appointment consisted of cleaning and shaping of the canals, using standard aseptic technique under local anesthesia. The root canal treatment procedure was conducted utilizing a crown-down technique. The canals were enlarged to minimum size of #25 file or larger, depending on the size of the canal. Sodium hypochlorite (2.6%) and saline were used as irrigants. After complete cleansing and shaping, the canals were dried and then all teeth were closed with a sterile cotton pellet and intermediate restorative material. The occlusion was evaluated and reduced when necessary. One operator treated all the patients in this study.

The patients were dismissed with a VAS to fill out at 4, 8, 12, 24, 48, and 72 h after initiation of therapy. Each patient was given an "escape" envelope containing 650 mg of acetaminophen in case of continued pain while taking the test medication in question. The patients were instructed to indicate in the pain survey if this additional medication was required and record the time it was taken.

The statistical package SPSS PC+ (version 4) was used for statistical analysis. The VAS pain scores for each drug at each time were analyzed by means of the Friedman nonparametric two-way ANOVA to test for differences between scores at different intervals for the same drug. If a difference was found, the Wilcoxon matched pairs signed rank test was used to show where any differences lay. 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 differences were. In this study, $p < 0.05$ was considered as the level of significance.

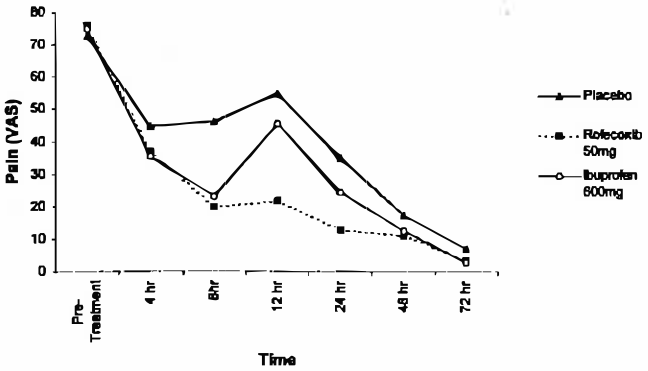

FIG 1. Effect of prophylactic drug administration on pain after endodontic treatment. Significant difference exists ($p < 0.05$) for ibuprofen versus placebo and for rofecoxib versus placebo. Significant difference exists ($p < 0.05$) for rofecoxib versus ibuprofen.

RESULTS

Pain scores were recorded by 45 patients with the use of 100-mm VAS. Twenty-nine males and 16 females participated in the study. There were 15 patients each in the placebo group, rofecoxib 50-mg group, and the ibuprofen group. Median pain VAS scores were plotted in relation to time after administration of the drugs (Fig. 1). At the 4-and 8-h periods, both rofecoxib and ibuprofen provided significantly better pain relief than placebo. There was no significant difference between rofecoxib and ibuprofen during both 4-h ($p = 0.30$) and 8-h ($p = 0.25$) periods. However, when comparing rofecoxib to both ibuprofen and placebo after 12 h and 24 h from initiation of root canal therapy, rofecoxib was significantly more effective at reducing pain (12-h p value = 0.003; 24-h p value = 0.047).

Nineteen patients presented with chronic apical periodontitis and two required additional medication for postendodontic pain. Seven patients presented with a normal periapex and zero required additional medication for postendodontic pain. Two patients presented with chronic apical abscess and both did not require additional medication for postendodontic pain. Seventeen patients presented with acute apical periodontitis and nine required additional medication for postendodontic pain. A Chi-square analysis showed that a significant difference existed for the periapical diagnosis and the need for additional medication ($p = 0.001$). Patients who presented with a periapical diagnosis of an acute apical periodontitis were more likely to require additional medication for postendodontic pain than patients who presented with a periapical diagnosis of a normal periapex, a chronic apical periodontitis, or a chronic apical abscess.

DISCUSSION

Reduction in postoperative pain after prophylactic administration of NSAIDs has been proved both in oral surgery models (6) and endodontic models (8). Preemptive administration of NSAIDs

before conventional root canal therapy can block the COX pathway and might block the pain sensation before it even begins. COX (also known as PG endoperoxide H synthase) catalyzes the conversion of arachidonic acid to PGH_2. This is the key and rate-limiting step in the biosynthesis of prostanoid. Of the two isoforms (COX-1 and COX-2), COX-1 are constitutively expressed in cells and are responsible for the production of cytoprotective prostanoids. In contrast COX-2 are regulated by extracellular stimuli such as cytokines and are considered to be associated with the production of inflammatory prostanoids (9).

Ibuprofen blocks both the COX-1 and COX-2 enzymes, but it is a safe, cost-effective with highly effective analgesic and anti-inflammatory action for postendodontic pain (10). In this study, Ibuprofen showed significantly lower pain ratings at 4-and 8-h posttherapy when compared with the placebo. However, the 12-h pain rating for ibuprofen was significantly higher than its rating at 8 h. This could be attributed to the drugs metabolic half-life, which is between 4 and 6 h. Ibuprofen and placebo gave similar pain ratings at 12- and 24-h posttherapy. This was expected, because the endodontic procedure should have reduced the pain by this time. Moreover, ibuprofen's maximal analgesic effect would not have lasted for more than 8 h.

Rofecoxib has been proven to be a highly specific COX-2 inhibitor. 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. This study found that prophylactic administration of 50 mg of rofecoxib before root canal therapy was more effective at reducing postendodontic pain at 12 and 24 h after initiation of treatment, when compared with 600 mg of ibuprofen or placebo. Rofecoxib and ibuprofen showed similar pain ratings at 4 and 8 h posttherapy; however, these two drugs were significantly better during these time intervals in reducing the postoperative pain when compared with the placebo. The findings of this study are in concurrence with other studies (11, 12) involving post extraction oral surgery models wherein rofecoxib provided measurable analgesia up to 24 h after therapy, whereas ibuprofen provided comparable analgesia for 4 to 6 h only.

The results from this study also demonstrates that definitive dental treatment combined with placebo medication reduced pain by > 50% by 24 h and 75% by 48 h after the initiation of therapy. These results confirm earlier studies demonstrating a reduction in pain symptoms in patients treated with pulpectomy (13).

The other objective of this study was to establish if any relationship exists between periapical diagnosis and the need for additional medication after completion of pulpectomy. Of the 45 patients analyzed, 28 patients presented with a normal periapex, chronic apical periodontitis, or chronic apical abscess. All three clinical entities are not painful on percussion. Of these 28 patients, only 2 required additional medication for postendodontic pain. This finding validates the concept that a patient with minimal or no preoperative pain does not develop significant postoperative pain.

The periapical status of the remaining 17 patients of this study were diagnosed as acute apical periodontitis characterized by pain on percussion. Of these 17 patients, 9 required additional medication to reduce postendodontic pain. This finding was in concurrence with the study by Menke et al. (14). They found that patients with severe preoperative pain needed additional medication postoperatively, irrespective of the prophylactic drug given. The present study indicates that if a patient originally presents with pain on percussion, it is likely that he/she will need additional medication to relieve postendodontic pain. This study also found that a significant difference did not exist for the type of drug and the need for additional medication after completion of root canal therapy. No difference in drug groups with respect to periapical status was noted.

In summary, prophylactic rofecoxib administration provides an effective reduction in postendodontic pain. Rofecoxib's analgesic efficacy, long duration of action, lower gastrointestinal toxicity, and apparent lack of inhibition of platelet function suggest that rofecoxib may be useful as a preemptive analgesic when postendodontic pain is anticipated. Furthermore, patients with a periapical diagnosis of acute apical periodontitis are more likely to require additional doses of pain medication for postendodontic pain.

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