Comparison of the Efficacy of Prophylactic Celecoxib, a Cox-2 Inhibitor Made in Iran, and Placebo for Post-Endodontic Pain Reduction: A Clinical Double-Blind Study

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Abstract

Objective: Pain control in dentistry especially endodontics is particularly important. Endodontic pain following root canal therapy (RCT) of vital teeth is closely correlated with inflammatory reactions. Increased level of prostaglandins has been reported in acute inflammatory reactions. Thus, cyclooxygenase-inhibiting drugs have a significant effect on reducing pain and inflammation. COX enzyme has two isoforms of COX-1 and COX-2. The conventional anti-inflammatory drugs inhibit both isoforms. In the recent years, COX-2 specific inhibitors have been the subject of extensive investigations. These inhibitors block the pain-inducing inflammatory mediators that are mostly derived from COX-2. The aim of this study was to compare the efficacy of prophylactic Celecoxib and a placebo in reducing post-endodontic pain using Visual Analog Scale (VAS).

Methods: This double blind clinical trial was conducted on 30 patients with a mean age of 18 to 57 yrs. complaining of severe pain based on VAS. The subjects were randomly assigned to two groups of 400mg Celecoxib and the placebo. Drugs were administered 30 min prior to root canal therapy. Patients were asked to keep a pain diary and mark their degree of pain on a VAS chart before the initiation of treatment, immediately after treatment and at 4, 8, 12, 24 and 48 hours post-treatment.

Results: No significant difference was found between the analgesic effects of prophylactic Celecoxib and the placebo in any of the understudy time points (p>0.05).

Conclusion: Considering the absence of a significant difference between the two groups, prophylactic Celecoxib is not recommended for post-endodontic pain reduction especially in cases with gastrointestinal (GI) problems.

Key words: Celecoxib, Placebo, Post-endodontic pain, Prophylactic, Root canal therapy VAS chart.

Introduction:

Pain control in dentistry especially endodontics is particularly important. The public belief is that RCT is a painful experience (1). Post-endodontic pain has been reported in 25-40% of endodontic patients (2-4). Pain in between treatment sessions is caused as the result of endodontic manipulation, use of intracanal medicaments and irrigation solutions, contamination of periapical region, long-term temporary dressings, traumatic occlusion (3, 4), trauma to the peri-radicular tissue, toxic irrigation solutions or contamination due to root canal therapy that can cause an acute inflammatory reaction; which leads to further pain and swelling (3, 4).

Several chemical mediators (prostaglandins, leukotrienes, bradykinin, histamine, etc.) are involved in this inflammatory process (3). Prostaglandins are the most important
inflammatory mediators. Their synthesis is initiated by the release of arachidonic acid from the injured cell membrane. They increase the sensitivity of nerve terminals to bradykinin and histamine, enhance vascular permeability and chemotactic activity, cause fever and increase the sensitivity of pain receptors to other active inflammatory mediators (2, 3).

Several methods have been suggested for endodontic pain control in between treatment sessions such as occlusal reduction, use of intracanal medicaments, administration of pain relievers and use of steroidal and non-steroidal anti-inflammatory drugs (3). If the inflammatory reaction at the periapical region is linked to the post-endodontic pain, use of a non-steroidal anti-inflammatory drug may be efficient for pain control. However, no specific anti-inflammatory protocol has been confirmed for prevention or management of post-endodontic pain (3).

NSAIDs inhibit the activity of cyclooxygenase enzyme and thus, control the inflammation and cause analgesia. Two isoforms of COX enzyme have been recognized: COX-1 and COX-2. COX-1 is always present in the tissue and is responsible for synthesis of prostanoids that are in charge of cell protection. COX-1 regulates normal function of cells in the stomach, kidneys and platelets. COX-2 is not normally present in cells (except for kidneys) and is produced in case of trauma and inflammation (2, 3). Use of an NSAID before root canal therapy may interfere with the inflammation process before it begins and cause a reduction in post-endodontic pain (2, 3).

Celecoxib is a specific COX-2 inhibitor used for the treatment of osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis (in children over 2 years of age), Ankylosing spondylitis, primary dysmenorrhea and acute pain (5).

The effect of consumption of COX-2 inhibitor prior to periodontal surgery on post-operative pain reduction has been investigated before (5), but no study has evaluated the efficacy of prophylactic Celecoxib for post-endodontic pain reduction. The aim of this study was to compare the efficacy of Celecoxib and a placebo for post-endodontic pain reduction using VAS.

Methods:

This study was approved by the Ethics Committee of Shahid Beheshti University, School of Dentistry (#9755). This prospective parallel randomized clinical trial was conducted on 30 patients with a mean age of 18-57 yrs. presenting to Imam Khomeini Clinic complaining of pain in their mandibular first or second molars. Subjects were selected for this double blind clinical trial using parallel sampling. The patients filled out the questionnaires, signed a written informed consent and enrolled (5). Patients were generally healthy, were not on any medication and had no contraindication for consumption of the understudy drugs. Medical and dental history of patients were taken, and clinical and paraclinical tests such as cold, heat, percussion, and palpation tests along with periodontal probing, evaluation of mobility and periapical radiography were all performed. Patients’ previous and current symptoms were asked and recorded. Pulpal and periapical diagnoses were made based on history, clinical examination and imaging data of patients. The exclusion criteria were: taking pain relievers or anti-inflammatory drugs during the past 6 hours, acute endodontic or periodontal abscess, periodontal disease, requiring prophylactic antibiotic therapy, pregnancy or nursing, mental disabilities, specific systemic diseases and any known allergy to NSAIDs.

Subjects were randomly divided into two groups of 15 using random allocation sequence (sequentially numbered containers). The first group received 400 mg Celecoxib (Tehran Chimie, Tehran, Iran) and the 2nd group received...
two placebo capsules 30 min before the initiation of treatment (considering the time of action of the respective drug). Sufficient number of empty capsules were prepared and divided into 2 groups. Group A capsules were filled with 400mg Celecoxib and group B with the placebo. The operator and the patients were both blinded to the content of capsules (double blind randomized clinical trial).

Root canal therapy was done in a single session by a single endodontist. In order to eliminate the operator bias, 30 min after receiving the drug, 2% lidocaine along with 1/80,000 epinephrine (Daroupakhsh, Tehran, Iran) was injected. The respective tooth (mandibular first or second molars) was isolated by a rubber dam and access cavity was prepared. Cleaning and shaping of the canals were performed using passive step back technique. Root canals were filled with a minimum MAF size of 30, 0.5 to 1mm shorter than the radiographic apex. Irrigation with 2.5% sodium hypochlorite (Golrang, Tehran, Iran) was performed in between instrumentation. Canals were dried with paper point (Ariadent, Tehran, Iran) and filled with gutta percha (Ariadent, Tehran, Iran) and AH26 sealer (Dentsply, Konstanz, Germany) using lateral condensation technique. A sterile cotton pellet was placed in the pulp chamber and the cavity was restored with Coltosol®. Patient’s occlusion was checked. Patients were asked to keep a pain diary and record their degree of pain before taking the medication, immediately after treatment, and at 4, 8, 12, 24, and 48 h post-treatment in the given chart using Heft-Parker VAS (6). Patients were contacted 48h later and the completed forms were collected.

In order to alleviate possible post-treatment pain, patients were provided with three 325mg acetaminophen tablets (Jalinus, Tehran, Iran) and were instructed to take them if required. Patients were asked to rate their degree of pain and mark it on the VAS chart before taking any of the mentioned pain relievers. VAS is a 0 to 170 mm scale with no pain=0, mild pain ≤54 mm, 54 <moderate pain <144mm and severe pain>144mm.

Data were analyzed using SPSS version 15 software. Descriptive statistics were collected and their normal distribution was evaluated. Since the distribution of data was not normal, non-parametric test was used. Mann-Whitney U test was applied for comparison of the two groups. Friedman test was used to compare pain scores at different time points in each group.

Results:

Subjects in the two groups were matched in terms of age, gender and number of tooth and no significant difference existed in this respect between the two groups ($p>0.005$). The mean age of patients is summarized in Table 1. Based on statistical analysis, no significant difference was found between the two groups in terms of mean age and gender.

Two patients were excluded from the study. One patient in the placebo group underwent third molar surgery along with root canal treatment. The second patient was in the Celecoxib group and was not able to answer the questions.

The mean severity of pain according to VAS at 4, 8, 12, 24 and 48h after treatment was calculated in the two groups. No significant difference was detected between the analgesic effects of Celecoxib and the placebo in any of the understudy time points ($p>0.05$).

Comparison of pain score after the consumption of drugs at different time points following treatment revealed that 35.7% and 14.2% of subjects in the Celecoxib and the placebo groups, respectively reported no pain (zero scale) at 4h post-treatment. This rate was 35.7% in the Celecoxib and 14.2% in the placebo group at 8 hours post-treatment. At 12h, these values were 28.5% and 14.2% in the two groups of Celecoxib and the placebo, respectively. At 24h,
28.5% of patients in the Celecoxib group and 28.5% in the placebo group and at 48h, 50% in the Celecoxib and 42.8% in the placebo group reported no pain.

### Table 1- The mean age and gender of patients in the two groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Number of samples</th>
<th>Number of males</th>
<th>Number of females</th>
<th>Mean age of patients</th>
<th>Number of tooth</th>
<th>Number of patients requiring additional pain relievers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>14</td>
<td>7</td>
<td>7</td>
<td>31.57</td>
<td>6 (57.14%)</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7 (42.86%)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>14</td>
<td>8</td>
<td>6</td>
<td>30</td>
<td>6 (50%)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7 (50%)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2- The mean pain score at different time points in the two groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mean pain score before treatment</th>
<th>Mean pain score at 4h</th>
<th>Mean pain score at 8h</th>
<th>Mean pain score at 12h</th>
<th>Mean pain score at 24h</th>
<th>Mean pain score at 48h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>148.9 (18.9)</td>
<td>55.2 (56.8)</td>
<td>55.2 (56.8)</td>
<td>70 (60.03)</td>
<td>31.4 (40.7)</td>
<td>15.7 (21.01)</td>
</tr>
<tr>
<td>Placebo</td>
<td>150</td>
<td>92.8 (59.7)</td>
<td>92.8 (59.7)</td>
<td>100.7 (58.9)</td>
<td>48.5 (48.9)</td>
<td>21.07 (39.1)</td>
</tr>
</tbody>
</table>

![Diagram 1- Comparison of mean pain score after using understudy drugs at different time points post-treatment](image)

**Discussion:**

Post-endodontic pain is a complication that leaves a bad experience for the patients (1) and has been reported in 25-40% of endodontic patients (2-4). Numerous studies have evaluated the analgesic effects of NSAIDs after dental procedures. Previous studies have shown that COX-2 specific inhibitors significantly decrease the inflammatory cell infiltration, edema and vascular dilation following inflammation. It means that as the result of action of these medications, pain-inducing metabolites are released in lower amounts and thus following
tissue injury, they significantly reduce pain (7). The majority of studies on pain reduction after dental procedures using COX-2 specific inhibitors have focused on pain following third molar extraction surgeries and less number of studies have investigated post-endodontic pain reduction. Studies focusing on pain control following periodontal surgery using COX-2 specific inhibitors are sparse (8-12).

Endodontic pain assessment protocol is different from that of oral surgery (impacted third molar and periodontal surgeries) in many aspects. Patients requiring endodontic treatment may have different systemic conditions or vary in terms of age range or degree of pulpal injury. These factors can cause a bias in the study. Anatomy of the periapical region is another important factor that can trigger different inflammatory responses following RCT. Thus, the efficacy results of analgesics and anti-inflammatory agents for oral surgery pain cannot be used as a direct approach for reduction of post-endodontic pain (4). Since the effects of COX-2 inhibitors on pain control have been evaluated to some extent, there was a need for the assessment of the efficacy of prophylactic Celecoxib made in Iran for post-endodontic pain management.

Based on our obtained results, although the degree of pain was lower in the prophylactic Celecoxib group compared to the placebo, no significant difference was found between the two groups in post-operative pain reduction in any of the time points ($p>0.05$). Due to ethical considerations, all patients were informed that they might be assigned to the placebo group. Patients in both groups were provided with 3 acetaminophen tablets (325 mg) for use in case of post-operative pain.

Marcia et al. in 2009 prescribed prophylactic dexamethasone for post-endodontic pain reduction and found that the combination of placebo and RCT resulted in pain reduction in 71% of patients. Also, in the dexamethasone group pain was significantly lower than in the placebo group at the first 4 and 12 hours but no significant difference was detected between the two groups in this respect at 24 and 48 hours (13). In our study, 42.8% of patients who received the placebo did not report any pain at 48h post-treatment. The difference between our study and the aforementioned one may be due to the fact that in our study all patients had spontaneous pain or pain on percussion before RCT but in the aforementioned study both groups of symptomatic and asymptomatic patients were enrolled.

In a study by Gopikrishna et al. in 2003 on the efficacy of prophylactic Rofecoxib in comparison with ibuprofen and the placebo, it was reported that both Rofecoxib and ibuprofen showed higher analgesic activity than the placebo. At 12 and 24h, Rofecoxib caused a significantly higher analgesia compared to the other two groups. They confirmed the effectiveness of prophylactic Rofecoxib for post-operative pain control. These results are different from ours; which can be explained by the use of different medications and different pre-treatment conditions of patients (2).

Menke et al. in 2000 compared prophylactic administration of Etodolac with ibuprofen and a placebo and showed that prophylactic ibuprofen caused a significant pain reduction at the first 4 and 8h after RCT compared to Etodolac and the placebo. They confirmed the efficacy of prophylactic ibuprofen for post-endodontic pain reduction. However, their obtained results are not comparable to ours because they performed two-visit RCT and used different medications (1).

Ashraf et al. (2003) compared the efficacy of Rofecoxib, ibuprofen and the placebo for post-endodontic pain control and reported significant differences between the analgesic effects of Rofecoxib and ibuprofen with that of the placebo at 6, 12 and 24 hours post-treatment. However, no significant difference existed
between the Rofecoxib and ibuprofen. Their study confirmed the efficacy of prophylactic administration of these two drugs; which is in contrast to our obtained results (14).

The amount of acetaminophen required for pain relief of patients was also evaluated and it was found that 7 and 3 patients in the placebo group had consumed 3 and 2 acetaminophen tablets, respectively. Three, 2 and 1 patient(s) in the Celecoxib group had taken 3, 2 and 1 acetaminophen tablet(s), respectively. As observed, patients in the placebo group had consumed more pain relievers than subjects in the Celecoxib group; which further indicates the efficacy of prophylactic use of pain relievers in reducing post-operative pain and decreasing the need for additional painkillers. Greater need for additional analgesics in the placebo group is in agreement with the results of previous studies (1, 2, 4).

By increasing the sample size to reduce the dispersion of data, statistically significant differences may be found.

In our study, no GI problems were noted in the Celecoxib group; which may be due to the fact that patients were only evaluated 48h after consumption of drugs and drugs were administered as single dose. Also, no patients with previous GI problems enrolled in our study. Our study had a double blind design and patients in the two groups had equal distribution and were matched in terms of age, sex, number of tooth and type and quality of treatment received (all done by one endodontist). Thus, the bias was minimized and the two groups were precisely compared.

**Conclusion:**

This study was part of the doctoral thesis of Tannaz Naghlachi (#3103). The thesis supervisor was Dr. Hengameh Ashraf from Shahid Beheshti University, School of Dentistry.

**Conflict of Interest:** “None Declared”

**References:**