

**Original Article**

# Effect of a Long-Acting NSAID Premedication on Postendodontic Pain in Mandibular Molars with Non-vital Pulp: A Preliminary Randomized Controlled Trial

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## Abstract

**Aim:** The aim of this prospective, randomized, double-blind, clinical trial was to evaluate the effect of preoperative, single, oral dose of a long-acting non-steroidal antiinflammatory drug (NSAID; 20mg piroxicam) compared to placebo on post-endodontic pain after single-visit endodontic treatment of mandibular molars with non-vital pulp.

**Subjects and methods:** Seventy patients were randomly equally divided into two groups (n=35): piroxicam and placebo. The medications were given 1hour before treatment. Canal preparation was done using the ProTaper Next system and obturation using the modified single-cone technique. Pain was assessed using the 11-point numerical rating scale (NRS) 6h, 12h, 24h, 48h, 72h and 1w postoperatively. The number of rescue analgesic tablets was recorded. Data were statistically analyzed; significance was set at  $p > 0.05$ .

**Results:** Piroxicam showed less postoperative pain level at 6, 12 and 24 hours ( $p > 0.05$ ). The mean and Standard deviation value for postoperative pain intensity piroxicam and placebo were 0.6 (1.97) and 2.66 (3.26) at 6 h, 0.63 (2.17) and 2.29(2.91) at 12 h and 0.54 (1.90) and 1.74 (2.44) at 24 h respectively. Patients receiving piroxicam required fewer analgesic tablets than those receiving placebo ( $p > 0.05$ ).

**Conclusion:** A preoperative single oral dose of piroxicam can be effective in reducing endodontic postoperative pain within the first 24 hours after treatment and the number of rescue analgesic tablets taken by the patient in patients with mandibular molars having a non-vital pulp treated in a single visit.

**Keywords:** Mandibular molar, non-vital pulp, NSAID, piroxicam, posroperative pain

## Introduction

Postoperative pain is a common complication of endodontic treatment with an incidence ranging from 3%–58% <sup>(1)</sup>. Despite the advances in root canal treatment and an increase in the awareness about pulpitis and periapical inflammation, postoperative endodontic pain can still be a major problem for both patient and dentist. Generally postoperative endodontic pain is attributed to

the inflammatory mediators that activate sensitive nociceptors and lead to central and peripheral hyperalgesia mechanisms <sup>(2)</sup>. Among inflammatory mediators, prostaglandins have crucial functions in the pathogenesis of pulpal and periradicular diseases <sup>(2)</sup>.

The pharmacological pain management usually includes administration of systemic analgesics, anti-inflammatory drugs, and/or antibiotics. The inhibition of the inflammatory

process is one of the methods to reduce or prevent pain during and after treatment<sup>(3)</sup>. Non-steroidal anti-inflammatory drugs (NSAIDs) have been the drug of choice for managing pain. They act primarily through the inhibition of cyclooxygenase (COX) enzymes 1 and 2. Inhibiting COX-2, blocks prostaglandin formation and ultimately prevents inflammation and sensitization of the peripheral nociceptors<sup>(3)</sup>.

Piroxicam is a non-steroidal, COX-1 and COX-2 inhibitor that has long-acting, anti-inflammatory action with minimal side effects such as gastric intolerance<sup>(4)</sup>. Piroxicam has a half life of 50 h, and its oral dose reaches peak concentration within 2 h<sup>(4)</sup>. The piroxicam postmedication significantly reduced postendodontic pain on endodontic treatment of teeth with vital and non-vital pulp<sup>(5-7)</sup>. In several studies, the intraligamentally piroxicam premedication had an effect on reduced postendodontic pain<sup>(7-9)</sup>. However, very few studies have assessed the effect of preoperative oral piroxicam administration on the postendodontic pain<sup>(10-12)</sup>. Thus, the purpose of this study was to assess the effect of a preoperative, single dose of oral fast-dissolving sublingual piroxicam tablets (20 mg) compared to placebo on postendodontic pain intensity and rescue-medication intake in patients with mandibular molars having non-vital pulps treated in a single visit.

## Subjects and Methods

### Study design, setting and sampling

The protocol of this prospective, two-arm, parallel-group, double blind, randomized, placebo-placebo controlled clinical trial and the informed consent format were approved by the Research Ethics Committee, Faculty of Dentistry, Cairo University, Egypt. Study reporting followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines. A written informed consent was obtained from each patient who kept a copy. This study took place in the outpatient clinic of the Department of Endodontics, Faculty of Dentistry by a single operator.

### Sample size calculation

The sample size was calculated using the (G power software). As regards the primary outcome (postoperative pain) we found that 24 patients per group was the appropriate sample

size for the study with a total sample size 48 patients (2 groups). This number was increased to 70 to compensate for dropouts. The magnitude of the effect to be detected was estimated as a proportion of the variable of interest and obtained from the scientific literature<sup>(13)</sup>. Sample size calculation was done using G\*Power software version 3.1.2 for MS Windows, Franz Faul, Kiel University, Germany.

### Eligibility criteria

Each patient participating in this study had a mandibular molar (First or second) with asymptomatic non-vital pulp, aged between 18-50 years old and was in good health [American Society of Anesthesiologists (ASA) Class I or II]. Exclusion criteria were as follows: patients who had allergies or sensitivity to piroxicam or any other medicament/material used in the study, pregnant or nursing females, patients with periapical abscess, sinus tract and/or a history of active peptic ulcer. or patients unable to provide informed consent.

### Diagnosis

The clinical diagnosis was based on the patient's chief complaint, history taking and clinical and radiographic examination. Each patient was asked to rate his/her pain intensity on an 11-point numerical rating scale (NRS) pre-operatively. Patients were asked to place a mark on the number that represented their level of perceived pain where pain intensity was assigned into 4 categorical scores: a score of zero indicates no pain, a score from 1-3 indicates mild pain, a score from 4-6 indicates moderate pain and a score from 7-10 indicates severe pain. Patients had no sensitivity response to a cold pulp-sensitivity test (Endo-Ice spray, Henry Schein, Germany), no tenderness to percussion or palpation. Each tooth showed normal periodontal probing and mobility. Teeth with or without periapical radiolucency ( $\leq 5$  mm in diameter) were included.

### Randomization and Blinding

Each patient had the same chance of being assigned to either group according to their number in the generated random sequence using computer software (Microsoft Excel). Allocation concealment was done through using sequentially-numbered, opaque, sealed containers containing either the drug or the placebo. Randomization was done by an

investigator not involved in the enrollment of patients into the study. Both piroxicam and placebo were packed in similar tablets and placed in similar opaque containers so that the patient and the operator were unaware of the assigned group. In this study, the patient, operator and statistician were blinded after assignment to interventions.

### Endodontic procedures

The patients randomly received either 20 mg sublingual piroxicam or placebo tablets one hour before anesthetic administration. Each patient, then, received an inferior alveolar nerve block using a standard dental aspiration syringe with 27-gauge needle. The anesthetic solution was 1.8 ml of 2% mepivacaine hydrochloride 1.8 mL with levonordefrin 1 : 20 000 (Mepecaine-L, Alexandria (Mepcaine-L, Alexandria Company for pharmaceuticals and Chemical Industries, Alexandria, Egypt). The endodontic access was performed using a size 4 round bur and an endodontic access bur (Endo-z™ Bur, DENTSPLY, Tulsa Dental, DENTSPLY Maillefer, TN). Each tooth was isolated using rubber dam. Working length was determined using an apex locator (Root ZX mini apex locator, J Morita Corp, Kyoto, Japan) and radiographically confirmed as 0.5-1 mm shorter from the radiographic apex. Root canal instrumentation was, then, done using a rotary nickel-titanium system (ProTaper Next, Dentsply, Maillefer, Ballaigues, Switzerland). Irrigation was done using 2mL of 2.5% sodium hypochlorite between every two consecutive instruments. Final flush was done using 2 ml of 17% EDTA followed by 5 ml distilled water. Canals were, then, dried with paper points (Paper points, META BIOMED CO., LTD, Korea) and were mainly filled using matched-size gutta-percha cones (Gutta Percha Pointa, Dentsply Tulsa Dental Specialties, Dentsply VDW, Munchen, Germany) and epoxy resin sealer (Adseal, Meta Biomed CO., Ltd., Chungbuuk, Korea). Access cavity was, then, sealed with a temporary filling (MD-TEMP, Meta Biomed CO., Ltd., Chungbuuk, Korea).

### Postoperative pain assessment

Each patient received a pain-diary form to record the intensity of pain felt after 6, 12, 24, 48, 72 hours and 1 week. Pain assessment was done using the 11-point NRS. The patients were instructed on how to use the 11-point NRS and trained to use it before recording their

pain at the pre-determined timepoints. The operator contacted patients by telephone at each time point to be checked upon and to be reminded of recording their pain. Patients were instructed to contact the operator in case of pain persistence and a rescue analgesic 200 mg ibuprofen (Brufen 200mg, Abbott International, Cairo, Egypt) was prescribed. The incidence of receiving rescue analgesics was recorded by the patients in the pain diaries. At the end of the follow-up duration, patients submitted their pain diaries to the operator. Patients were referred to the restorative department for final restoration. The primary outcome was postoperative pain intensity assessed using the 11-point NRS felt after 6, 12, 24, 48, 72 hours and 1 week. The secondary outcome was the number of analgesics tablets taken during 1 week. The patients were contacted by telephone at the previous time intervals to remind them to evaluate their level of pain and to return to the clinic to submit the pain diary.

### Statistical analysis

Data were collected and statistically analyzed using the Statistical Package for Social Sciences version 22 (SPSS Inc., IBM Corporation, NY, USA). Comparisons between the two groups with respect to normally-distributed numeric variables were done using the Student's t-test. Non-normally-distributed numeric variables were compared by Mann-Whitney U test. Comparisons among time points within each group were done using Friedman's test followed by Wilcoxon's sign rank test for multiple comparisons. For categorical variables, differences were analyzed using Pearson's Chi square (X<sup>2</sup>) test and Fisher's exact test when appropriate.

### Results

Of 193 patients assessed for eligibility, 70 (43 females, 27 males) were randomized (Figure 1). There was no significant difference between groups regarding baseline characteristics: age, gender distribution, tooth-type distribution, number-of-canal distribution, and periapical radiolucencies ( $p > 0.05$ , Table 1). The piroxicam group showed significantly less pain intensity than the placebo group at 6, 12, 24 h postoperatively ( $p = 0.014$ , Table 2). The change in pain intensity over time for both groups is shown in Figure 2. A significant increase in

pain intensity from preoperative pain level occurred at 6, 12, 24, 48 and 72 h in the placebo group; no such increase occurred in the piroxicam group. Patients in the piroxicam group took less number of rescue analgesic tablets than those in the placebo group

( $p=0.019$ , Table 2). For the piroxicam group, 4 participants out of 35 received analgesics. For the placebo group, 13 participants out of 35 received analgesics. There were no swelling or adverse effects in both groups.

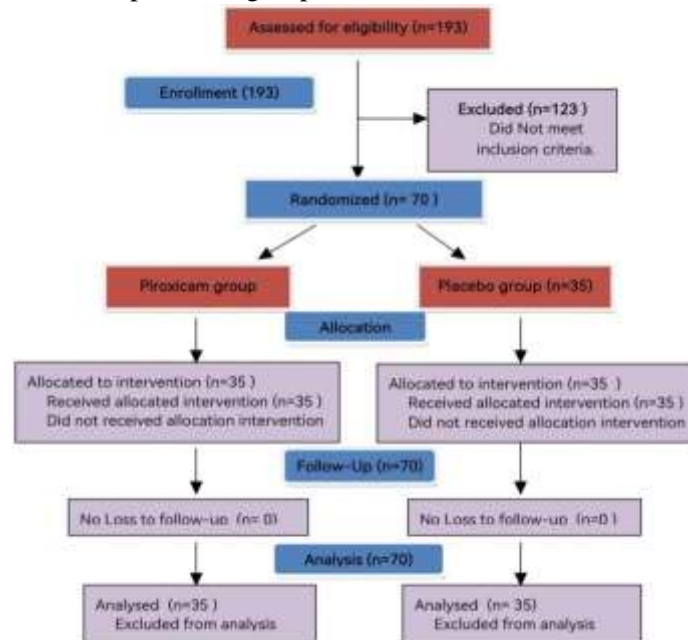


Figure (1): CONSORT flow diagram of the trial.

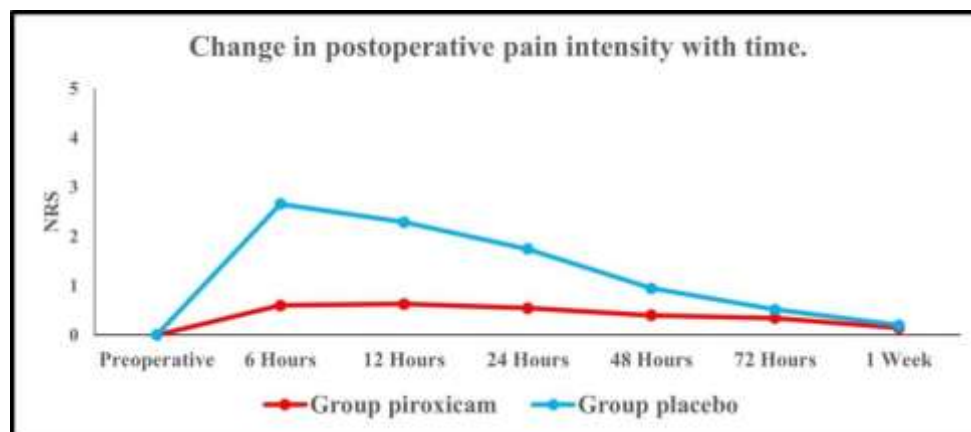


Figure (2): Pain intensity level over time for the piroxicam and the placebo groups.

Table (1): Baseline characteristics of the included study participants in the piroxicam and the placebo groups.

		Piroxicam group (n=35)	Placebo group (n=35)	P-Value
Age	Mean ± SD	32.66 (10.30)	33.4 (9.95)	0.76
	Median	33	32	
	(Min- Max)	(19 - 60)	(18 - 60)	

<b>Gender</b>	<b>Males</b>	<b>n (%)</b>	10/35 (28.60%)	17/35 (48.60%)	0.086
	<b>Females</b>	<b>n (%)</b>	25/35 (71.40 %)	18/35 (51.40%)	
<b>Molar Type</b>	<b>1<sup>st</sup> molars</b>	<b>n (%)</b>	26/35 (74.30%)	25/35(71.40%)	0.788
	<b>2<sup>nd</sup> molars</b>	<b>n (%)</b>	9/35 (25.70%)	10/35 (28.6%)	
<b>Number of canals</b>	<b>3 canals</b>	<b>n (%)</b>	30/35 (85.70%)	25/35 (82.90%)	0.743
	<b>4 canals</b>	<b>n (%)</b>	5/35 (14.30%)	10/35 (17.10%)	
<b>Periapical radiolucency</b>	<b>Present</b>	<b>n (%)</b>	24/35 (68.60%)	18/35(51.40%)	0.143
	<b>Absent</b>	<b>n (%)</b>	11/35 (31.40%)	17/35(48.60)	

SD, standard deviation; MDAS, Modified Dental Anxiety Scale.

**Table (2):** Pain intensity and number of analgesic tablets taken for the piroxicam and the placebo groups

	<b>Piroxicam Group</b>	<b>Placebo Group</b>	<b>p<sub>1</sub> - Value</b>
<b>Preoperative</b>			
<i>Mean (SD)</i>	0 (0)	0 (0)	
<i>Median (Range)</i>	0 (0 - 0)	0 (0 - 0)	1.000
<b>6 Hours</b>			
<i>Mean (SD)</i>	0.6 (1.97)	2.66 (3.26)	
<i>Median (Range)</i>	0 (0 - 10)	2 (0 - 10)	<0.001*
<b>12 Hours</b>			
<i>Mean (SD)</i>	0.63 (2.17)	2.29 (2.91)	
<i>Median (Range)</i>	0 (0 - 10)	2 (0 - 10)	<0.001*
<b>24 Hours</b>			
<i>Mean (SD)</i>	0.54 (1.90)	1.74 (2.44)	
<i>Median (Range)</i>	0 (0 - 9)	0 (0 - 8)	0.001*
<b>48 Hours</b>			
<i>Mean (SD)</i>	0.4 (1.42)	0.94 (1.88)	
<i>Median (Range)</i>	0 (0 - 7)	0 (0 - 7)	0.071
<b>72 Hours</b>			
<i>Mean (SD)</i>	0.34 (1.30)	0.51 (1.34)	
<i>Median (Range)</i>	0 (0 - 7)	0 (0 - 5)	0.45
<b>1 Week</b>			
<i>Mean (SD)</i>	0.14 (0.60)	0.20 (0.58)	
<i>Median (Range)</i>	0 (0 - 3)	0 (0 - 2)	0.432
<i>p<sub>2</sub> - value</i>	0.014*	< 0.001*	
<b>Number of analgesic tablets taken</b>			
<i>Mean (SD)</i>	0.43 (1.33)	1.11 (1.73)	
<i>Median (Range)</i>	0 (0 - 5)	0 (0 - 6)	0.019*

## Discussion

Postoperative pain management is one of the most challenging aspects of the clinical practice of endodontics<sup>(14)</sup>. Various classes of drugs have been studied for the management of postendodontic pain including NSAIDs, acetaminophen, opioids and steroids<sup>(15)</sup>. NSAIDs are commonly used for postendodontic pain control of which some types have not been much studied for pretreatment oral administration e.g. piroxicam<sup>(10-12)</sup>. Half lives of the NSAIDs vary but in general they can be divided into short-acting NSAIDs with half-lives less than six hours e.g. ibuprofen and long-acting NSAIDs with half-lives more than six hours e.g. piroxicam<sup>(16)</sup>. Thus, the aim of the study was to evaluate the effect of preoperative, single-dose piroxicam on postoperative pain in patients with asymptomatic non-vital pulp in mandibular molars treated in single visit.

This study was conducted as a double-blind parallel randomized clinical trial in which randomization permits the same chance for each patient to be allocated to either the intervention or the control group without operator's interference. A placebo was used for comparison since the incidence of a possible flare-up is low, ranging between 2.1% to 5.7% in non-vital teeth<sup>(17, 18)</sup>, and so the use of a premedication is still not routinely used by clinicians. The outcomes of the groups were compared after sufficient follow-up time. Randomized clinical trials are one of the designs providing the strongest evidence of the clinical efficacy of preventive and therapeutic procedures in the clinical setting. This should provide an unbiased estimate of the treatment effect<sup>(19)</sup>.

Studies evaluating the effect of 20 mg sublingual piroxicam in vital diseases cases showed promising results. Joshi et al.<sup>(7)</sup> evaluated the efficacy of preoperative oral piroxicam (40 mg) for the management of postendodontic pain in patients with symptomatic irreversible pulpitis and showed that piroxicam was effective in reducing postendodontic pain. Balasubramanian and Urrilcrishna<sup>(10)</sup> assessed if the preoperative use of a single dose of 20mg sublingual piroxicam and 20mg ketorolac would significantly reduce postendodontic pain when compared with 600mg ibuprofen following single-visit root canal treatment and showed that ketorolac and

piroxicam demonstrated significantly better pain relief than ibuprofen. Konagala et al.<sup>(11)</sup> compared the efficacy of preoperative administration of 20 mg piroxicam, with 4 mg dexamethasone or 30 mg deflazacort on postoperative endodontic pain in patients with symptomatic irreversible pulpitis and found that piroxicam, dexamethasone and deflazacort were equally effective in reducing the postoperative pain at 6, 12, and 24 hours. Suresh et al.,<sup>(12)</sup> compared the effect of preoperative oral administration of piroxicam, prednisolone, dexamethasone or placebo on postoperative endodontic pain after single-visit root canal treatment on patients diagnosed with symptomatic irreversible pulpitis and symptomatic apical periodontitis and found that piroxicam, prednisolone and dexamethasone equally effective in reducing the incidence and severity of postoperative pain up to 24h. Thus, it was worthy to study 20 mg piroxicam in a single visit necrotic cases.

Various tools are used for pain measurement. In the present study, the numerical rating scale (NRS) was used due to its higher compliance rates and responsiveness, its being easier to use, its being better understood by most patients and its having good applicability relative to other pain scales<sup>(20,21)</sup>. It was commonly used in previous studies to record pain after root canal treatment<sup>(22, 23)</sup>. It is, also, characterized by its high test reliability and validity<sup>(24)</sup>.

The experience of postoperative pain is multifactorial with several preoperative, intraoperative and postoperative contributing variables that could act as confounders requiring management to allow for more accurate results<sup>(25)</sup>. Preoperative factors that have been associated with postoperative pain include gender, age, tooth type and location, periapical radiolocencies and apprehension/anxiety<sup>(25, 26)</sup>. In the present study, baseline characteristics were balanced between the two groups (Table 1). The precautions to avoid flare up were used where a rubber dam was applied for isolation, the working length was determined using an electronic apex locator together with a confirmatory radiograph such that the working length was 0.5-1 mm from the radiographic apex, the canal preparation was done in a crown-down approach using NiTi system (ProTaper Next) which could lead to less debris extrusion, the canals were irrigated with 2.5%

sodium hypochlorite and a final flush was done using 17% EDTA to remove smear layer to allow for better sealer penetration into dentinal tubules and obturation was done using epoxy resin sealer with documented antibacterial properties<sup>(27, 28)</sup>.

Based on the results of the present study, it was found that the administration of 20 mg sublingual tablet piroxicam 1 hour before root canal treatment decreased postoperative pain level compared to placebo within the first 24 h. Postoperative pain decreased significantly earlier with piroxicam compared to placebo. This was in agreement with several previous studies<sup>(7, 10-12)</sup>. In the current study, the administration of piroxicam preoperatively also significantly reduced the number of rescue analgesic tablets used by patients.

Piroxicam is a NSAID with the main mechanism of action is by inhibition of the cyclooxygenase enzyme, resulting in reduced prostaglandin synthesis, which is responsible for pain and inflammation<sup>(29)</sup>. Piroxicam, also, inhibits thromboxane synthesis in platelets and, thus, inhibits the secondary phase of platelet aggregation. Since platelets can be involved in the inflammatory process, this action may contribute to the efficacy of piroxicam. Piroxicam has a long half-life, but, due to its slower absorption in the gastrointestinal tract, its onset of action is also slow<sup>(29)</sup>. When administered orally, it takes more than 30 minutes to produce appreciable relief of pain. Any formulation that could expedite the absorption of the active ingredient, and, thereby, the onset of analgesia, could, therefore, have a practical benefit in the management of postoperative pain. With this in view, a formulation of piroxicam, termed flash tablet (FT), was developed by Emcure Pharmaceuticals which, when administered sublingually, was observed to dissolve almost instantaneously and produced therapeutic serum levels of piroxicam earlier than the conventional piroxicam<sup>(30)</sup>. Such a formulation would be expected to induce analgesia earlier than a conventional formulation. The elimination half-life of piroxicam (50 h) is relatively long due to a low systemic clearance rate<sup>(30)</sup> which could explain its long-acting property.

In the present study, only mandibular molars were included; this could limit the

generalizability of the results to such teeth only. Future clinical trials including patients with different maxillary and mandibular teeth types are recommended to improve generalizability.

Within the conditions of this study, the preoperative administration of an oral, single dose of 20 mg sublingual, fast-dissolving piroxicam tablet can reduce the intensity and incidence of postoperative pain within the first 24 h and the number of analgesic tablets taken by the patient after single-visit treatment of patients with non-vital pulp in mandibular molars.

### Conclusion

Within the conditions of this study, the preoperative administration of an oral, single dose of 20 mg sublingual, fast-dissolving piroxicam tablet can reduce the intensity of postoperative pain within the first 24 h, and the number of analgesic tablets taken by the patient after single-visit treatment of patients with non-vital pulp in mandibular molars.

### Conflict of Interest:

Authors deny any conflict of interest.

### Funding:

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### Ethics

This study protocol was approved by the ethical committee of the Faculty of Dentistry- Cairo University on: 28/7/2019, approval number:19716.

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