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Research Article

The Effect of Premedication with Curcumin on Post-operative Pain in Single Visit Endodontic Treatment of Acute Pulpitis in Mandibular Molars: A Randomized Controlled Trial

Mohamed Sobhy Abdelnaby[1], Ghada El Hilaly Eid[1]* and Mohamed Ahmed El Nabarawi[2]

[1]Faculty of Dentistry, Department of Endodontics, Cairo University, Egypt

[2]Faculty of Pharmacy, Department of Pharmaceutics and Industrial Pharmacy, Cairo University, Egypt

***Corresponding Author:** Ghada El Hilaly Eid, Faculty of Dentistry, Department of Endodontics, Cairo University, Egypt.

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Abstract

Purpose: The purpose of this triple-blinded (patient, operator, and outcome assessor), 1:1 randomized clinical trial was comparing the effect of a single preoperative dose of Curcumin versus placebo on post-operative pain after single visit root canal treatment for symptomatic irreversible pulpitis in mandibular molars.

Methods: Forty-four patients suffering from symptomatic irreversible pulpitis of mandibular molars were randomly and equally allocated into two groups. Single oral dose of Curcumin (400 mg + 20 mg pepper) or placebo capsules was administered one hour before treatment. After inferior alveolar nerve block, root canal treatment was completed in a single visit. The need for supplemental anesthesia was recorded. Patients were instructed to score pain using visual analogue pain scale (VAS): preoperatively, immediately post-operative, 8, 12, 24 and 48 hours postoperative, as well as to state number of rescue analgesic tablets. Data were statistically analyzed; significance was set at P value ≤ 0.05.

Results: Baseline characteristics of both groups showed non-significant difference (P > .05). Curcumin group at 8, 12 and 24 hours revealed significantly less VAS values (44.2, 26.7, 19.1) than the placebo (58.5, 43.3, 30.3), respectively, (P < .05). Curcumin group significantly needed lower percentages supplemental anesthesia (27.3%) compared to placebo (68.2%), (P < 05). All patients in Curcumin group did not need rescue medication, while two patients in placebo took it.

Conclusions: Single preoperative oral dose of Curcumin proved to be an effective premedication that reduced post-operative pain as well as the need of supplemental anesthesia for patients diagnosed with symptomatic irreversible pulpitis of mandibular molars.

Keywords: Symptomatic Irreversible Pulpitis; Mandibular Molars; Post-operative Pain; Curcumin; Randomized Controlled Trial

Introduction

Post endodontic pain is one of the primary problems in single visit treatment in cases of irreversible pulpitis of mandibular molars. A systematic review reported post endodontic pain ranging from 25% to 40% in single visit treatment of diseased vital pulp cases [1]. The severity of pain is highest at six to eight hours after endodontic treatment[2]. Post-operative pain is attributed to periapical wound and inflammation resulting from pulp extirpation; whereby pain fibers get directly stimulated or sensitized by the released inflammatory mediators. In addition, the vascular dilation

and increased permeability cause edema and increased interstitial tissue response[3,4]. Common effective pharmacological premeditations are corticosteroids [5-7] and non-steroidal anti-inflammatory drug (NSAIDS) [8-11]. A systematic review showed ibuprofen 600 mg to be effective in relieving six-hour post endodontic pain [12] NSAIDS suppress the inflammation and pain by inhibition of cyclooxygenase enzymes (COX-1 and COX-2) which are responsible for production of the inflammatory mediator prostaglandin. However inhibition of the protective COX-1 to stomach lining increases the possibility of gastric ulcer occurrence [13]. Thus, nowadays there is a trend to shift to study natural (herbal) analgesic medication to overcome some of adverse effects of NSAIDS.

Curcumin (diferuloylmethane), the main yellow bioactive component of turmeric has been shown to have a wide spectrum of biological actions such as powerful antioxidant [14], anti-inflammatory [15], anti-bacterial, anti-viral and fungal effect [16], anti-platelets aggregation [17], effective in treatment of gastric ulcer [18]. Furthermore, medical clinical trials have been reported on the analgesic effect of Curcumin in reducing postsurgical pain [19], osteoarthritis [20] and rheumatoid arthritis [21]. In an vitro study; when used as intracanal medication, Curcumin reveals potent antibacterial activity against a number of pathogenic bacteria including Enterococcus Feacales [22]. While in an in-vivo, the use of Curcumin as intra canal medication, shows high analgesic and anti-inflammatory effect [23].

To the best of authors' knowledge, no randomized controlled trial evaluated the oral premedication effect of Curcumin on post-operative pain. Thus, the aim of this study to determine the effect of preoperative oral administration of Curcumin on the post-operative pain in single visit endodontic treatment of symptomatic irreversible pulpitis in mandibular molars teeth. The null hypothesis was that there will be no effect of preoperative administration of Curcumin on post-operative pain as compared to placebo.

Materials and Methods

Study design and setting

This 1:1 parallel randomized controlled trial was approved by evidence base and ethical committee, Faculty of Dentistry. The study protocol was registered on www. clinicaltrials.gov (Clinical Trials. Gov identifier: NCT04012424). Study reporting followed the Consolidated Standards of Reporting Trials guidelines. The trial took place in the outpatient clinic of the Department of Endodontics. Participants were asked to sign printed informed consent**;** after the investigator (a master's degree candidate) explained the aim of the study, treatment procedures and possible side effects.

Participant's eligibility criteria

Inclusion Criteria were males and females, with age range 20 - 55y suffering from symptomatic irreversible pulpitis in mature mandibular first or second molar teeth. Selected teeth were in normal occlusion. Exclusion criteria were cases with non-vital pulp, acute apical periodontitis or cases who took analgesic medication within 12-hour time. Non- restorable or periodontally affected teeth or cases with anatomic abnormalities as well as medically compromised patients were excluded.

Sample Size

The minimum sample required to detect differences between 2 groups (with type I error at 5% and power at 80%) was calculated to be 19 subjects/group; based on a previous study [24], using a clinical important difference of 40%. The sample size was increased to 22 participants per group considering a 15% dropout rate.

Randomization and blinding

Eligible participants were assigned to either intervention group: Curcumin (400 mg Curcumin" Curcumin, Shanghai, China" + 20 mg pepper) or a placebo group (420 mg starch). The random allocation sequence was generated by the main supervisor via (http://www.random.org/); with 22 participants/ group. Allocation concealment until intervention was done by placing the loaded capsules in sequentially numbered sealed opaque envelop according to the generated sequence. Both Curcumin and placebo capsules had the same color and shape. Thus, after assignment to the groups both operator and patients were blinded to the capsule content, the outcome assessor was also blinded. The code details were not revealed until the end of the study.

Diagnosis

Diagnosis was based on patient's chief complaint, and clinical and radiographic examination. Preoperatively patients experienced moderate to severe pain (45 - 100 mm readings on the visual analogue scale VAS). Pain was spontaneous or stimulated by thermal changes. Clinically they gave positive early response to ethyl

chloride cold test as well as to electric pulp testing (Denjoy DY310 Dental Pulp Tester, Denjoy Dental Co, Hunan, China). Healthy pulp was expected to respond to sensitivity testing by eliciting a short, sharp pain which subsides when the stimulus was removed. However, a lingering pain which continued despite the removal of the stimulus was indicative of irreversible pulpitis. Response of the suspected tooth at much lower current than the control tooth indicated diagnosis of symptomatic irreversible pulpitis. There was no pain on palpation or percussion. Periapical radiographs revealed absence of periapical involvement.

Intervention

Eligible participant was given the envelope containing the capsule and was asked to take the capsule-containing-premedication which was either: (Curcumin + pepper) or a placebo. One hour after medication, the tooth was anesthetized by Inferior Alveolar Nerve Block (IANB) using 1.8 ml of 4% Articaine HCl with 1:100,000 epinephrine (Artinibsa (4% carpule. inibsa, spain). Post-injection lip numbness was a subjective sign of IANB success.

After isolation with rubber dam, access cavity preparation was performed and canal patency confirmed with K-file size #10 (Mani, Mani Inc. Utsunomiya, Tochigi, Japan). Working length was determined using apex locator (iPex II, NSK, Japan), and confirmed radiographically to be 1 mm short of the radiographic apex. Root canals were prepared using M-Pro nickel titanium rotary instruments at a speed 450 rpm and torque 1.5Ncm (Endo motor, NSK, Japan). The rotary files were introduced inside the canal lubricated with EDTA Cream for easier negotiation (dMD-Chelcream, META BIOMED CO, Korea). Preparation was in crown down sequence as follows: orifice opener, # 20 4%, # 25 6%, and finally # 35 4%. The canals were irrigated using 2.5% NaOCl, at a rate 1 ml/30 seconds, by side vented 27-gauge needles reaching a maximum depth of 1 mm short of working length. If the patient experienced intraoperative pain, it was controlled by supplemental anesthesia, and treatment continued. Canals were dried using proper sized paper points and obturated with gutta-percha (Gutapercha, METABIOMED CO, Korea) using lateral compaction technique and ADSEAL sealer (ADSEAL, META BIOMDED CO., LTD, Korea). Access cavity was filled with temporary filling Coltosol; Coltene Brasil, Rio de Janeiro, RJ, Brazil), occlusal adjustment was made to avoid high spot. Post-obturation periapical radiograph (Kodak, USA, speed D, size 2) was taken.

Assessment of postoperative pain intensity

It was measured by marking on the 100 - mm line visual analog scale (VAS). Patients were given pain scale and were asked to mark on VAS sheet: immediately after treatment and at 8, 12, 24, 48 hours post-operatively. Patients delivered their sheets after 48 hours and were referred for permanent restoration. Readings were transformed into categories; no pain (ranges of 0 - 4 mm), mild pain (ranges of 5 - 44 mm), moderate pain (45 - 74 mm) and severe pain (75 - 100 mm) [25]. In case of severe pain, a rescue analgesic (ibuprofen 600 mg tab/8 hr) was prescribed and recorded for both groups. Primary outcome was postoperative pain. Secondary outcomes were the need for supplemental anesthesia and rescue medication.

Statistical analysis

Data were tested for normality with Kolmogorov-Smirnov test. Mann-Whitney U-test compared groups at each time point, while Repeated-Measure ANOVA and Wilcoxon Signed Rank test compared time points within each group A p - value < 0.05 was considered statistically significant.

Results

Sixty participants were accessed for eligibility. Sixteen patients were excluded for not meeting inclusion criteria. Forty-four were enrolled, randomly allocated in two groups. All participants were analyzed. None of the patients reported any side effects for up to 48 hours after the procedures.

Baseline characteristics

There was no significant difference between the groups regarding the following baseline characteristics: age, gender and pre-operative pain VAS scores and incidence of pain categories (P > .05), (Table 1).

Comparison of the pain scores between studied groups at each time point: Curcumin group had lower VAS scores values than placebo group at all-time interval and revealed significantly lower values at three intervals; 8 hours, 12 hours, and 24 hours. (p < .05), (Table 2).

Comparison of pain scores at different time points within each group: There was a statistically significant change in pain scores over almost all time points, (Table 2). Both groups showed the

			Curcumin Group A (n = 22)	**Placebo Group B** (n = 22)	***P*-value**
Age (years)		Mean ± SD (Range)	31.6 ± 9.8 (18 - 50)	38.7 ± 9.6 (20 - 52)	0.949
Gender		Male n (%)	10 (45.5%)	11 (50%)	0.763
Female n (%)		12 (54.5%)	11 (50%)		
Pre-operative pain	VAS score	Mean± SD (range)	83.9 ± 7.3 (65 - 94)	83.8 ± 7.5 (66 - 93)	0.814
	Pain incidence	Moderate: n (%)	3 (13.6%)	5 (%22.7)	0.698
		Severe: n (%)	19 (86.4%)	17(77.3%)	

Table 1: Comparison of demographic characteristics: age, gender and preoperative pain of studied group.

	Curcumin Group A (n = 22)		**Placebo Group B (n = 22)**		**P-value**
	Mean ± SD	95% CI	Mean ± SD	95% CI	
Preoperative	83.9 ±7.3	80.6, 87.1	83.8 ± 7.5	80.5, 87.2	0.814
Immediately post-operative	26.6 ± 17.7	18.8, 34.5	27.5 ± 17.9	19.5, 35.4	0.510
8-hours	44.2 ± 15.8	37.2, 51.2	58.5 ± 13.5	52.5, 64.4	0.001
12-hours	26.7 ± 13.4	20.8, 32.7	43.3 ± 17.5	35.5, 51.0	0.001
24-hours	19.1 ± 8.4	15.4, 22.9	30.3 ± 14.3	23.9, 36.6	0.002
48-hours	9.0 ± 8.5	5.3, 12.8	15.2 ± 10.1	10.7, 19.7	0.054
P-value	< 0.001*		<0.001*		

Table 2: Stastitical analysis of the VAS pain scores between studied groups at each time point (horizontal) and comparison of all time points within each group (vertical).

*. Statistically significant mean difference (p-value < 0.05)

same pattern of decrease of pain up to immediate post-operative followed by a sharp increase at the 8-hour time point followed by a decreasing tend up to 48- hour time point.

Comparison of incidence of pain categories between the two groups at each time point: In Curcumin group there was significant difference at 8 hours post-operative where nearly half patients had mild pain (54.5%) and the remaining had moderate pain (45.5%), while in placebo group almost all patients (95.5%) had moderate pain (P value < 0.001). At 12 hours post-operative significantly lower incidence of pain also occurred in Curcumin group; where mild or no pain occurred in nearly all patients in Curcumin group (95.5%) versus half patients (50%) in placebo group (P value = 0.002), (Figure 1).

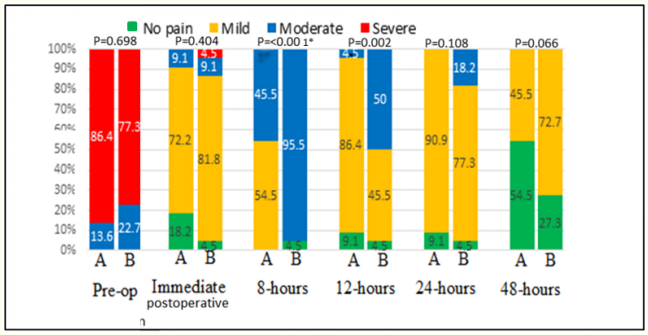

Figure 3: Stacked bar chart showing comparison of incidence of pain categories between the two groups at each time point; Group A: Curcumin, and Group B: Placebo.

*Statistically significant (p-value <0.05).

Comparison between groups for the need of supplemental anesthesia: Significantly lower percentages of patients needed supplemental anesthesia in Curcumin group (n = 6, 27.3%) compared to placebo (n = 15, 68.2%); (p value = 0.004).

Comparison between groups for the need of rescue analgesic: All patients in Curcumin group did not need analgesics, while two patients in placebo group took analgesics (p value = 0.488).

Discussion

Ultimate Control of pain during and after root canal treatment still presents a clinical demand. Patients with severe preoperative pain still present challenge for intraoperative pain and postoperative pain control especially in cases of mandibular molars [1,26]. A decreased susceptibility to pulpal anesthesia of mandibular molars compared to maxillary molars which might be due to various factors such as the different bony landmark, anatomical variation, needle deflection, accessory innervations[27].

Premedication proved to be effective in both reduction of postoperative pain [28] and pain during root canal treatment [26]. Nevertheless, Pharmacological premeditations do not guarantee a 100% pain free endodontic treatment and still with possible adverse effect.

Up to date, no randomized controlled trial studied the effect of the natural herb, Curcumin on post endodontic pain.

Curcumin was chosen on basis of the medical clinical trials that reported on its analgesic effect and role in reducing postsurgical pain [19], osteoarthritis [20] and rheumatoid arthritis [21]. This analgesic and inflammatory effects were explained by; first Curcumin capacity to inhibit prostaglandin2 production via the inhibition of COX-2 gene expression and inhibition of arachidonic acid metabolism via lipoxygenase and scavenging of free radicals generated in this pathway. Thus cyclo oxygenase path would be blocked and pain sensation would be prevented before it even begins, second to stimulate cortisol production by adrenal gland, third to deplete nerve ending of the neurotransmitter substance, fourth Curcumin provides down regulation of inflammatory cytokines namely: interleukins-1, 2, 5, 6, 8, 12 and TNF-a [15,19], fifth it down regulates enzymes, such as protein kinase C that mediate inflammation [15]. The efficacy and safety of Curcumin were reported in a randomized controlled trial that studied Curcumin versus diclofenac in patients with active rheumatoid arthritis [21], as well as another trial that studied curcuma domestica extracts versus ibuprofen in patients with knee osteoarthritis [20]. Both studies concluded that most of adverse effects occurred more frequently with sodium diclofenac or ibuprofen Interestingly, Curcumin group showed significantly better improvement in cases of rheumatoid arthritis than the patients in the diclofenac sodium group (19). Pain reduction in Curcumin group was non inferior to those for the ibuprofen group in patients with knee osteoarthritis (18). The pharmacokinetics and pharmacodynamics of Curcumin have been widely investigated; the liver appears to be the major organ responsible for metabolism of Curcumin [29].

The present study used 400 mg Curcumin in accordance with Drobnic., *et al.* [30] who reported that 400 mg Curcumin was better in analgesic effect and gastric tolerability compared with 500 mg acetaminophen. Furthermore, 20 mg pepper was added for increasing Curcumin bioavailability [31]. Curcumin has poor bioavailability, piperine had been shown to significantly enhance curcumin's bioavailability 2000% [31]. Additionally, nanotechnology-based novel strategies are being aggressively explored worldwide to enhance curcumin's bioavailability [32].

The control group was chosen to be placebo to avoid bias and assures that if improvement occurred only in the intervention group, this surely resulted from the investigated treatment. A standard rescue medication (ibuprofen600 tab/8hr) and emergency appointment were offered for patients in case of severe pain.

During shaping and cleaning; Irrigation was done during mechanical preparation using 2.6% freshly prepared sodium hypochlorite [33]. Several precautions aided to decrease the possibility of extrusion of irrigants to periapical area with its possible confounding effect on postoperative pain: first, a side vented needle 27-gauge was inserted to maximum depth of 1mm shorter of the working length. Second, irrigation was delivered at a slow rate 1 ml/30 second.

Curcumin was tolerated by the patient. No patient reported any side systemic effects from this single preoperative dose of Curcumin + pepper capsule. This may be attributed to the fact that Curcumin blocks cox2 only while NSAIDS block both cox1 and cox2, which can cause gastrointestinal effects [13].

Base line characteristics; age, gender, and the preoperative pain, were homogenous and statistically non-significant in both groups This eliminates their possible confounding effects[34].

The present study revealed that the null hypothesis was rejected at 8 and 12 hours. At these time points, there was significant decrease of both pain scores readings and incidence of pain categories in Curcumin group compared to placebo at these time points. The pattern of pain along different time points was similar in both groups, though Curcumin group revealed lower pain scores compared to placebo group.

The decrease in immediate-postoperative-pain in both groups to 26.6 mm in Curcumin group and to 27.5 mm in placebo group is expected because of the effect of local anesthesia where pulpal anesthesia usually lasts for 60 to 90 minutes [35].

The spike in pain values at 8 hours post-operative in both groups was similarly observed when using pharmacological analgesics or placebo [8,9,11]. It was explained that post treatment severity levels may be caused by ongoing inflammatory processes; apical instrumentation; injection of local anesthetic; pressure from a rubber dam clamp; or discomfort because of prolonged mouth opening [2]. The good news is that pain spike values was lower in Curcumin 44.2 mm, compared to placebo 58 mm, and that it was nearly within the mild range.

A further reduction of pain occurred at 12 hours postoperative in both groups. Similar pain reduction at 12 hours was observed in other studies with other pharmacological drugs [36,37] or placebo [8,36,37]. The reduction was more in Curcumin group 26.7 mm than placebo 44.3 mm. This reduction can be attributed to pharmacodynamics of Curcumin where it is reported that peak analgesia and anti-inflammatory is experienced at 1 to 2 hours and has long half-life lasts for 12 hours [38]. On the other hand, the placebo group lacks this anti-inflammatory effect, thus the pain spike was of greater value.

At 24 hours postoperative further reduction in pain values occurred in both groups, which was more in Curcumin group 19.1 mm versus placebo 30.3 mm. Both values were in the mild tolerated range. Similar trend of reduction of postoperative pain at this point was observed in other studies that used pharmacological drugs [7-9,11,39] or placebo [8,36,37]. At 48 hours post-operative pain decreased to 9 mm in Curcumin and 15.2 mm in placebo. All patients in both groups had mild or no pain**.** Moderate and Severe pain were absent in both groups. Similar trend of pain reduction trend was revealed in other studies [8,39]. This follows the decline of inflammatory reaction in the tissues by time.

Regarding the need of supplemental anesthesia, results showed that higher proportions of patients in Curcumin group (72.7%) did not need supplemental anesthesia, compared to patients in placebo group (31.8%). It was observed that all patients who took supplemental anesthesia in both groups suffered from preoperative severe pain. However, well organized observational studies might be useful to decide risk factors. Worthy to state that in Curcumin group, the percentage of patients who did not need supplemental anesthesia was almost similar to a study that used diclofenac potassium (75%) [40]. Also in the placebo group of the current study, the percentage of patients who did not need supplemental anesthesia was almost similar to a previous study [41].

Ibuprofen was prescribed as rescue medication for post-operative pain relief after root canal treatment [12]; where only two patients (9%) in placebo group took the rescue medication. The low percentage in the present study might be related to the low intensity and short duration of pain.

Thus, by using Curcumin premedication, though participants exhibited the pain spike at 8-hour, pain values along postoperative time points lied in the mild range (tolerable); explaining the reason that no one in the Curcumin group took rescue medication and lower proportion of patients (27.8%) needed supplemental anesthesia compared to placebo (68.2%). It appeared that preoperative Curcumin administration aided intraoperative pain control and reduced post-operative pain duration and intensity to a tolerable level. These emphasize the possible anti-inflammatory role of Curcumin use as a routine oral premedication. However, further randomized clinical trials are recommended to establish the direct comparison of Curcumin versus other NSAIDS.

Conclusion

Within the limitations of this study, it could be concluded that: premedication with single oral dose Curcumin is recommended as it provides an effective, safe, inexpensive reduction in intraoperative and post endodontic pain in single visit endodontic treatment

of mandibular molars with symptomatic irreversible pulpitis. Further clinical studies are recommended: first to examine the effect of Curcumin premedication on both success of inferior alveolar nerve block and postoperative pain control in different pulp and periapical conditions, second: to compare the effect of premedication of Curcumin versus other non-steroidal anti-inflammatory drugs on post endodontic pain.

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