10.21608/adjc.2023.211035.1310 Advanced Dental Journal
Volume 6 (2024) | Issue 1| Pages 51-59

Original Article

Effect of Preoperative Single Dose of Sodium Ibuprofen versus Placebo on Postoperative Pain for Patient with Symptomatic Irreversible Pulpitis Related to Mandibular Molar Teeth: Double Blind Randomized Controlled Trial

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Submitted: 14-5-2023
Accepted: 26-9-2023

Abstract

Aim: The purpose of this study was to compare postoperative pain and the amount of analgesic intake after administration of preoperative single dose of sodium ibuprofen versus placebo in lower molar teeth with symptomatic irreversible pulpitis (SIP).

Subjects and methods: Fifty patients were randomly divided into two groups, in the experimental group, patients were given one tablet of sodium ibuprofen (NUROFEN) 256 mg, 30 minutes before endodontic treatment and control group patients received one placebo tablet, 30 minutes before endodontic treatment. Participants rated their pain using visual analogue pain scale (VAS) preoperatively and at 5 time points: immediately post-operative, 6, 12, 24 and 48 hours and number of analgesic tablets taken up to 48 hours postoperatively.

Results: Baseline characteristics of both groups showed non-significant differences (P >0.05). Sodium ibuprofen group revealed statistically significantly less postoperative pain levels as mean VAS values (14.08, 13.04, 9.64) were lower than the placebo (36.68, 26.68, 19.04) at 6, 12, and 24 hours. No patient reported analgesic intake

Conclusion: : Within the study limitations, Single preoperative oral dose of Nurofen proved to be an effective premedication that reduced post-operative pain for patients diagnosed with symptomatic irreversible pulpitis of mandibular molars.

Keywords: symptomatic irreversible pulpitis; mandibular molars; post-operative pain; sodium ibuprofen; randomized controlled trial.

I. INTRODUCTION

The main goals of endodontic treatment are to avoid post-operative pain and to eliminate bacteria from the root canal system [(1)]. More than 40% of endodontic patients have reported various degrees of pain after endodontic treatment [(2, 3)]. Many factors affect the occurrence of postoperative pain including mechanical, chemical, and microbial factors which are responsible for periradicular irritation [(4, 5)]. The cause of postoperative endodontic pain is inflammatory mediators (prostaglandin, leukotriens, bradykinin, serotonin ..etc) that activate sensitive

nociceptors leading to both peripheral and central mechanisms of hyperalgesia, among inflammatory mediators, prostaglandins play a critical role in the pathogenesis of pulp and periapical disease [6, 7, 8, 9].

Many pharmacological agents have been used to manage endodontic pain, including nonsteroidal anti-inflammatory Drugs (NSAIDs), corticosteroids, opioids, and combinations of drugs [10, 11, 12, 13]. Currently, studies have recorded that administration of single dose of some of these pharmacological agents have the ability to decrease the incidence and severity of postoperative endodontic pain, as it acts to reduce the inflammatory process before it begins [14]. In 2016, the ADA Delegation House adopted a statement that said, "Dentists should consider non-steroidal anti-inflammatory analgesics as a first-line therapy for the management of acute pain (ADA Science Institute 2019). In human dental pulps with irreversible pulpitis, there is a higher level of expression of COX 2. NSAIDs are widely used to control post-endodontic pain. They act by blocking the activity of cyclooxygenase (COX1 and 2) enzyme [15]. They can be administered preoperatively were they reduce the level of PGE2, which is responsible for sensitization of nociceptors[16, 17]. Ibuprofen is one of the most commonly used NSAIDs and a potent inhibitor of prostaglandin (PG) synthesis that can manage various pain types and has anti-inflammatory activity[18, 19, 20]. Enhancements in ibuprofen acid's pharmacokinetics have led to the development of ibuprofen salts with a faster dissolution rate and onset of action. These ibuprofen salts include ibuprofen lysine, ibuprofen arginine, and ibuprofen sodium dihydrate [21, 22].
Fast acting formulations of analgesics like Sodium ibuprofen, have valuable addition in managing endodontic pain regarding the onset of action, analgesic efficacy, saving time for the patient and clinician due to its rapid onset of action it, delivering maximum plasma drug concentrations at about 30 to 40

minutes, compared with around 90 to 120 minutes for standard ibuprofen acid formulations [23]. A comprehensive search of literature was done, and no studies were found on the effect of ibuprofen's onset of action on postoperative pain in endodontics. Therefore, the aim of this study was to compare postoperative pain and the amount of analgesic intake after administration of preoperative single dose of sodium ibuprofen versus placebo in lower molar teeth with symptomatic irreversible pulpitis (SIP) following endodontic treatment.

II. SUBJECTS AND METHODS

This study was conducted in the Endodontics department, Faculty of Dentistry, Cairo University, Cairo, Egypt between November, 2021 and September 2022. The Research Ethics Board of the University approved the study protocol. Sample size was calculated using the (PS software) and was found to be 22 patients per group, making the total sample size 44 patients (2 groups), increased to 50 patients to compensate for the 15% dropout. For the allocation concealment in this study, the medication and placebo were packed by the assistant supervisor in 50 sequentially arranged, opaque, sealed envelopes. Patients were randomly distributed into two groups by using a Web program available at www.randomizer.org.

A. Inclusion and Exclusion Criteria

The inclusion criteria were healthy patients, aged 18-45, having restorable mandibular molars with symptomatic irreversible pulpitis with preoperative sharp, moderate, or severe pain with normal periapical radiographic appearance or slight widening in lamina dura.

The exclusion criteria were medically compromised, intolerance to NSAIDS, Patients taking analgesic or antibiotics in the last 12 hour, pregnant women and lower molars that were non-restorable, necrotic, swelling, immature, mobile or with pocket depth greater than 5mm. Radiographically, evidence of vertical root fracture, perforation or calcification excluded the tooth.

B. Treatment Procedure

Pre-operative pain assessment: All included cases were symptomatic.

After proper diagnosis, informed consents were signed. Demographic data (age, gender, and tooth number) were recorded and preoperative pain levels were taken on VAS charts (The VAS consists a 10-cm line anchored by 2 extremes, ''no pain'' and ''pain as bad as it could be.'' Patients were asked to make a mark on the line that represents their level of perceived pain). Readings were transformed into categories; no

pain (range of 0-4mm), mild pain (range of 5-44mm), moderate pain (range of 45-74mm) and severe pain (range of 75-100mm) [24]. the patient who conformed to all eligibility criteria was enrolled in the study. The operator treated all included cases in a single visit. Each patient was given pain scale chart in order to record his /her pain level before any intervention.

According to the randomization sequence, patients were assigned to one of two groups and the treatment was done in a single appointment, the endodontic procedure was written in a special form. In the experimental group, patients were given one tablet of Nurofen (Figure 1), 30 minutes before endodontic treatment and control group patients received one placebo tablet, 30 minutes before endodontic treatment.

A single operator performed all the procedures. Patients received 1 cartridge of mepivacaine hydrochloride 2% with 1:100,000 epinephrine (Scandonest, Septodont, France). Rubber dam isolation and access cavity preparation were performed. The canals were explored using #8 hand stainless steel K files (Dentsply Maillefer, Ballaigues, Switzerland). Working length was determined using a Root ZX apex locator (J Morita Corp, Kyoto, Japan) and confirmed radiographically. Rotary MPro (IMD, Shanghai, China) system with a gear reduction torque-controlled motor X-Smart (X-Smart, Dentsply, Maillefer, USA) set to the instructions provided by the manufacturer was used to prepare the canals.

The files were used sequentially. The coronal two-thirds of the canal was enlarged using MPro file (18/.09) as an orifice opener in a continuous motion (speed 500 rpm, torque 3Ncm) followed by, file (20/.04) and then (25/.06) (Speed 500 RPM, torque 1.5 Ncm). In and out motions were used in the cervical, middle, and apical thirds with stroke lengths no greater than 3 mm till the full working length. In and out motions were used in the cervical, middle, and apical thirds with stroke lengths no greater than 3 mm till the full working length. The final file reached in the case of 4 canaled molars was (25/.06), while in case of single distal canal, (35/.04) was used and canals were thoroughly irrigated using 3ml 2.5% sodium hypochlorite by a side-vented needle. To achieve standardization, the volume of irrigation was fixed (3ml) after each file. EDTA gel was used as a lubricant and was applied on each file upon using it. Also, between every two subsequent instruments. To remove the smear layer, final irrigation was done with 5 ml of 2.5 % sodium hypoclorite followed by 3 ml of EDTA solution for 1 min. Final rinse was done with saline. Master cone-fit radiograph, with the corresponding- size cones as the master apical files, was taken to ensure proper length and preparation. The canals were dried with paper points corresponding to the same size of the master cone. Obturation was carried out using modified single-cone technique with resin sealer (Adseal, Meta Biomed Co. Ltd, Korea) and a spreader was selected to provide space for auxiliary cones. After obturation, a cotton pellet was placed in the pulp chamber and the access cavity was sealed with intermediate restorative material (IRM).

Patients were asked to rate their pain levels according to given instructions on a Visual Analogue Scale (VAS) immediately after obturation, 6, 12, 24, and 48 hours after treatment. If needed, the operator prescribed a suitable analgesic (Ibuprofen 400 mg) and instructed the patients to record the number of analgesic tablets taken in the previously provided chart. Patients returned for follow up after the 2-day interval to hand in the given charts to the operator.

C. Statistical Analysis

Continuous data were tested for normality using Shapiro Wilk test. Continuous data were presented as mean, standard deviation (SD), median and range values. Independent t test was used for between-group comparison of normally distributed data, while Mann – Whitney U test was used for between-group comparison of non-normally distributed data. Friedman and Wilcoxon signed rank tests were used for within-group comparison of non-normally distributed data. Categorical data was presented as frequencies (N) and percentages (%) and were analyzed using Chi square or Fisher exact tests. Significance level for primary tests was set at $p < 0.05$. Statistical analysis was performed using SPSS software.

Figure (1): NUROFEN

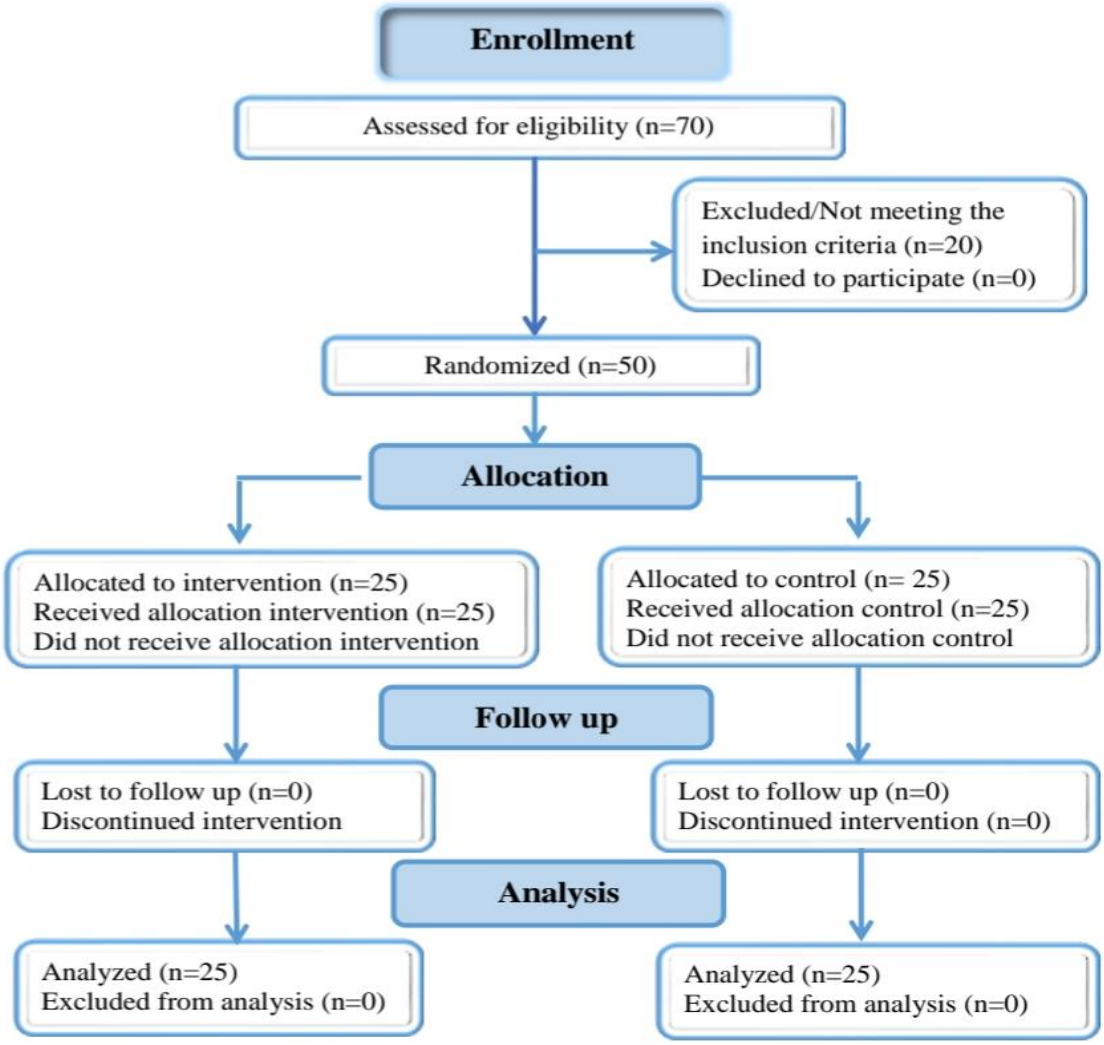

Figure (2): CONSORT flow diagram

III. RESULTS

A summary of the study is in the Consort diagram (Fig. 2). A total of 70 patients were assessed for eligibility in the department of endodontics, Cairo university. 20 patients were excluded leaving 50 patients to be randomly divided into 2 groups of 25. There were no statistically significant differences among the groups in terms of demographic data ($P > .05$) (Table 1). The intergroup and intragroup comparisons are presented in table (2) regarding pain intensity in both intervention and control groups. Statistically significant difference was found among the groups ($P < .05$) at 6, 12, and 24 hours postoperatively. In each group, a statistically significant difference was found when comparing preoperative pain to all other time intervals ($P < 0.001$) (Table 2). Intergroup comparisons between both techniques regarding analgesic intake have shown no statistically significant difference within different follow-up periods ($P > .05$). No patient reported analgesic intake in the two groups.

Table (1): Summary of statistics of Demographic Data for Intervention Group and Control Group

Parameter			Intervention	Control	p – Value
Gender	**Male**	**N**	13	12	
		%	52%	48%	0.777
	Female	**N**	12	13	
		%	48%	52%	
Age	***Mean (SD)***		30.96 (4.28)	31.08 (3.98)	0.919
	Median (Range)		30 (24 - 39)	31 (25 - 39)	

Table (2): Descriptive statistics, results of Mann – Whitney U test for comparison of pain intensities at different time intervals between the two groups and results of Friedman test for comparison of pain intensities at different time intervals within each group

*: significant ($p<0.05$)

Follow-up	Intervention group		Control group		P value
	Mean (SD)	**Median (Range)**	**Mean (SD)**	**Median (Range)**	
Preoperative	76. (10.12)	78 (52 -93)	76.4 (11.81)	79 (49 - 92)	0.641
Immediately postoperative	20.92 (21.26)	25 (0 - 72)	31.92 (23.1)	35 (0 - 72)	0.109
6 hours	14.08 (17.58)	0 (0 - 65)	36.68 (22.82)	40 (0 - 70)	<0.001*
12 hours	13.04 (15.57)	0 (0 - 40)	26.68 (19.3)	30 (0 - 55)	0.012*
24 hours	9.64 (13.82)	0 (0 - 38)	19.04 (17.16)	25 (0 - 49)	0.044*
48 hours	5.24 (9.87)	0 (0 - 31)	11.0 (13.04)	0 (0 - 30)	0.091
P value	<0.001*		<0.001*		

IV. DISCUSSION

Postoperative pain presents an important concern for both clinicians and patients. Patients may even think that the clinician's success in controlling postoperative pain is a reflection of his or her skills and knowledge [(25)]. Many pharmacological agents have been used to manage endodontic pain, including non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, opioids, and combinations of drugs [(10, 11, 12, 13)]. It has been demonstrated that a preoperative single oral dose of anti-inflammatory drugs can regulate the release of inflammatory mediators and reduce the amount of side effects compared with repeated doses during the postoperative period [(3, 26, 27)].

Several Systematic reviews reported that the preoperative use of a single dose of NSAIDs such as Ibuprofen, Tenoxicam, Rofecoxib, Etodolac, Piroxicam, Ketoprofen, Diflunisal, Fast acting ibuprofen, Flurbiprofen, Naproxen, Lornoxicam, Celecoxib, Ketorolac, Mefenamic acid, Endomethacin, Diclofenac, and Nemosulide are effective in reducing the post-operative pain [(28, 29, 30, 31, 32, 13)].

Modifications in analgesics pharmacokinetics lead to the development of formulations with faster absorption and onset of action. Pharmacokinetic studies showed that fast-dissolving ibuprofen formulations had faster absorption, resulting in a greater maximum plasma concentration (Cmax) and shorter times to maximum concentration (Tmax). Tmax for sodium ibuprofen was less than

half that of standard ibuprofen (median 35 minutes vs 90 minutes) and had a significantly higher Cmax [34]. Also clinical trials recorded that the Tmax with ibuprofen sodium is achieved in approximately 30 to 40 minutes, in contrast to the 1 to 2 hours reported for standard ibuprofen tablets [18, 35, 36]

In the present study, fifty symptomatic mandibular molars were selected, in double-blinded parallel randomized clinical trial. Randomization makes the groups of the study as similar as possible and allows each patient to take the same chance of being assigned to either the intervention or the control group without any choice of the operator [37, 38]. All the selected teeth were symptomatic as it has been established through many studies that the presence of pre-operative pain is a significant predictor of post-operative pain [39, 40, 41, 42, 43].

Post-operative pain which is the primary outcome of our study is a subjective outcome which is based on patients' perception of pain and degree of pain threshold. Using Visual Analogue Scale (VAS) to assess pain levels was proven to be a reliable and efficient method [42, 44]. In our study pain was assessed with a VAS consists a 10-cm line anchored by 2 extremes, ''no pain'' and ''pain as bad as it could be [45].'' Patients were asked to make a mark on the line that represents their level of perceived pain. Readings were transformed into categories; no pain (range of 0-4mm), mild pain (range of 5-44mm), moderate pain (range of 45-74mm) and severe pain (range of 75-100mm**)** [24].

In the present study Nurofen (NUROFEN, Reckitt Benckiser Healthcare UK) which is sodium ibuprofen belonging to NSAIDs was used as a preoperative medication and was given 30 minutes before endodontic treatment. Modification in analgesic pharmacokinetic lead to development of fast-dissolving ibuprofen formulations which had faster absorption, so faster onset of analgesia.

A follow up period of 48 hours was chosen for this study as it represents short term postoperative pain [40]. The same follow up period was adopted by similar studies [45, 46]. According to a comprehensive reviews**,** post-operative pain levels dramatically decreased in the first two days [44, 47]. Additionally, it was noted that the first 24 hours had the highest documented pain levels.

Findings of our study revealed that using single dose of sodium ibuprofen preoperatively significantly reduced postoperative pain severity at 6, 12, and 24 hours compared to placebo.

Our finding that sodium ibuprofen significantly reduced postoperative pain agreed with Taggar et al, who recorded that using a single dose of sodium ibuprofen (Advil tablet) provided faster and greater pain relief and greater reduction in the mechanical allodynia compared with conventional Ibuprofen acid for patients with symptomatic irreversible pulpitis and symptomatic apical periodontitis before initiation of endodontic treatment[48]. It has been reported that using fast acting formulations of ibuprofen provided faster and better overall pain relief with less frequent need for additional analgesics following third molar extraction [22, 49]. Moore et al in his review stated that fast acting ibuprofen formulations gave both earlier pain relief than normal formulations and more patients with good pain reduction throughout the first 6 hours according to data from almost 10,000 patients [23]. Furthermore it has been shown that lower doses of faster onset ibuprofen can be as effective as higher doses of standard formulations [34]; furthermore faster onset formulations lead to quicker pain relief and higher serum concentrations. This earlier onset and higher serum concentration lead to greater benefits without an apparent increase in adverse events [50].

Results of our study are in contrast to Attar et al, who investigated the pre-treatment use of a single-dose of fast acting ibuprofen (liquigel) with conventional ibuprofen tablets and placebo for postoperative endodontic pain. They found that using ibuprofen liquid gel as well as conventional ibuprofen did not significantly reduce postoperative pain [51]. The small sample size (nearly 13 in each group) that is additionally underpowered by the variability in patient characteristics (pulpal and periapical conditions) and the type of root canal treatment procedures (single visit and multiple visits) in this study design may prevent findings from being extrapolated.

No significant difference between the two groups at 48 hours as pain declines after 24 hours in agreement with **Pak and White** [47]. No analgesics were taken postoperatively as pain decreased with time.

V. CONCLUSION

Within the limitations of the present study, Single preoperative oral dose of Nurofen proved to be an effective premedication that reduced post-

operative pain for patients diagnosed with symptomatic irreversible pulpitis of mandibular molars.

Conflict of Interest:

The authors declare no conflict of interest.

Funding:

No specific grant was given to this research by funding organizations in the public, private, or not-for-profit sectors.

Ethics:

This study protocol was approved by the ethical committee of the faculty of dentistryCairo University on: 28/9/2021, approval number: 14 9 21.

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