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Research Article

Effect of Ketorolac Premedication on Anesthetic Efficiency of Inferior Alveolar Nerve Block, Pre-Treatment and Post-Endodontic Pain in Teeth with Irreversible Pulpitis: A Randomized Controlled Double Blinded Trial

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Abstract

Introduction: Anesthetic efficacy of inferior alveolar nerve block (IANB) decreases in patients with irreversible pulpitis (IP). It was hypothesized that premedication with nonsteroidal anti-inflammatory (NSAID) drugs might improve the success rates in patients with inflamed pulps. The aim of this study was to assess effect of ketorolac premedication on the effectiveness of the IANB anesthesia, pretreatment and postoperative pain in patients with symptomatic (IP).

Materials and Methods: Thirty-eight adult patients with symptomatic IP of a mandibular molar tooth participated in this randomized, controlled, double-blinded study. The patients indicated their preoperative pain scores on NRS and were divided into 2 groups and were randomly given 1 of the 2 drugs including 10 mg ketorolac or placebo tablet 1h before anesthesia. The patients were again asked to rate their preoperative pain scores after 1h from analgesic intake on the numerical rating scale (NRS). All patients received standard IANB of 2% mepivacaine with 1:100,000 epinephrine. After 15 minutes of IANB, the teeth were tested with cold spray and endodontic access preparation was initiated after confirmation of lip numbness and success of cold testing. Pain during treatment was recorded by using NRS. Success was defined as none or mild pain during cold testing, access cavity preparation and instrumentation. Single-visit root canal treatment was done. Patients were asked to record their pain level 6, 12, 24 and 48 h after endodontic treatment on the NRS.

Results: Premedication with ketorolac gave 57.9%, and premedication with placebo gave 47.4% success rate of IANB. There was no significant difference between the 2 groups. A statistically significant difference between the two groups was found in the preoperative pain intensity at 1h after premedication intake and no differences were found in terms of the intensity of postoperative pain at the assessed time points.

Conclusion: Preoperative administration of ketorolac significantly decreased the preoperative pain intensity at 1 h after premedication intake but did not seem to affect the success rate of IANB nor the postoperative pain intensity at different time intervals in patients with IP in mandibular molars.

Keywords: Inferior Alveolar Nerve Block; Irreversible Pulpitis; Ketorolac; NSAIDS; Postoperative Pain; Numerical Rating Scale; Root Canal Treatment

Abbreviations

EDTA: Ethylenediaminetetraacetic Acid; IANB: Inferior Alveolar Nerve Block; IP: Irreversible Pulpitis; NSAID: Nonsteroidal Anti-Inflammatory; NRS: Numerical Rating Scale; PGs: Prostaglandins; TTXr: Tetrodotoxin Resistant.

Introduction

Pain management in clinical practice represents a challenge for each endodontist. Profound pain control starts with effective local anesthesia. Conventional IANB is the most common technique used in root canal treatment of mandibular posterior teeth. However, the success rate is greatly reduced in cases with IP [1,2]. Various mechanisms have been hypothesized to explain the failure of local anesthetics including anatomic variations like cross innervations and accessory innervations, tachyphylaxis of anesthetic solutions, ion trapping, reduced local pH, patient's level of anxiety, presence of preoperative pain, and activation of nociceptors including tetrodotoxin resistant (TTXr) class of sodium channels. In pulp diagnosed with IP, there is an increased expression of this class of channels that are shown to be resistant to the action of local anesthetics [3-8].

Several approaches have been attempted for managing local anesthetic failures, such as use of supplemental anesthesia, using different type of local anesthetic solution, changing the local anesthetic volume, and adding adjuvants to the local anesthesia [9-12]. During endodontic procedures, oral premedication with can result in an increase in success rate of IANB in teeth with IP. NSAID reduce nociceptor activation by blocking the cyclooxygenase enzyme in the pathway that produces prostaglandins (PGs); hence reduce levels of inflammatory mediators. PGs act by sensitizing nerve endings to bradykinins and histamines and hence enhance the pain and tenderness of inflammation [13-15].

Ketorolac is a non-selective NSAID, which is considered as effective as narcotics for pain relief [16]. It is pyrrole-pyrrole derivative. The mechanisms proposed for the efficiency of ketorolac include inhibition of conduction of C fibers, which are more resistant to local anesthesia than A-delta fibers. In addition to opening of the K+ channels located within the primary afferent nerve endings resulting in anti-nociceptive state, thus increasing the success rate of IANB anesthesia [17].

Decision-making in modern endodontic practice should be based on evidence-based investigations. A search of the PubMed, Cochrane databases and hand searching resulted in showing that ketorolac was effective in improving the success rate of IANB using 2% lidocaine with 1:100,000 epinephrine [18-20] and 4% articaine with 1:100,000 epinephrine [21]. It was of interest to assess the efficacy using other anesthetic solutions. Thus, this prospective, randomized, double blind, placebo-controlled study was presented to evaluate the effect of preoperative oral administration of ketorolac on the success of mandibular IANB with 2% mepivacaine containing 1:100,000 epinephrine and postoperative pain in patients with symptomatic IP.

Materials and Methods

Ethics

The protocol of this randomized clinical trial was approved by the institutional review boards/ethical committees (IRBs/ECs) of the Faculty of Dentistry, Cairo University. The clinical trial was registered on www.clinicaltrials.gov (Code: NCT02940405).

Selection of subjects

All included patients signed an informed consent after the explanation of the involved procedures and the possible risks. The patients were recruited from the outpatient clinic of the Department of Endodontics from September 2016 to May 2017. Interventions were done by a master's degree student in the Department of Endodontics.

Sample size

The sample size was calculated by the G power program (Universität Düsseldorf, Düsseldorf, Germany), based on an alpha error = 0.05 and a power of 0.8, indicated that a total sample of 32, 16 in each group, would be required to detect differences between the study groups. This number was increased to a total number of 38, 19 in each group to correct for non-parametric usage.

Inclusion and exclusion criteria

Thirty-eight adult patients with a diagnosis of IP in a posterior mandibular tooth were invited to participate in this study. All patients (males and females) were 18 years old or older; in good health (ASA class I); with a history of preoperative sharp, moderate or severe pain; with normal periapical radiographic appearance or slight widening in lamina dura; and able to understand the use of pain scales.

Patient exclusion criteria included those with known allergy or contraindications to any analgesic used in the study; those with a history of active peptic ulcer; history of bleeding problems or anticoagulant use within the last year; those taken any analgesics 12 h before administration of the study drugs; and those who were pregnant or breast feeding.

Diagnostic criteria for symptomatic IP was confirmed by a chief complaint of spontaneous pain, marked moderate to severe pain on the NRS scale [22] and lingering moderate to severe painful response to cold testing (> 10 s) which was done by ethyl chloride spray (Ethyl chloride spray; Walter Ritter GmbH, Germany). Final confirmation of pulp vitality was achieved during the access cavity preparation.

Randomization, allocation concealment and blinding

To randomize the participants, a table of random numbers from 1 to 38 distributed into two groups was generated using a computer program (www.random.org) and table was kept with the assistant supervisor. The patient and the operator were blinded (double-blind study). The placebo was similar in size and color to the ketorolac (intervention) tablet. All samples were pre-packed by the assistant supervisor in 38 sequentially-arranged, opaque, sealed envelopes for the allocation concealment.

Clinical Procedures

Before starting the treatment, preoperative pain was recorded using the NRS. In the experimental group, patients were given one tablet of 10mg ketorolac and in the control group; they received one placebo tablet, 1 h before endodontic treatment. Analgesic ef-

fect measured by preoperative pain, defined as pain at 1 hour after administration of analgesic or placebo, was recorded in the NRS before initiation of endodontic treatment.

After 1 hour of oral administration of the drugs, the participants received a standard mandibular IANB injection of 1.8 ml of 2% mepivacaine with 1: 100,000 epinephrine (Scandonest; Septodont, Saint-Maur-des-Fossés Cedex, France) using a standard aspirating syringe and a 27-G long needle (Neopoint; Servoprax GmbH, Germany).

After 15 minutes of the initial IANB, each patient was asked if his /her lip was numb. The involved teeth were isolated with a rubber dam and access cavity preparation was done using round bur and Endo-Z bur (Dentsply Maillefer, Ballaigues, Switzerland) only in patients who reported lip numbness after administration of the anesthetic and no or mild response to cold pulp sensitivity test; moderate-or-severe response was considered failure, and supplemental anesthesia was given. Patients were instructed to raise their hand if they felt any pain during the procedure. In case of pain during the treatment, the procedure was stopped, and the patients were asked to rate their pain in the NRS during access preparation and instrumentation. Success was defined as no or mild response to cold testing and no pain or mild pain during endodontic access preparation and instrumentation. If the patient's level of pain was categorized as moderate or severe pain at any stage, supplemental anesthesia was needed using buccal infiltration injection with 4% articaine HCI and adrenaline 1:100,000 (Septanest SP; Septodont, Saint-Maur-des-Fossés Cedex, France). If pain persisted, intrapulpal injection was given.

Working length was determined using an electronic apex locator (Root ZX II; J.Morita, California, USA) together with a confirmatory radiograph to be 1mm short of the radiographic apex. Single-visit endodontic treatment was done. Canal preparation was in a crown-down approach using a rotary nickel-titanium system (Revo-S™, Micro Mega®, Besançon, France) in an endodontic motor (X-Smart, Dentsply Maillefer, Ballaigues, Switzerland), with adjusted torque and speed according to the manufacturer's instructions. The rotary files will be introduced inside the canal using EDTA gel (MD-Chelcream; Meta Biomed Co. Ltd., Chungbuk, Korea). The canals were prepared till corresponding manual file that snugly fit at apex and were thoroughly irrigated using 3ml 2.5% sodium hypochlorite by a 27-G side-vented needle (Endo-Top; Cerkamed, Poland). To remove the smear layer, final irrigation was done with 5 ml of 2.5 % sodium hypochlorite followed by sterile saline and 3 ml of 17% EDTA solution (Calix E; Dharma Research, Florida, USA) for 1 min. Final rinse was done with saline.

Master cone-fit radiograph was done with the corresponding size cones. The canals were then dried with paper points and obturated using a modified single-cone technique using matched-size gutta-percha points (Meta Biomed Co., Ltd, Chungbuuk, Korea) and a resin-based sealer (Adseal, Meta Biomed Co., Ltd, Chungbuuk, Korea). Finally, a cotton pellet placed in the pulp chamber and the access cavity sealed with temporary filling (MD-Temp; Meta Biomed Co. Ltd. Chungbuk, Korea). At the end of the visit, participants were asked to record their pain intensity (using NRS) after 6, 12, 24, 48 h and to return the pain diary back to the investigator. Participants were also instructed to take analgesics (200 mg Ibuprofen) in case of intolerable pain and to record the number of analgesic tablets. Participants were then referred to the Operative Department for final restoration placement.

Pain assessment and outcomes

Pain was measured using an 11-point NRS where the endpoints are the extremes of no pain and worst pain. Pain intensity was assigned into one of four pain categories: none (0); mild (1-3); moderate (4-6); and severe (7-10).

The primary outcome in this study was success of mandibular IANB anesthesia (binary outcome) during endodontic treatment, which was measured with NRS in which no or mild pain was considered as anesthetic success and moderate or severe pain was considered as anesthetic failure.

Secondary outcomes included: the analgesic effect determined by pre-operative pain intensity (continuous outcome) measured using NRS before initiation of root canal treatment and 1 h after intake of analgesic or placebo, and intensity of postoperative pain measured using an NRS at 6, 12, 24 and 48 hours after the end of endodontic treatment (continuous outcome).

Statistical Analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS), version 21 (IL SPSS, Inc, IBM Corporation, Chicago, USA). Numerical data were described as mean and standard deviation or median and range. Categorical data were described as numbers and percentages. Data were explored for normality using Kolmogorov-Smirnov test and Shapiro-Wilk test. Comparisons between two groups for normally distributed numeric variables were done using the Student's t-test, while for non-normally distributed numeric variables by Mann-Whitney test. Comparisons between categorical variables were performed using the Chi square test. A p-value less than 0.05 was considered statistically significant. All tests were two tailed.

Results and Discussion

Results

Of the 80 enrolled participants assessed for eligibility, 38 participants were included in the study and were randomly distributed between two groups, 19 patients in each group. The trial design followed the CONSORT 2010. The flow of the participants throughout the study is presented in (Figure 1). There was no significant difference found between the two groups regarding age, gender, tooth type distribution and preoperative pain ($p > 0.05$). Baseline demographic data is presented in (Table 1).

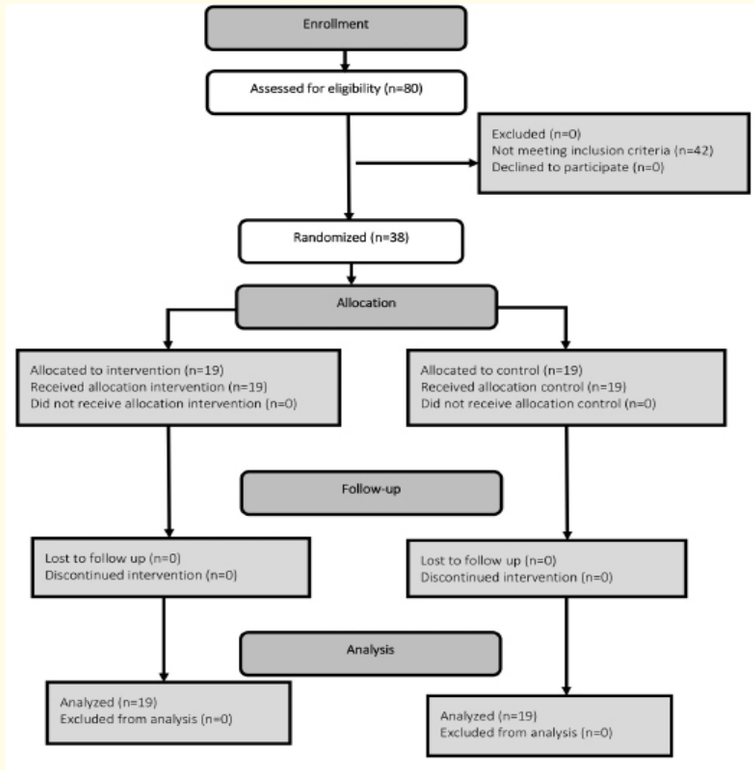

Figure 1: CONSORT flow diagram

Variable Group	Ketorolac	Control	P -Value
Age (y) Median Range	 30 18 - 45	 36 19 - 44	0.309
Gender Males {n (%)} Females {n (%)}	 5 (26.3%) 14 (73.7%)	 3 (15.8%) 16 (84.2%)	0.426
Tooth type 1st Molar {n (%)} 2nd Molar {n (%)}	 12 (63.2%) 7 (36.8%)	 12 (63.2%) 7 (36.8%)	1.000
Preoperative pain (NRS score) Median Range	 6 5 - 9	 7 5 - 9	0.416

Table 1: Baseline demographic features of participants in the study groups.

The primary outcome was the anesthetic success of IANB. The comparison of percentage of patients with successful anesthesia (no pain or mild pain during cold testing, endodontic access preparation and instrumentation) is presented in (Table 2). Control group gave 47.4% success rate (9 of 19 patients). Premedication with ketorolac gave 57.9 % success rate (11 of 19 patients). There was no significant difference between the two groups. Of the 10 failures in the control group, 5 occurred during cold testing, 4 during access cavity, and 1 during instrumentation. Of the 8 failures in the ketorolac group, 1 occurred during cold testing, 7 during access cavity and none during instrumentation.

Group Success/Failure	Ketorolac	Control	P-Value
Success {n (%)}	11 (57.9%)	9 (47.4%)	0.516
Failure {n (%)}	8 (42.1%)	10 (52.6%)	

Table 2: Comparison of Incidence of overall anesthetic success/failure of IANB and calculated p-value in the two groups.

The analgesic effect at 1 h after premedication intake and prior to initiation of root canal treatment as a secondary outcome showed a statistically significant difference between the two groups (p = 0.022). Data of median and range values of preoperative pain intensity at 1 h after premedication intake is presented in (Table 3).

Group		Ketorolac	Control	P -Value
Pain intensity				
Preoperative after 1h	Median Range	4 2 - 7	5 3 - 7	0.022*
6 h	Median Range	2 0 - 9	3 0 - 9	0.258
12 h	Median Range	2 0 - 6	2 0 - 8	0.603
24 h	Median Range	1 0 - 6	0 0 - 7	0.817
48 h	Median Range	0 0-5	0 0 - 7	0.84

Table 3: Median and range values of preoperative pain (1 h after premedication intake), postoperative pain intensity at different time intervals, and calculated p-value in the two groups.

The assessment of the intensity of postoperative pain as a secondary outcome showed no statistically significant difference between the study groups at any of the four time points (6, 12, 24 and 48 h). Data of median and range values of post-endodontic pain intensity at different time periods in the two groups is presented in (Table 3).

Discussion

Achieving proper depth of IANB local anesthesia has been shown to be one of the most difficult challenges in endodontics. Intraoperative pain control by means of local anesthetics is an integral part of the treatment planning. The effect of pulpal inflammation together with patients' anxiety contributes to decrease the pain threshold of the patients [4].

Pre-medication with ketorolac before IANB injection was a suggested solution for improving the anesthetic efficacy of IANB [18,23,24] and reduction of post-endodontic pain levels [25,26]. Ketorolac is useful in the management of short term, moderate to severe postoperative pain, like other NSAIDs, it has analgesic, anti-inflammatory, and antipyretic properties [27]. However, it is still necessary to obtain more evidence regarding the effect of ketorolac on IANB success, especially because similar clinical trials have reported disparate data [18,23,24]. Moreover, in those investigations, IANB was performed with lidocaine, an anesthetic with possibly decreased effects during inflammation. Mepivacaine was a suggested alternative to lidocaine in the present study, because of its increased effect over TTX-r sodium channels when compared with lidocaine [28].

In the present study, patients with a non-contributing history, who did not take analgesic medication during the preceding 12 h before treatment, were included to avoid any drug interaction and to prevent any variable from influencing the results of the study 29. Mandibular multi-rooted teeth with symptomatic IP were chosen because they showed significantly lower success rate of IANB and higher incidence of postoperative pain [30-32]. The baseline data regarding the patients' age, gender, tooth type and pre-operative pain before premedication intake were similar for the two groups, thus, the effect of these variables on the study outcome were minimized by successful randomization. Standardization of the instrumentation technique, irrigation protocol, obturation technique and sealer used were followed in both groups to isolate potential factors from influencing the postoperative pain.

Pain was recorded using the NRS because it showed higher compliance rates, higher responsiveness, easier to use, better understood by most patients and good applicability relative to other pain scales [33,34].

Regarding the preoperative pain intensity after premedication administration as a secondary outcome, it was significantly less in the ketorolac compared to control group. Ketorolac is a strong NSAID that induces an anti-nociceptive state [17]. Dentists might benefit from this by gaining more patient confidence before and during treatment; as patients with less preoperative pain level are expected to be less anxious and more cooperative.

IANB success was considered an essential issue to determine, because the effect of the anesthetic blockade may be evaluated not only by lip numbness but also by a second cold test and ultimately by direct endodontic access. The three-step evaluation of IANB may be a mandatory practice when the clinical scenario includes preoperative pain, such as in cases with IP [23].

Anesthetic success of IANB was confirmed in the presence of no or mild response to cold stimuli and no or mild pain during endodontic procedures. After confirmation of lip numbness, pulpal anesthesia was assessed by applying cold test. The overall success rate of cold test after IANB was 95% for ketorolac group and 74% for the control group. The overall success of IANB as the primary outcome was 57.9% for ketorolac group and 47.4% for the control group. The overall IANB success rate in the current study falls within the reported success rates in the literature which ranged from 30% - 80% [15]. The higher success rate of cold test than IANB success is in agreement with previous studies by Saha., *et al.* [18],

Prasanna., *et al,* [23], and Ianiro., *et al*. [24] despite differences in methodological designs e.g. greater volume of local anesthetic solution initially (3.6 mL versus 1.8 mL) and different cold spray type. Variation in success rates in different studies may be explained by difference in the local anesthetic agent used (mepivacaine or lidocaine), different definitions of IANB success from study to another (no pain versus no and mild pain as anesthetic success).

Ketorolac increased the IANB success rate compared to control group, but not significantly. This is in agreement Aggarwal., *et al*. [20] and Jena., *et al.* [27], yet, in disagreement with Saha., *et al*. [18]. This disagreement is explained possibly by different local anesthetic agent used, being lidocaine in the previous study compared to mepivacaine in the present study. Several explanations have been proposed by Maingret., *et al.* [35] to clarify the lack of effect of different NSAIDs on the success of IANB. The NSAIDs usually inhibit prostaglandins to mediate pain relief. Other inflammatory mediators are involved in the mechanism of pain rendering the inhibition of one of them ineffective in preventing pain. Another explanation could be the degree and duration of the pre-existing inflammatory damage of the pulp rendering premedication with NSAIDs ineffective in cases with inflamed pulp in endodontics compared to cases with normal pulp.

Ketorolac did not seem to significantly influence the post-endodontic pain intensity at different time intervals (6, 12, 24 and 48 h) between both groups. This is in disagreement with Sethi., et al. [26] and Praveen., *et al*. [25]. Variation in results may be attributed to differences in study methodology (irrigation technique, irrigation type, type of files used, and instrumentation technique), besides operator skills and sample size variations.

Postoperative analgesics were prescribed on-demand only in cases of severe pain. Ethical practice indicates that rescue medication should be prescribed for patients to use if they feel pain after root canal treatment [36]. Ibuprofen has commonly been prescribed as postoperative pain control medication [25,26].

Conclusion

Preoperative administration of a single dose of 10 mg ketorolac significantly decreased the preoperative pain intensity at 1 h after premedication intake but did not seem to affect either the anesthetic success of IANB or the postoperative pain intensity for patients suffering from symptomatic IP in lower molars.

Conflict of Interest

The authors deny any conflicts of interest in this study.

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