Double-blind Randomized Placebo-controlled Clinical Trial of Efficiency of Nonsteroidal Anti-inflammatory Drugs in the Control of Post-endodontic Pain

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Abstract

Introduction: The present clinical trial aimed to evaluate the efficiency of paracetamol alone and in combination with 3 different nonsteroidal anti-inflammatory drugs for control of post-endodontic pain. **Methods:** The inclusion criteria were moderate to severe pain of irreversible pulpitis, by using the Verbal Rating Scale and a 4–10 score on the Numerical Rating Scale, on anterior or premolar teeth, as well as the absence of signs and symptoms of apical periodontitis. One hundred eighty-five trial medications with placebo were prepared, and 170 participants completed the trial. There were 5 groups. P-group received 4 gelatinous capsules of a single dose of paracetamol alone. The IP-group received similar capsules of a single dose of combined ibuprofen/paracetamol. MP-group received combined mefenamic acid/paracetamol, and DP-group received combined diclofenac K/paracetamol. A Plb-group received doubled gelatinous capsules with no medications as a single dose, which had the same weight and appearance as the medicated capsules, to be the placebo. **Results:** Pain intensity was measured after initial endodontic therapy and instrumentation by using the Verbal Rating Scale and Numerical Rating Scale. IP-group (ibuprofen/paracetamol) had the most pain reduction, followed by DP-group (combined diclofenac K/paracetamol), then MP-group, followed by P-group, whereas Plb-group had the least pain reduction ($P < .05$). **Conclusions:** The combination of ibuprofen/paracetamol, taken immediately after initial endodontic therapy and root canal preparation in teeth with irreversible pulpitis, reduced post-endodontic pain (ClinicalTrials.gov no.: NCT02417337). *(J Endod 2016;42:835–842)*

Key Words

Endodontic, irreversible pulpitis, Numerical Rating Scale, pain, randomized clinical trial, Verbal Rating Scale

The incidence and severity of postoperative pain are associated with specific dental treatments; the highest is with root canal therapy (1). Post-endodontic pain, particularly after initial endodontic therapy, should ideally be eliminated by the therapy; however, analgesics are frequently required to diminish pain (2).

There is a strong relationship between pulp status and postoperative pain, influencing the experience of pain, which may undermine the patient's confidence in the procedure and the clinician (3).

Patients with severe preoperative endodontic pain tend to experience pain during and after endodontic procedure than do patients with mild and no preoperative pain (4). In one study, root canal treatment of teeth with vital pulp resulted in a significantly higher incidence and intensity of post-endodontic treatment pain than did the treatment of teeth with necrotic pulp or re-treated teeth (5). It was also reported that postoperative pain was significantly associated with the treatment of symptomatic teeth without periradicular lesions (6). The level of anxiety also influences the level of postoperative pain, demonstrating an interrelationship between postoperative pain, apprehension, and preoperative pain (7).

Pain intensity is therefore influenced by numerous factors, including environmental, previous experience, and attitude, making it a challenge to measure. Several scales have been used for pain intensity evaluation. Of these, the numerical rating scale (NRS), which is an 11-, 21-, or 101-point scale with end points of the extremes of no pain and as bad as it could be or the worst pain. There is also the visual rating scale (VRS), which is made up of a list of descriptors that represent the level of pain intensity. It is subjective, and its association with disease may be indirect; however, it is a personal qualitative judgment of patients' perception of pain intensity (8). The visual analogue scale (VAS) is a 10-cm line arrangement that relates to verbal parameters, typically "no pain" and the "worst imaginable pain". Although its value as a measurement is well-documented, it is believed to be the least favorite and the most difficult to use and has the highest failure rate for pain assessment and evaluation (8).

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Von Korff et al (9) suggested that the VAS could be used if ratio qualities are essential to analysis. Furthermore, so long as the population being studied is limited to people at low risk for cognitive difficulties, they recommend against using it as the primary measure of pain intensity.

It is believed the NRS is preferred once sensitivity is required, whereas the VRS is preferred by patients for its simplicity because it is easier to comprehend and has a high compliance rate (10). The NRS is probably a more useful tool for pain assessment in research than the VRS or VAS, because it provides a descriptive numerical value to the patient and for statistical analysis (9). Its validity has also been well-documented, and it has demonstrated positive and significant correlations with other measures of pain (10, 11). In this trial, the NRS-11 was used to quantitatively analyze pain reduction, and the VRS-4 was used to qualitatively analyze patients' perception of pain reduction after endodontic treatment and the use of nonsteroidal anti-inflammatory drugs (NSAIDs).

NSAID use is aimed at reducing the chemical inflammatory mediators that activate or sensitize peripheral nociceptors and the related subsequent events involved in pain perception (12). Their efficacy as mono-analgesics is well-documented (4); nevertheless, improvements have been suggested to overcome their low effect by combining them with analgesics of different mechanisms of action, without increasing potential adverse effects (13, 14).

There are limited numbers of randomized clinical trials on combining NSAIDs in the management of post-endodontic pain (10). In this regard, Menhinick et al (15) found acetaminophen and ibuprofen to be more effective than ibuprofen alone in managing post-endodontic pain. The question remains as to what would be the ideal combinations of analgesics for controlling post-endodontic pain. The objective of the present trial was to evaluate the efficiency of paracetamol alone and its combinations with 3 other NSAIDs to control post-endodontic pain in an attempt to enhance the scope of prescription for this problem. The primary outcome was to evaluate the overall pain reduction, and the secondary outcome was to evaluate which combination with paracetamol would be most effective.

Materials and Materials

This is a placebo-controlled double-blind factorial trial on the efficiency of paracetamol alone and in combination with 3 other analgesics for the control of post-endodontic pain in patients with moderate to severe spontaneous preoperative odontogenic pain. The sample was made up of patients attending the clinics of the Faculty of Dentistry, University of Khartoum and the Khartoum Teaching Hospital emergency clinic, which were the setting and location of the trial. Participants' eligibility was assessed at the recruitment stage by the principal investigator (W.Z.) by using both the verbal rating scale (VRS-4) and numerical rating scale (NRS-11). Patients who had moderate to severe pain on the VRS-4 and 4–10 score on the NRS-11 and whose periapical radiographs confirmed the absence of periapical lesions were considered suitable and invited to participate in this study.

Subject Enrollment

After submission of the study protocol, both postgraduate studies boards of the Faculty of Dentistry and the Ethical Research Committee of medical health sciences granted approval. The participants were assured anonymity and confidentiality and that their current and future treatment would not be affected if they declined participation. The participants were informed of the study, and consent forms were reviewed and signed.

Patients reporting symptoms of irreversible pulpitis were requested to participate. Irreversible pulpitis indicates the presence of a severe degenerative process of the pulp that will not heal, and if left without treatment, it will result in pulpal necrosis that is followed by apical periodontitis (16–19). The diagnosis of symptomatic irreversible pulpitis was based on mild to severe pain that lingers after removal of a stimulus and could also be spontaneous (16). The tooth in question should exhibit pain when exposed to thermal irritants (heat and/or cold) that is prolonged well beyond the removal of the stimulus (17, 18). The history of spontaneous pain in symptomatic irreversible pulpitis may last for few seconds to several hours and may also be radiating. The exacerbation of pain by hot and cold confirmed the diagnosis as prerequisite for recruitment (19).

Sample Size

The minimum sample required to detect differences between the 5 groups by using Kruskal-Wallis test (with type I error at 5% and power at 80%) is 22 subjects per group (20). The sample size was increased to 37 participants per group, which was more than in previous similar studies (15, 21, 22), to account for the potential refusal to participate, loss of patients during the trial, or damaged medications.

Inclusion/Exclusion Criteria

Strict inclusion and exclusion criteria similar to those reported by Menhinick et al (15) were used with some modifications, and hence the participants' inclusion criteria for this study were as follows:

1. Presented with moderate to severe pain and scoring between 4 and 10 on the NRS
2. Presented for emergency endodontic treatment with a symptomatic maxillary or mandibular tooth (anterior and premolar) with irreversible pulpitis and normal periapical appearance on radiographs (23)
3. Presented with American Society of Anesthesiologists I or II medical history (24)
4. Read and understood the pain score level sheet (written in Arabic)
5. Informed consent obtained; signed agreement to have root canal treatment

Patients were excluded because of the following:

1. Presented with American Society of Anesthesiologists III or VI medical history (24)
2. Younger than 18 years of age
3. Analgesic taken within the past 4 hours
4. History of allergy to NSAIDs, aspirin, or local anesthetics
5. History of gastrointestinal disorders, esophageal reflux, active asthma, decreased hepatic function, hemorrhagic disorders, or poorly controlled diabetes mellitus
6. Currently taking opioids, monoamine oxidase inhibitors, tricyclic antidepressants, carbamazepine, diuretics, or anticoagulants
7. History of opioid addiction or abuse
8. Pregnant or nursing

Preparation of the NSAIDs and the Randomization Method

The NSAIDs and placebo were prepared at the Faculty of Pharmacy laboratories. They were placed in 185 gelatinous capsules, 37 doses per experimental group. Each dose was placed in a concealed white sachet, with 1 dose per sachet. The dose was made up of 4 gelatinous capsules per dose. Identical sachets were coded following a