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Effects of three oral analgesics on postoperative pain following root canal preparation: a controlled clinical trial

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Abstract

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Aim To compare the effects of single doses of three oral medications on postoperative pain following instrumentation of root canals in teeth with irreversible pulpitis.

Methodology In this double-blind clinical trial, 100 patients who had anterior or premolar teeth with irreversible pulpitis without any signs and symptoms of acute or chronic apical periodontitis and moderate to severe pain were divided by balanced block random allocation into four groups of 25 each, a control group receiving a placebo medication, and three experimental groups receiving a single dose of either Tramadol (100 mg), Novafen (325 mg of paracetamol, 200 mg ibuprofen and 40 mg caffeine anhydrous) or Naproxen (500 mg) immediately after the first appointment where the pulp was removed, and the canals were fully prepared. The intensity of pain was scored based on 10-point VAS before and after treatment for up to 24 h postoperatively. Data were submitted to repeated analysis of variance.

Results At the 6, 12 and 24 h postoperative intervals after drug administration, the intensity of pain was significantly lower in the experimental groups than in the placebo group ($P < 0.01$). Tramadol was significantly less effective ($P < 0.05$) than Naproxen, and Novafen that were similar to each other ($P > 0.05$).

Conclusion A single oral dose of Naproxen, Novafen and Tramadol taken immediately after treatment reduced postoperative pain following pulpectomy and root canal preparation of teeth with irreversible pulpitis.

Keywords: endodontics, NSAIDs, pain, post-instrumentation pain.

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Introduction

One of the aims of root canal treatment is to prevent or eliminate pain. Although dental procedures can be performed without producing pain using local anaesthetics, postoperative pain is relatively common after some procedures especially in patients with preoperative pain (Albashaireh & Alnegrish 1998). Postoperative pain following root canal treatment occurs because of acute inflammation within the periradicular tissues in response to an increase in the intensity of stimulants coming from the root canal (Georgopoulou *et al.* 1986). The prevalence of postoperative pain following root canal treatment has been reported to be 3–58% (Ng *et al.* 2004, Sathorn *et al.* 2008) although it varies between studies and following different stages of the

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treatment. Some studies have reported mild pain after chemo-mechanical preparation in about 10–30% of cases (Georgopoulou *et al.* 1986, Siqueira *et al.* 2002), and others have reported that the frequencies of interappointment emergencies ranged from 1.4% to 16% (Morse *et al.* 1986, Trope 1990, Imura & Zuolo 1995, Siqueira *et al.* 2002). Furthermore, a positive association has been demonstrated between postoperative pain and the presence of apprehension and preoperative pain (Morse *et al.* 1986, Torabinejad *et al.* 1994, Glennon *et al.* 2004).

Some drugs can prevent the production of inflammatory mediators involved in producing pain, such as prostaglandins owing to pulpal inflammation and necrosis, and the corresponding periradicular tissue changes (McNicholas *et al.* 1991). Prostaglandin tissue levels are associated with patient reports of pain (McNicholas *et al.* 1991, Nakanishi *et al.* 1995), and therefore, nonsteroidal anti-inflammatory drugs (NSAIDs) may be key drugs for inflammatory pain abatement. NSAIDs are widely available, and they have been reported to be effective in managing endodontic pain (Morse *et al.* 1990, Doroschak *et al.* 1999). Nonnarcotic analgesics, NSAIDs and acetaminophen can all produce analgesia; therefore, they can be effective for managing pulp and periradicular pain (Roszkowski *et al.* 1997, Holstein *et al.* 2002, Keiser & Hargreaves 2002). Several double-blind, placebo-controlled trials in patients with endodontic pain indicate that 400 mg of ibuprofen, 50 mg of ketoprofen, 100 mg of flurbiprofen and 30–60 mg of ketorolac can all produce significant analgesia when compared to placebos (Torabinejad *et al.* 1994, Penniston & Hargreaves 1996, Keiser & Hargreaves 2002). Ibuprofen is one of the most frequently used NSAIDs for control of postoperative pain associated with root canal treatment, and it has good efficacy and safety profiles (Dionne *et al.* 1983, Whitten *et al.* 1996, Holstein *et al.* 2002, Dionne 2003). Naproxen is a NSAID that inhibits the cyclooxygenase pathway, thus preventing the release of inflammatory mediators such as prostaglandins (Thun *et al.* 2002). Novafen is a mixture of acetaminophen, ibuprofen and caffeine. Acetaminophen affects the central and peripheral nervous systems. Ibuprofen has anti-inflammatory effects by inhibiting the synthesis of arachidonic acid metabolites (Haas 2002). A suitable method for controlling moderate to severe pain is to combine two or more drugs so a lower dose of each drug is used with fewer side effects. The combination of a NSAID and acetaminophen has shown additive analgesia for treating dental pain in several studies (Wright *et al.* 1983, Breivik *et al.* 1999, Keiser & Hargreaves 2002). In cases not controlled by this combination, a narcotic analgesic may also be given for additional effects (Breivik *et al.* 1999, Wideman *et al.* 1999). Acetaminophen and ibuprofen are more effective than ibuprofen alone in alleviating endodontic pain after treatment, but surprisingly, no differences were detected between ibuprofen and placebo (Menhinick *et al.* 2004).

As it may be possible to benefit from using lower doses of NSAIDS with fewer side effects in combination with acetaminophen to achieve better results compared with higher doses of NSAIDS, the effects of Novafen and Naproxen on postoperative endodontic pain were evaluated. In addition, Tramadol, an opioid with CNS effects, was used in comparison with NSAIDS, which have mainly PNS effects (such as Naproxen), and Novafen with a combined CNS and PNS effects as it is important to take advantage of CNS and PNS effects simultaneously. This study compared the effects of single doses of these three oral medications on moderate to severe postoperative pain following instrumentation of root canals in teeth with irreversible pulpitis.

Materials and methods

Patients

One hundred patients participated in this double-blind, placebo-controlled parallel design clinical trial that was approved by the Committee of Ethics, Tehran Azad University. Participants were selected consecutively from patients referred to the Endodontic Department of Tehran Azad University from 1 October to 27 November 2009; all were fully informed about the investigation, and their written consent to participate was received. The sample size was determined using the results of a pilot study on 20 cases (five in each group) (Table 1) by means of the one-way analysis of variance formula for sample size determination for four groups using Minitab Software (Minitab Inc., State College, PA, USA) assuming alpha- and beta-errors at 0.05 level.

The inclusion criteria were as follows:

Patients were aged between 20 and 60 years with no systemic diseases, and women were not pregnant;

Table 1 Results of the pilot study

	Before drug	6 h
Naproxen	5.8 (5–7)	0.6 (0–1)
Novafen	6 (5–7)	0.6 (0–1)
Tramadol	5.6 (4–6)	3.2 (1–6)
Placebo	5.6 (5–7)	4.8 (4–6)

No history of taking analgesics in the previous 12 h or other drugs prior to presenting for treatment; and

Patients with moderate to severe spontaneous pain associated with irreversible pulpitis in single-rooted premolars or anterior teeth with no clinical or radiographic signs or symptoms of acute or chronic apical periodontitis.

Medical and dental histories were taken, and a thorough clinical examination, including pulp sensibility testing, was carried out to diagnose the pulp status. Irreversible pulpitis was defined by considering the response of teeth to sensibility tests (thermal and EPT). Patients with prolonged moderate to severe pain were selected. All the patients had just one tooth with irreversible pulpitis. Patients were divided randomly into four groups of 25 patients each (Figure 1) – a control group receiving a single dose of a placebo (a starch containing capsule – Darou Pakhsh, Tehran, Iran), and three experimental groups receiving either a single dose of a Tramadol tablet (100 mg of Tramadol hydrochloride; Tehran Darou Co., Tehran, Iran), Novafen capsules [325 mg of paracetamol (acetaminophen)], 200 mg of ibuprofen and 40 mg of caffeine anhydrous (Brown & Burk, Richmond, UK), or Naproxen tablets (500 mg of naproxen, Pars Darou, Tehran, Iran), immediately on completion of the first appointment (Table 2). Balanced block random allocation was made (12 blocks contained eight patients and one block contained four patients) by generating random digits via Microsoft Excel 2007 software (Microsoft Corporation, Redmond, WA, USA). A nurse who was blinded to the aim and the protocol of the study generated the numbers. The intensity of the preoperative pain was measured by instructing the patient to complete a Visual Analogue Scale (VAS) (Torabinejad *et al.* 1994). The markings on the VAS were measured, and the degree of pain was categorized as mild (scores 1–3), moderate (scores 4–6) or severe (scores 7–10).

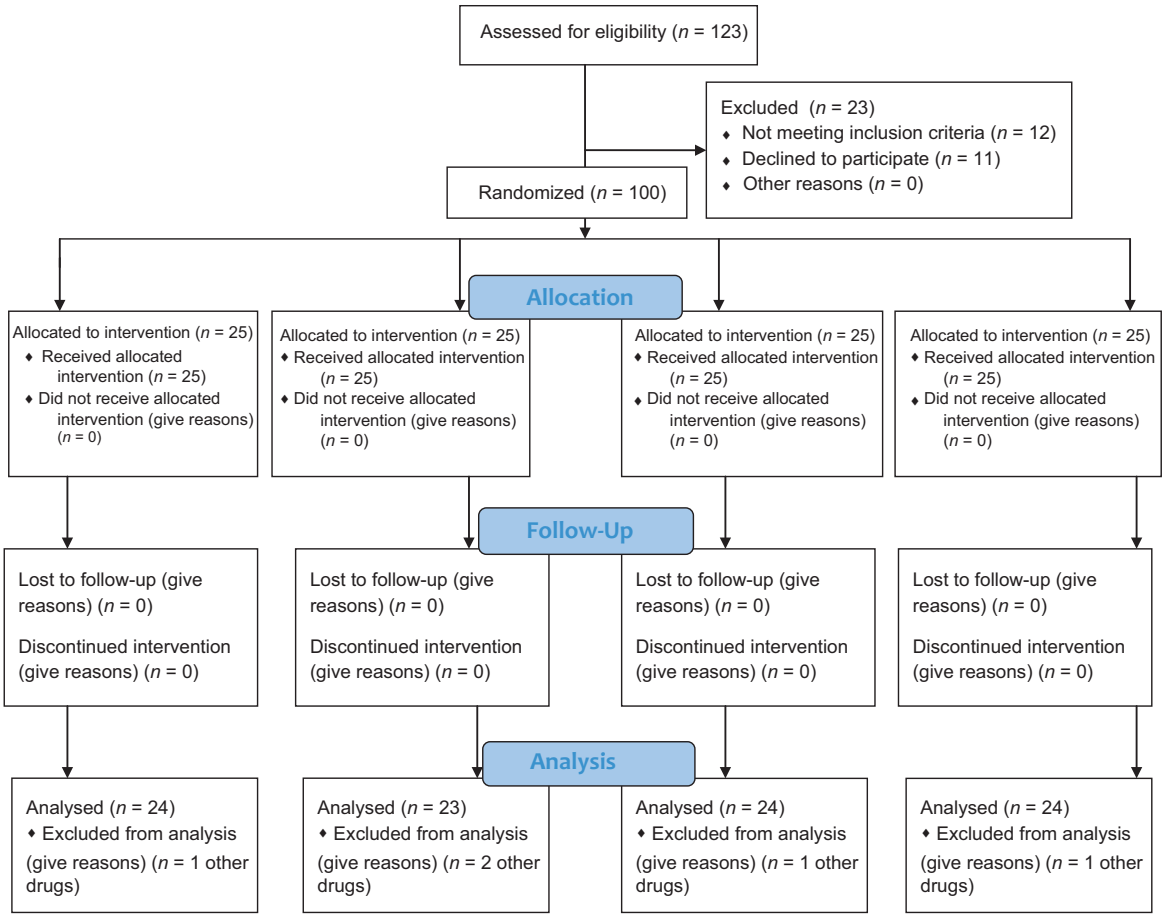

Figure 1 Consort 2010 flow diagram of the trial.

Table 2 Details of the medication under investigation

Medications	Contents of the medication	Manufacturer
Tramadol tablet	100 mg of tramadol hydrochloride	Tehran Darou Co., Tehran, Iran
Novafen capsule	325 mg of paracetamol (acetaminophen), 200 mg ibuprofen and 40 mg caffeine anhydrous	Brown & Burk, Richmond, UK
Naproxen tablet	500 mg of naproxen	Pars Darou, Tehran, Iran

Intervention

After explanation of the treatment procedures, the tooth was anaesthetized using one cartridge (1.8 mL) of Persocaine-E (Lidocaine 2% plus epinephrine 1:80000; Darou Pakhsh Co, Tehran, Iran) local anaesthetic solution. The teeth were considered anaesthetized when two consecutive negative responses to electric pulp testing were achieved. If pain still remained during access cavity preparation, intrapulpal anaesthesia was used as supplementary anaesthesia. All treatment was performed under rubber dam isolation by one of the investigators (a general dentist). The investigator who performed the root canal treatment was blinded to the assignment. An access cavity was prepared, and the working length was determined electronically using an apex locator (Dentaport ZX; J. Morita, Kyoto, Japan) 1 mm short of the apex with a size 15 or 20 K-file and confirmed by periapical radiographs. The apical part of each root canal was prepared to a size 25 K-file with the step-back technique in a circumferential manner. Normal saline was used as the irrigant solution between each instrument. Canals were then dried with paper points, and the access cavities were restored temporarily with Cavit (3M ESPE, St Paul, MN, USA). Each patient's tablet/capsule was inserted into a sealed coded packet by a trained person who was blinded to the drugs, and the packet remained sealed until it was given to the patient. The patients were supervised by one of the investigators when taking the oral medications.

Assessment of pain experience following canal preparation

A questionnaire containing the VAS was given to each patient for them to record the intensity of pain felt after 6, 12 and 24 h. At the second appointment, 24 h later, the root canal treatment was completed.

Statistics

Normal distribution was tested by the Kolmogorov–Smirnov test. Data were analysed using repeated measure analysis of variance considering baseline VAS as a covariate and the intervention as the between subject comparison. The alpha-level was adjusted at 0.05 for main effect, and adjusted Bonferroni correction for multiple comparison data was analysed with SPSS 16 for windows (SPSS inc., Chicago, IL, USA). The missing data were imputed by carrying the last observation forward (LOCF).

Results

Two patients from the Novafen group and one patient from the Tramadol, Naproxen and placebo groups took additional analgesics and were excluded from the study because of the homogeneity of the noncompliance between groups and lack of the evidence of the severity of pain amongst them. The number of noncompliance samples was almost equal amongst the groups.

Table 3 Demographic and baseline characteristics for each group

	Naproxen (n = 24)	Novafen (n = 23)	Tramadol (n = 24)	Placebo (n = 24)
Age (years)	28.4 ± 7.6	29.6 ± 8.1	29.5 ± 6.9	31.4 ± 10.7
Gender				
Male (%)	14 (58.3)	11 (47.8)	13 (54.2)	15 (62.5)
Female (%)	10 (41.7)	12 (52.2)	11 (45.8)	9 (37.5)
Tooth				
Maxillary anterior (%)	11 (45.8)	12 (52.2)	10 (41.7)	13 (54.2)
Mandibular anterior (%)	3 (12.5)	3 (13)	4 (16.6)	2 (8.3)
Mandibular premolar (%)	10 (41.7)	8 (34.8)	10 (41.7)	9 (37.5)

Table 4 The means and their 95% confidence intervals of the mean (in parenthesis) of VAS before and after administration of the experimental or placebo drugs

	Before drug	6 h	12 h	24 h
Naproxen	5.8 (4.9–6.7)	0.8 (0.3–1.2)	0.5 (0.3–.7)	0.7 (0.3–1.1)
Novafen	5.8 (4.6–6.9)	0.6 (0.2–1.0)	0.7 (0.2–1.2)	0.4 (0.1–.8)
Tramadol	5.1 (4.2–6.0)	3.2 (2.1–4.3)	2.1 (1.5–2.7)	2.2 (1.2–3.1)
Placebo	5.7 (4.9–6.5)	4.8 (3.5–6.2)	3.7 (3.1–4.3)	3.2 (2.6–3.9)

Otherwise, excluding the noncompliance samples was not allowed.

The analysis was carried out on the VAS of 95 fully compliant samples with baseline and demographic data shown in Table 3. All patients reported postoperative pain at the 12- and 24-h time intervals. In the 6-h group, the samples with no response were replaced using LOCF. Table 4 shows the mean and 95% confidence intervals of the mean of VAS before and at 6, 12, and 24 h after drug administration. The incidence of moderate to severe pain in the experimental groups was lower than that in the control group, and this difference was significant ($P < 0.01$). In addition, the mean intensity of pain in the experimental groups was significantly lower than that of the control group ($P < 0.01$). There was no significant difference between Naproxen and Novafen ($P > 0.05$), but Tramadol was less effective than the other two drugs ($P < 0.05$).

Discussion

This double-blind, placebo-controlled parallel design clinical trial compared the analgesic effects of three different drugs with those of a placebo under controlled clinical conditions. However, it is recognized that eliminating the placebo effect can produce some bias in the results (Torabinejad *et al.* 1994). Only patients with moderate to severe pain were selected for two reasons: first, controlling this type of pain is challenging for clinicians and, secondly, because the greatest predictor for postoperative pain intensity is the severity of preoperative pain (O'Keefe 1976). Double-blind drug administration and the elimination or matching of other variables can lead to increased internal validity and more precise results. Patient cooperation and relying on their answers to a questionnaire are other potential problems associated with these types of studies.

The effects of the drugs were assessed for up to 24 h after treatment whereas some other studies have only assessed the effects of drugs for up to 8 h (Jung *et al.* 2004, Menhinick *et al.* 2004). Most patients experience pain in the first 24 h after root canal treatment (Torabinejad *et al.* 1994), and therefore, this longer period for assessment was chosen even though the drugs tested would not be expected to provide ongoing analgesia for this entire period owing to their relatively short plasma half-lives, which is much less than 24 h (McVerry *et al.* 1986, Dayer *et al.* 1997). After some time and inflammation reduction, the pain intensity would be expected to decrease. The administration of Tramadol, and especially Novafen and Naproxen, is likely to speed up the reduction of pain resulting from inflammation because of their anti-inflammatory effects.

To evaluate just the effect of drugs and achieve better control of the interfering factors, normal saline was used as the root canal irrigant instead of sodium hypochlorite. Even a dilute solution of sodium hypochlorite can cause untoward reactions and pain if injected periapically or exposed to the oral tissues. Also, intracanal medicaments such as calcium hydroxide may have some effects on post-instrumentation pain (Rosenberg 2002), and no intracanal medicament was used. As the pulps were vital prior to root canal treatment and the procedure was performed under aseptic condition, intracanal medications such as calcium hydroxide seem to provide no further benefits for 24 h prior to filling of the root canals.

Patients with irreversible pulpitis without apical periodontitis were selected for this study. They usually respond well to a pulpectomy, which can eliminate the primary cause of the symptoms, thereby reducing the pain (as can be seen in the placebo group). Therefore, it is likely that effective pain relief may result from this procedure and by administering a single dose of an analgesic drugs.

Patients with no history of taking analgesics in the previous 12 h or other drugs prior to presenting for treatment were selected to eliminate the interfering effects of these other agents. Also, variables such as the patient's metabolism, gastrointestinal condition may affect the effective therapeutic dose of drugs in each individual. Further studies should consider these variables.

The results demonstrated that a single oral dose of a Tramadol tablet, a Novafen capsule or a Naproxen tablet immediately after root canal preparation, reduced the intensity of postoperative pain. Different doses of Tramadol (Collins *et al.* 1997) as well as Naproxen (Gottesdiener *et al.* 1999) can effectively

reduce the intensity of pain after third molar surgery. The results of these two studies are in agreement with the results of the current study.

The combination of a NSAID with other analgesics such as acetaminophen and Tramadol can reduce moderate to severe endodontic pain more effectively than single medications (Holstein *et al.* 2002). The combination of acetaminophen and ibuprofen has been shown to be more effective in reducing pain after root canal treatment (Menhinick *et al.* 2004), and a combination of acetaminophen, ibuprofen and codeine has been found to reduce acute pain after third molar surgery more than a combination of Tramadol and acetaminophen (Jung *et al.* 2004). Similarly, in the present study, Novafen (a mixture of acetaminophen, ibuprofen and caffeine) was effective in reducing postoperative pain.

The NSAIDs inhibit the production of inflammatory mediators; thus, they reduce pain, especially moderate to severe pain after root canal treatment (Madison & Anderson 1992). Opioids have the ability to affect the pain threshold and pain perception (Schnitzer 2003). In the present study, Tramadol could not produce as effective analgesia as the other two drugs. A combination of ibuprofen and acetaminophen appears to be a suitable choice for alleviating moderate to severe pain after endodontic treatment or surgery. However, only the effects of these drugs on pain were evaluated in this study and not the adverse effects; thus, it is not possible to assess the risk to benefit ratio of using these drugs in this manner.

Conclusion

A single oral dose of NSAID drugs such as Naproxen and Novafen immediately after root canal preparation relieved postoperative pain more than Tramadol or a placebo when there was moderate to severe preoperative pain associated with irreversible pulpitis, in the first 24 h after treatment.

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