International Endodontic Journal

doi:10.1111/j.1365-2591.2010.01833.x

The efficacy of pre-operative oral medication of lornoxicam and diclofenac potassium on the success of inferior alveolar nerve block in patients with irreversible pulpitis: a double-blind, randomised controlled clinical trial

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Abstract

Prasanna N, Subbarao CV, Gutmann JL. The efficacy of preoperative oral medication of lornoxicam and diclofenac potassium on the success of inferior alveolar nerve block in patients with irreversible pulpitis: a double-blind, randomised controlled clinical trial. *International Endodontic Journal*, **44**, 330–336, 2011.

Aim To determine the effect of administration of pre-operative lornoxicam (LNX) or diclofenac potassium (DP) on the success of inferior alveolar nerve blocks (IANB) in patients with irreversible pulpitis in a double-blind randomised controlled trial.

Methodology One hundred and fourteen patients with irreversible pulpitis of a mandibular posterior tooth participated. Patients indicated their pain scores on a Heft Parker visual analogue scale, after which they were randomly divided into three groups ($n = 38$). The subjects received identical capsules containing 8 mg LNX, 50 mg DP or cellulose powder (placebo, PLAC), 1 h before administration of IANB with 2% lidocaine containing 1 : 200 000 epinephrine. Lip numbness was assessed after 15 min, following which the teeth were tested with cold spray and their responses (negative or positive) were recorded. Access cavities were then prepared and success of IANB was defined as the absence of pain during access preparation and root canal instrumentation. The data were analysed using chi-squared tests.

Results The percentages of teeth giving a negative response to cold test were 42.8% (PLAC), 78.5% (LNX) and 67.8% (DP), with no significant differences amongst the groups ($P > 0.05$). The success rates for the IANB in descending order were 71.4% (LNX), 53.5% (DP) and 28.5 (PLAC). A significant ($P < 0.001$) difference was found between the LNX and the PLAC groups only.

Conclusions Pre-operative administration of LNX significantly improved the efficacy of IANB in patients with irreversible pulpitis, whilst the effect of pre-medication with DP was not significantly different from the PLAC.

Keywords: diclofenac potassium, inferior alveolar nerve block, irreversible pulpitis, local anaesthesia, lornoxicam, nonsteroidal anti-inflammatory drugs.

Received 30 April 2010; accepted 30 October 2010

Introduction

Although the inferior alveolar nerve (IAN) block is the most frequently used injection technique for achieving local anaesthesia for root canal treatment of mandibular teeth, it does not always result in successful pulpal anaesthesia. Clinical studies in endodontics have found failure with the IAN block occurring between 44% and 81% of the time (Cohen *et al.* 1993, Nusstein *et al.* 1998).

Various mechanisms have been hypothesized to explain the failure of local anaesthetics, including

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anatomical variations, such as cross-innervations and accessory innervations from the lingual nerve, buccal nerve, mylohyoid nerve or cervical plexus, decreased local pH, tachyphylaxis of anaesthetic solutions and activation of nociceptors, including tetrodotoxin and capsaicin-sensitive transient receptor potential vanilloid type 1 (TRPV1) (Rood 1977, Chaudhary *et al.* 2001, Hargreaves & Keiser 2002). Interestingly, the success rates of local anaesthesia were found to be worse in patients with inflamed pulpal tissues (Aggarwal *et al.* 2009, 2010, Tortamano *et al.* 2009).

The high failure rate of local anaesthesia in symptomatic teeth with irreversible pulpitis could be attributable to the prostaglandin-induced sensitization of peripheral nociceptors (Henry & Hargreaves 2007). The receptors expressed by the peripheral terminals of nociceptors can detect chemical and physical stimuli. This results in activation of various ion channels expressed on peripheral terminals. Inflammatory mediators such as prostaglandins produce their effects by binding to these various protein receptors. Prostaglandins (PGs) up-regulate a variety of mechanisms that might decrease the efficacy of local anaesthetics: altering the kinetics of activity of the voltage-gated sodium channels, resulting in increased depolarization; activation of EG protein-coupled receptors namely P2 or EP3 receptors, which are expressed on trigeminal sensory neurons (Vane & Botting 1998, Gould *et al.* 2004). There is an increase in prostaglandins in inflamed pulps (Reuben & Duprat 1996, Hargreaves & Keiser 2002), and activation of nociceptors by PGs is a major cause of increased incidence of failure of inferior alveolar nerve blocks (IANB) in patients with irreversible pulpitis (Modaresi *et al.* 2006, Wells *et al.* 2007). Therefore, decreasing the amount of prostaglandins may increase the efficacy of local anaesthetics.

Clinicians prescribe nonsteroidal anti-inflammatory drugs (NSAIDs) on a routine basis for a range of mild-to-moderate pain (Mickel *et al.* 2006). NSAIDs reversibly inhibit cyclooxygenase (prostaglandin endoperoxide synthase), the enzyme-mediating production of prostaglandins (PGs) and thromboxane A2. Given the ability of NSAIDs in reducing nociceptor activation by decreasing the levels of inflammatory mediators (Gokin *et al.* 2001), it has been hypothesized that pre-medication with NSAIDs will influence the success rate of local anaesthesia in patients with irreversible pulpitis. One study concluded that acetaminophen with codeine or ibuprofen improved the efficacy of IANB (Modaresi *et al.* 2006), whilst another report showed that neither ibuprofen nor ketorolac caused any improvement (Aggarwal *et al.* 2010). A report by Ianiro *et al.* (2007) concluded that acetaminophen or a combination of acetaminophen and ibuprofen improved the success of IANB for teeth with irreversible pulpitis.

Lornoxicam (LNX) is a compound of the so-called oxicam class of NSAIDs, acting in part through the nonselective inhibition of cyclo-oxygenase-1 and -2 to produce analgesic and antipyretic effects (Berg *et al.* 1999). It is generally prescribed for osteoarthritis, rheumatoid arthritis, acute lumbar-sciatica pain and for post-operative pain management. Various preparations are available, including 4 or 8 mg oral (standard or quick release) or injection (intravenous or intramuscular) preparations. A systematic review concluded that a single dose of 8 mg LNX offered a high level of pain relief to patients with moderate to severe post-operative dental pain (Hall *et al.* 2009). Diclofenac, which is also a NSAID, is a benzene acetic acid derivative used to treat the pain and swelling associated with rheumatic disorders. It is available in two different formulations, diclofenac potassium (DP) and diclofenac sodium, with the sodium salt used more frequently. The immediate-release potassium formulation might provide pain relief more quickly (Bakshi *et al.* 1992).

Both LNX and diclofenac sodium have demonstrated wide-spread effectiveness in their use, primarily through their nonselective inhibition of cyclo-oxygenase. Furthermore, both are provided in an immediate-release formulation; their impact on inflammation would therefore be beneficial in those cases where an accentuated inflammatory response, because of the presence of an irreversible pulpitis, may have an impact on the success of mandibular local anaesthesia. Moreover, they have a short half-life, which would make them ideal for a single dosage prior to the management of severe tooth pain, in addition to ameliorating post-treatment pain (Bakshi *et al.* 1992, Berg *et al.* 1999, Hall *et al.* 2009). Therefore, the purpose of this prospective, randomized, double-blind study was to compare the efficacy of oral pre-medication of LNX, DP and a placebo (PLAC) medication on anaesthetic efficacy of IANB with lidocaine with 1 : 200 000 epinephrine in patients with irreversible pulpitis. The null hypothesis tested was that there is no significant difference amongst the three groups.

Materials and methods

One hundred and fifty adult volunteer subjects, within the age range of 21–40 years, who reported to the dental emergency department, were assessed for

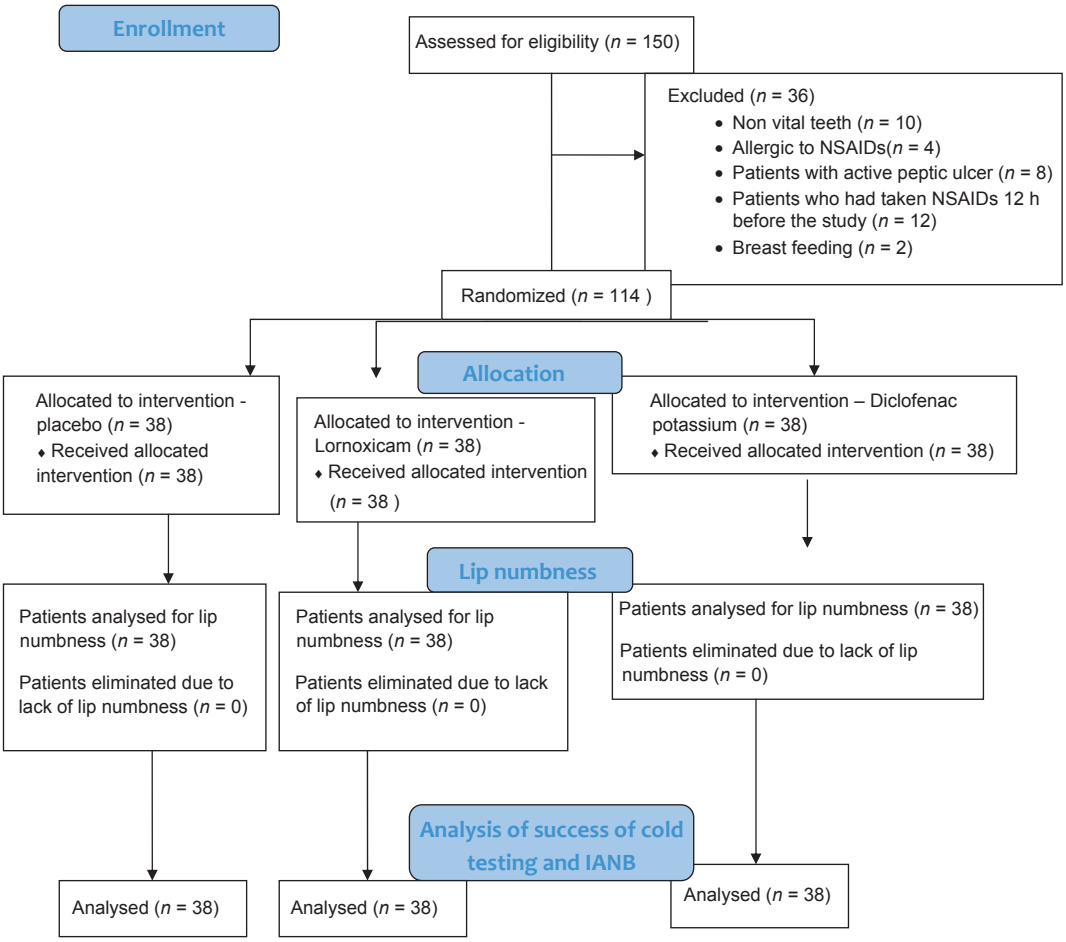

Figure 1 Consort flowchart.

eligibility to participate in this clinical trial, which spanned over a period of 4 months (Figure 1). The sample size was determined after performing a pilot study with 15 patients per groups. A power calculation showed that a sample size of 114 subjects would detect a 30% difference in the success rate of the two test groups at a power of 80% (α type I error of 0.05 and β type II error of 0.20). Ethical approval was sought from the Institutional Review Board and Ethical committee of the University. Informed written consent was obtained from each subject. Pre-operative radiographs were obtained.

The inclusion criteria were as following: healthy patients (ASA I or II) experiencing pain in a mandibular molar with prolonged response to cold testing (lingering pain for more than 45 s) with Green Endo Ice (1,1,1,2 tetrafluoroethane; Hygienic Corp, Akron, OH, USA) and an electric pulp tester (Kerr, Analytic Technology Corp, Redmond, WA, USA), teeth with vital pulp, the absence of periapical radiolucency on radiographs, except for a widened periodontal ligament (not more than 0.75–1 mm) and patients with the ability to understand the use of pain scales. The results of the cold testing and electric pulp testing (EPT) were used to establish a confirmatory diagnosis of irreversible pulpitis. Patient exclusion criteria included those with known allergy, sensitivity or contraindications to any opioid or nonopioid analgesics including aspirin or NSAIDs; those with a history of active peptic ulcer within the preceding 12 months, a history of bleeding problems or anticoagulant use within the last month, or a history of known or suspected drug abuse; those had taken opioid, nonopioid analgesics, steroids, antidepressants or sedatives within 12–24 h before administration of the study drugs; and those who were pregnant or breast feeding. Patients experiencing active

pain in more than one mandibular molar were also excluded. Following application of the criteria, 36 patients were excluded from the study, resulting in the enrolment of 114 subjects for this trial.

Before initiating the treatment, the patients were asked to rate their pain on a Heft Parker visual analogue scale (VAS) with 170-mm line marked with various terms describing the levels of pain (Heft & Parker 1984). The millimetre marks were removed from the scale, and the scale was divided into four categories: no pain corresponded to 0 mm; faint, weak or mild pain corresponded to 1–54 mm; moderate to severe pain corresponded to 55–114 mm; and strong, intense, maximum possible pain corresponded to more than 114 mm (Claffey *et al.* 2004).

A trained dental hygienist divided 114 empty capsules of the same colour and size into three bottles: LNX, DP and PLAC groups. LNX capsules were filled with 8 mg of LNX, DP capsules were filled with 50 mg DP and PLAC capsules were filled with cellulose powder. The bottles were masked with an opaque label and were randomly assigned a three digit alphanumeric value by the pharmacist. All the patients were randomly divided into three groups of 38 patients each and were given one capsule 1 h before the procedure. Randomization of patients was achieved by simple random sampling with a linear congruential generator by a trained dental hygienist who was blinded to the treatment procedures. Only the alphanumeric values were recorded on the data sheets to blind the experiment. After 1 h of oral administration of the capsules, all patients received standard IANB injections using 1.8 mL of 2% lidocaine containing 1 : 200 000 epinephrine (Xylocaine; AstraZeneca Pharmaceutical Products, Wilmington, DE, USA). The solution was injected by the same clinician (first author) using self-aspirating syringes (Septodont, Saint-Maur-des-Fosses Cedex, France) and 27-gauge long needles (Septoject, Septodont, France). The solution was deposited at a rate of 1 mL min^{-1}.

After 15 min of the initial IANB, each patient was asked whether his or her lip was numb. If profound lip numbness was not recorded within 15 min, the block was considered unsuccessful and the patients were to be excluded from the study. However, none of the subjects were eliminated as a result of lack of lip numbness. The tooth in question was tested again with cold spray (Green Endo Ice, Hygienic Corp, OH, USA), and two possible outcomes were recorded. First, if the patient felt pain or sensitivity, the test was recorded as a failure and supplemental anaesthesia was provided. Second, if the patient did not feel pain or sensitivity to the cold spray, a rubber dam was placed and a standard endodontic access cavity was begun with a bur under water spray coolant. If the patient felt pain during access, the outcome was recorded as a failure and supplemental anaesthesia was administered. Success of IANB was defined as no pain during endodontic access preparation and root canal instrumentation.

The data were recorded on a Microsoft Excel sheet (Microsoft Office Excel 2003; Microsoft Corp, Redmond, WA, USA) for statistical evaluation using a commercial program (SPSS 19, Somers, NY, USA). The pre-medication codes were sent directly to the statistician by the pharmacist. Age, initial and post-injection VAS scores were tabulated and compared using multiple comparison analysis of variance and post hoc tests. The gender of the patients and type of tooth were compared by chi-squared test. The significance level was set at $P = 0.05$ for these analyses. The proportions of successful IANB in the LNX, DP and placebo groups were compared using the chi-squared test.

Results

The age, gender, mean initial VAS scores and tooth type were tabulated (Table 1). There were no significant differences ($P > 0.05$) between the three groups. One hundred per cent of the patients had subjective lip anaesthesia with the IAN blocks. All patients reported a significant decrease in active pain after local anaesthesia ($P < 0.05$). The post-injection VAS scores are given in Table 2. There was no significant difference between

Table 1 Comparison of age, gender and initial Heft Parker visual analogue scale (VAS) scores amongst the three groups

	Control (Placebo)	Lornoxicam	Diclofenac potassium
Total number of subjects	38	38	38
Age (Mean ± SD) (years)*	28 ± 7	26 ± 9	30 ± 6
Gender*			
Males	18	22	15
Females	20	16	23
Initial pain (Heft Parker VAS)*	98 ± 21	103 ± 26	101 ± 22
Tooth*			
First molar	20	19	22
Second molar	18	19	16

*There were no significant differences between the three groups ($P > 0.05$).

Table 2 Comparison of percentage of successful cold test and inferior alveolar nerve block amongst the three groups

Treatment group	Cold test successful (%)	IANB successful (%)	Post-injection visual analogue scale scores (Mean ± SD)
Control – Placebo	16 OF 38 (42.8)	10 OF 38 (28.5)	18 ± 2[a]
Lornoxicam	30 OF 38 (78.5)	28 OF 38 (71.4)	6 ± 3[b]
Diclofenac potassium	26 OF 38 (67.8)	24 OF 38 (53.5)	8 ± 3[b]

Mean values that share a superscript letter were not significantly different at the 5% level.

LNX and DP in the post-injection VAS scores ($P > 0.05$), whilst both LNX and DP resulted in significantly lower mean VAS scores than PLAC ($P < 0.05$).

The number and percentage of patients with no response to the cold test and successful IAN block (no pain during access cavity preparation and canal instrumentation) by the test, and control groups are presented in Table 2. The percentage of patients with negative response to cold test was as following: 42.8% (16 of 38 patients) for the control PLAC groups; 67.8% (26 of 38 patients) for pre-medication with DP; and 78.5% (30 of 38) for pre-medication with LNX. There were no statistically significant differences amongst the three groups. On the basis of absence of pain during access and canal instrumentation, the percentage of successful IAN blocks was as following: 28.5% (10 of 38 patients) in the control PLAC group, whilst pre-medication with LNX and DP resulted in 71.4% (28 of 38 patients) and 53.5% (24 of 38 patients) successful IANBs, respectively. The percentage of successful IANBs was significantly higher in the LNX group when compared with the PLAC group ($P < 0.001$).

Discussion

The present study evaluated the efficacy of pre-medication with LNX or DP on the success of IANB. The results of the present study demonstrate that the success of IANB was significantly greater in patients pre-medicated with LNX when compared to PLAC ($P < 0.001$). There were no significant differences between DP and LNX or PLAC ($P > 0.05$).

Two per cent lidocaine was chosen in this study because several studies comparing lidocaine to other anaesthetics including articaine, in the success of pulpal anaesthesia found little or no significant difference in efficacy. Articaine (4%) with 1 : 100 000 epinephrine has been shown to be similar to 2% lidocaine with 1 : 100 000 epinephrine in inferior alveolar nerve blocks (Mikesell *et al.* 2005).

It is a commonly held belief that lip numbness implies pulpal anaesthesia, yet in two clinical trials only 75% and 80% of the patients with lip numbness had pulpal anaesthesia (Fuss *et al.* 1986, Petersson *et al.* 1999). In the present study, 100% of the patients exhibited lip numbness. Therefore, lip numbness may not be a good indicator of pulpal anaesthesia, at least in inflamed pulps. However, it was possible to draw a correlation between success of cold test and IANB. These results are comparable to previous reports (Ianiro *et al.* 2007). Thus, cold testing may be considered more reliable than lip signs to determine when to begin endodontic access for patients with irreversible pulpitis. However, it is important to note that negative response to cold testing does not necessarily indicate a successful IANB.

The proposed mechanisms for the efficacy of LNX include inhibition of conduction of C fibres (Sen *et al.* 2006), which are more resistant to local anaesthesia than A-delta fibres. Also, opening of the K^+ channels located in the primary afferent nerve endings produces antinociception and represents an important step in the peripheral antinociceptive effect of several NSAIDs. Activation of the NO–cyclic guanosine mono phosphate (GMP) pathway could also induce antinociception through the opening of K^{2+} channels. Such a mechanism has been implicated for the antinociceptive action of rofecoxib (Deciga-Campos & Lopez Munoz 2004). It is possible that LNX produces a peripheral analgesic effect via the same mechanism and thereby increase the success rate of IANB.

Transient receptor potential vanilloid channels have been implicated in pain signalling and thermo reception. TRPV1 plays a major role in hyperalgesia and allodynia and is expressed in both the parasympathetic nervous system and central nervous system, (Patwardhan *et al.* 2009). The TRPV1 channel is sensitized by prostaglandins and other inflammatory mediators, leading to a potentiation of currents through the channel. This lowers the temperature threshold for activating the channel. It is likely that TRPV receptors might partially mediate the pain of pulpal origin and thus explain the exaggerated response of teeth with irreversible pulpitis to thermal stimuli (Alessandri-Haber *et al.* 2006). The activation

of TRPV4 channel does not occur by the action of a single inflammatory mediator but rather through the concerted action of multiple mediators (Simmons *et al.* 2004). The present study revealed that 78.5% of the patients pre-medicated with LNX had a negative response to cold testing after IANB in contrast to 67.8% of patients who were administered DP. Although this difference was not statistically significant, it is possible that this may be because of the ability of LNX to inhibit TRPV channels more effectively than diclofenac. Further research is, however, required in this direction.

The degree and duration of the damage and up-regulation occurring before the prostaglandins were inhibited by the NSAIDs is also a factor in influencing success of IANB (Simmons *et al.* 2004). Prostaglandins are effectively blocked by LNX and DP, and they have a relatively short half-life. From the results of the present study, it may be speculated that LNX may be more effective than DP in inhibition of PGs, though no specific evidence exists in this regard. This also warrants further inspection.

Conclusions

Oral pre-medication with 8 mg LNX but not 50 mg DP resulted in significantly higher percentage of successful inferior alveolar block in patients with irreversible pulpitis than pre-medication with PLAC.

Acknowledgements

The authors wish to thank Dr Matthias Zehnder, Universität Zürich for his valuable guidance in pre-reviewing the manuscript.

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