The effect of preoperative submucosal administration of tramadol on the success rate of inferior alveolar nerve block on mandibular molars with symptomatic irreversible pulpitis: a randomized, double-blind placebo-controlled clinical trial

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Abstract


Aim This randomized, double-blind, placebo-controlled, clinical trial was designed to improve the success of inferior alveolar nerve blocks (IANB) in mandibular molars with symptomatic irreversible pulpitis (SIP) by means of preoperative submucosal administration of 50 mg tramadol.

Methodology Forty-two patients with a mandibular molar diagnosed with SIP took part in the trial. Patients were assigned randomly to one of two groups: tramadol group (n = 21), who received 50 mg tramadol in 1 mL by mandibular infiltration, and a placebo group (n = 21), who received 1 mL of normal saline administered to the affected tooth by the same means. Ten minutes later, all patients received an IANB with 4% articaine with epinephrine 1 : 100 000. A 10-min waiting time was established after local anaesthetic (LA) administration before carrying out three consecutive tests to assess anaesthesia of the pulp, that is two consecutive negative responses to an electric pulp test, positive or negative response to a cold test and no pain during access cavity preparation. IANB was considered successful only if the patient did not experience pain arising from these tests. Data were analysed by the Chi-squared frequency test and the Fisher’s exact test, for qualitative variables, Mann–Whitney U-test for independent samples and two-way ANOVA for more than two independent samples.

Results In the tramadol group IANB was achieved successfully in 57% of the sample, whilst the placebo group obtained 29%. The difference between groups was not significant (P = 0.06). When performing endodontic access, the anaesthetic success rate was significantly in favour of tramadol (P = 0.03).

Conclusions Preoperative submucosal administration of 50 mg tramadol in mandibular molars with SIP significantly improved the success of IANB using 4% articaine with 1 : 100 000 epinephrine during access cavity preparation in comparison with a placebo.

Keywords: anaesthesia failure, articaine, inferior alveolar nerve block, mandibular infiltration, symptomatic irreversible pulpitis, tramadol.

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Introduction

Local anaesthetics are the most effective way to manage pain during endodontic therapy, but in
mandibular molars with irreversible pulpitis, local anaesthesia failure during inferior alveolar nerve block (IANB) is high (Claffey et al. 2004, Poorni et al. 2011). This phenomenon has been attributed to several possible causes (Sessle 2000, Bennet & Townsand 2001, Suwanchai et al. 2011), but the exact mechanism has not yet been determined.

One of the most widely studied measures for increasing IANB success is the use of preoperative medication (Ianiro et al. 2007, Aggarwal et al. 2011, Yadav et al. 2015). Drug administration by mandibular infiltration introduces the local anaesthetic (LA) or medication to the mucobuccal fold adjacent to the tooth undergoing treatment. In endodontics, local administration of medication for pain and inflammation management via this route has drawn widespread interest as it permits the use of stronger analgesics, such as opioids (Uhle et al. 2001, Mohajeri et al. 2015), reduces the first-pass hepatic effect of some drugs (Scott & Perry 2000 Grond & Sablotzki 2004), and concentrates the therapeutic effect at the site of the affected tooth (Penniston & Hargreaves 1996, Aggarwal et al. 2011).

Tramadol is a central action opioid analgesic with a multimodal mechanism of action. It possesses a weak binding affinity for μ receptors and, at the same time, inhibits the neuronal reuptake of serotonin and noradrenaline (Scott & Perry 2000, Grond & Sablotzki 2004). It has also been suggested that tramadol could have an anaesthetic effect on peripheral nerves. Some authors agree that tramadol possesses anaesthetic properties similar to lidocaine (Mert et al. 2002, Güven et al. 2005). Several research initiatives have even used tramadol as an anaesthetic solution for the excision of small cutaneous lesions or maxillary molar extraction (Altunkaya et al. 2003, 2004, Al-Haideri 2013). Nevertheless, the mechanism whereby tramadol produces its anaesthetic effect remains unknown.

The working hypothesis of this study was that preoperative submucosal administration of 50 mg tramadol to the mucobuccal fold adjacent to the affected tooth would increase the success rate of IANB using 4% articaine with 1 : 100 000 epinephrine, for treating mandibular molar canals with symptomatic irreversible pulpitis (SIP). Therefore, the aim of the study was to increase the anaesthetic success rate of the IANB with 4% articaine with 1 : 100 000 epinephrine by preoperative administration of submucosal tramadol.

As secondary outcome measures, the study evaluated gender-related differences regarding the effect of tramadol, if the administration of tramadol enhanced the local anaesthetic effect to provide adequate profound pulpal anaesthesia during access cavity preparation, and if submucosal administration of tramadol affected the duration of LA.

**Materials and methods**

This randomized, double-blinded, placebo-controlled, clinical trial was conducted according to the latest update of Declaration of Helsinki guidelines (October 2013).

The trial was approved by the Ethics Committee for Clinical Research at the Defensa Gómez Ulla Central Hospital (Madrid, Spain) and by the Spanish Medicines and Healthcare Products Agency (SMHPA).

**Inclusion and exclusion criteria**

Nonprobabilistic sampling of consecutive cases was used to generate the sample of patients. All patients were recruited from the dental clinic run by the Master’s program in Endodontics at the Center for Innovation and Advanced Specialties at Alfonso X el Sabio University (Madrid, Spain), aged between 18 and 64 years, and had a mandibular molar diagnosed with SIP. Diagnosis of SIP was determined by the following symptoms: spontaneous pain, extreme prolonged sensitivity to cold, pulp exposure and/or pain deriving from changes of posture. Exclusion criteria were established on the basis of contraindications and possible interactions of 100 mg/2 mL tramadol in an injectable solution, as stated by the technical information data of the drug published by the SMHPA (available here: http://www.aemps.gob.es/cima/pdfs/es/lt/63734/FT_63734.pdf).

Sample size was calculated on the basis of the results of a pilot study performed previously. Finally, 21 patients per group were included, making a total patient sample of 42.

**Randomisation and blinding**

As patients joined the study, each was assigned a sealed envelope, numbered in the order of recruitment. A code had been assigned to each envelope consisting of two letters and two numbers generated by randomisation software, allotting the patient to one of the two treatment groups. This system of block randomisation guaranteed the homogeneity of the two groups. The different steps of the study followed the guidelines suggested by the CONSORT group for
planning and improving the quality of reports of parallel group randomised trials (Fig. 1).

The envelopes containing the 1 mL syringes with tramadol or placebo were prepared by an independent pharmacist. Therefore, both patients and clinicians were blinded.

Procedure

Baseline levels of pulp reaction were registered before carrying out treatment. Reactions to cold were assessed by applying a cotton pellet wetted with cold spray (Henry Schein, Endo Cold Spray, Melville, NY, USA) to the cervical third of the buccal surface of the affected tooth. Baseline reactions to electrical stimulation were assessed using an electric pulp tester (EPT), applying the electrode (Elements Diagnostic Unit; SybronEndo, Anaheim, CA, USA) to the mesio-buccal cusp of the mandibular molar (Lin et al. 2007).

Pain was assessed using a visual analogue scale (VAS) consisting of a 100 mm line marked from 0, indicating no pain, to 100, indicating unbearable pain, as follows: 0: no pain; >0 and <30: slight pain; >30 and <70: moderate pain; >70: intense pain. Patients were instructed in the correct use of the VAS, and pain levels were registered. As soon as baseline evaluations had been performed, the treatment assigned to each patient was performed. This was administered to the mucobuccal fold adjacent to the affected mandibular molar. In the pilot study performed previously, the application of tramadol did not cause any pain when applied.

After a waiting time of 10 min (Carnaval et al. 2013), the same clinician carried out all the anaesthetic blocks by a direct (traditional Halsted method) approach using a self-aspirating syringe and 27G diameter needle. Each patient received 1.8 mL of 4% articaine with 1 : 100 000 epinephrine.

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**Figure 1** CONSORT flow diagram.
After LA administration, the patient was asked to advise the clinician as soon as the lower lip was numb. This time was registered to measure the latency period of the LA in soft tissue. A 10-min period was established (Tófoli et al. 2003) from LA injection to the start of pulp anaesthesia testing by three different methods. If, after this 10-min period, the patient reported no lip numbness, he/she was withdrawn from the study.

To evaluate the success of the IANB in both groups, three consecutive tests were performed. First, pulp anaesthesia was tested with an EPT three times every 2 min. The test result was considered successful when two consecutive negative responses at maximum electric stimulation (80 mA) were registered. Secondly, pulp anaesthesia was assessed by cold testing. Anaesthesia was considered successful when patient responses to the application of cold were negative. Performing the endodontic access cavity was considered as the final test. Anaesthesia was considered successful when it was possible to access and clean the root canals without the patient experiencing pain. In each case, whenever the patient experienced discomfort, the extent of access achieved was recorded.

Overall success of pulp anaesthesia was defined as negative responses during the whole evaluation process.

Duration of the sensory block was the time interval between the onset of the anaesthetic effect to normal sensation. Patients were asked to write down the hour when they stopped feeling lip numbness.

Statistical analysis

Numerical variables were analysed applying the Mann–Whitney U-test for independent samples. Two-way ANOVA was used to analyse more than two samples. For qualitative variables, the Chi-squared frequency test and the Fisher’s exact test were applied. Statistical significance was set at \( P < 0.05 \).

Results

No differences between the groups were found in terms of age, gender, nationality or the molar treated (Table 1). The LA latency period in soft tissue was 195.07 s in the tramadol group and 289.50 s in the placebo group (Fig. 2). This difference was not significant \( (P = 0.154) \), although the tramadol group had a shorter latency period.

Overall IANB success in the placebo group was 29%, and 57% in the tramadol group. Table 2 shows...
success rates as percentages for each of the pulp anaesthesia tests performed. The third test, performing endodontic access cavity, obtained a significant difference in favour of tramadol \((P = 0.03)\).

When the duration of the anaesthetic effect was measured, no significant differences were obtained between the groups \((P = 0.969)\). However, when analysis in relation to gender was performed, the duration of anaesthesia was significantly longer amongst men receiving tramadol (284.83 min) than women in the same group (257.09 min); (Fig. 3).

None of the patients had any side effects.

**Discussion**

Under the conditions of the present study, mandibular infiltration of 50 mg tramadol in mandibular molars with SIP prior to IANB significantly improved pulpal anaesthesia when the access cavity preparation was performed in comparison with the placebo group.

Opioids have been shown to exert their pharmacologic effect when administered in peripheral tissue (Hargreaves et al. 1991, Uhle et al. 1997, Dionne et al. 2001, Garlicki et al. 2006, Elsharrawy & Elbaghdady 2007). Peripheral tissue inflammation causes an enhanced transport of opioid receptors from the trigeminal ganglion neurons to the peripheral endings of sensory neurons (Lesniak & Lipkowski 2011), resulting in an increased number of opioid receptors in the inflamed tissue.

Tramadol is an opioid analgesic with a dual mechanism of action. On the one hand, it has a weak
affinity for μ opioid receptors, and on the other, inhibits the neuronal reuptake of serotonin (5-HT) and noradrenaline (NA) (Scott & Perry 2000, Grond & Sablotzki 2004).

Moreover, it has been suggested that tramadol may have local anaesthetic-type properties. Pang et al. (1998a,b) observed that intradermal injection of 25 mg tramadol significantly decreased the pain produced by propofol injection in a similar manner to lidocaine. Altunkaya et al. (2003, 2004) even used tramadol intradermally for excision of cutaneous lesions with a success similar to prilocaine.

Several authors agree that tramadol could block sodium channels similar to lidocaine (Mert et al. 2002, Güven et al. 2005, Haeseler et al. 2006), presenting greater affinity for slow inactivation channels Nav 1.8 and Nav 1.9, both present and with increased expression in inflamed dental pulp tissue (Cummins et al. 2007). Jaber et al. (2003) demonstrated the presence of μ receptors in human coronal and radicular pulp tissue, suggesting that, when administered locally on the affected tooth, tramadol could exert its pharmacological effect directly on the inflamed pulp tissue.

Infiltrative injection techniques are used daily by dentists worldwide. They introduce the LA or the drug in the mucobuccal fold of the affected tooth. In endodontics, this route of administration has been studied extensively as supplemental anaesthetic technique after an IANB (Rosenberg et al. 2007, Haase et al. 2008, Aggarwal et al. 2009, 2011, Kanaa et al. 2009, Matthews et al. 2009, Ashraf et al. 2013, Dou et al. 2013, Rogers et al. 2014). Additionally, one of the great advantages of peripheral administration of drugs is to allow a single dose to be used. When administering the drug peripherally in a single dose, the therapeutic effect is concentrated on the affected tooth, reduces the adverse effects caused by its systemic absorption, reduces the consumption of postoperative analgesics and avoids the risk of development of physical dependence associated with a prolonged use of this type of medication (Pozos et al. 2007, Isiordia-Espinoza et al. 2014, Rodríguez-Wong et al. 2016).

In the present study the local injection of tramadol was evaluated as to whether it could improve the quality of transoperative anaesthesia in order to increase the success rate of IANB. Previous studies reported that the submucosal administration of tramadol did not cause pain (Pozos et al. 2006, 2007, Isiordia-Espinoza et al. 2012, Rodríguez-Wong et al. 2016). The injection site postoperatively was not evaluated due to the extensive period of time between the appointments after the clinical session in which root canal treatment was performed.

The overall success of IANB in the present study (Table 2) was similar to results obtained by Rodríguez-Wong et al. (2016) for the tramadol group. These authors obtained a 46.4% success rate in the placebo group compared with 57.1% in the tramadol group. There was a slight difference between their study groups regarding the clinical effect achieved. The main difference between this study and the present one was that the authors not only administered a smaller dose of tramadol (25 mg), but also administered tramadol together with the LA in the IANB injection area. As stated before, under inflammatory conditions the axonal transport of opioid receptors from the trigeminal ganglion to the peripheral nerve endings is enhanced (Dionne et al. 2001, Stein & Machelska 2011). In fact, opioids are more effective with the progression of the inflammatory pathosis, and their action is better under inflammatory and hyperalgesic conditions (Linley et al. 2010). Perineural administration of opioids in areas close to the nerve where there is no tissue damage, in other words, at a distance from its site of action, will not produce any pharmacological effect (Picard et al. 1997, Bigby et al. 2007, Stein & Machelska 2011). Nevertheless, it must borne in mind that in spite of the wide difference between the study groups regarding the overall success of the IANB, it was not significant. For that reason, a larger sample would be needed to increase the statistical

![Figure 3 Boxplot representing the duration of the anaesthetic effect in relation to patient gender.](image-url)
power of the trial to determine whether this trend is significant.

The tramadol group obtained significantly greater anaesthesia success when evaluating IANB success when the endodontic access cavity was performed (Table 2). This percentage was very similar to other reports that evaluated IANB success during endodontic access cavity preparation (Aggarwal et al. 2011, Poorni et al. 2011, Yadav et al. 2015).

When analysing anaesthetic success, there has always been variations between reports. Most researchers have limited their analysis to one test, that is, lip numbness, lack of response to cold or electric stimuli or absence of pain when performing access cavity (Cohen et al. 1993, Claffey et al. 2004, Ianiro et al. 2007, Haase et al. 2008, Tortamano et al. 2009, Parirokh et al. 2010, Aggarwal et al. 2011, Poorni et al. 2011, Prasanna et al. 2011).

In the present study the application of several diagnostic tests to confirm pulpal anaesthesia after an IANB in mandibular molars with SIP was considered a better method to obtain more accurate outcome of anaesthetic success than using only one. Weisleder et al. (2009) found that only 83% of the pulp of teeth that gave a positive response to EPT were really vital, compared to 97% when evaluated with both EPT and cold.

It is well documented that a negative response to lip numbness or to cold or electric tests does not guarantee pulp anaesthesia when performing access cavity preparation. Thus, it was considered the most reliable test to rate anaesthetic success in mandibular molars with SIP.

As a secondary outcome, the duration of anaesthesia in relation to gender was evaluated. Significant differences were found within the group treated with tramadol. Men had an anaesthetic effect of longer duration than women, 284.83 and 257.09 min, respectively. The literature contains contradictory findings regarding the influence of gender on pharmacology of tramadol. Whilst Ardakani & Rouini (2004) did find differences between the sexes when administering tramadol to Chinese volunteer subjects.

Moreover, in a study of patient-controlled analgesia (PCA), De Cosmo et al. (2008) observed a positive correlation between gender and tramadol consumption. The authors found that the analgesic effect of tramadol was greater amongst men, so men required lower doses of postoperative tramadol. But it is important to note that the differences observed in the present study were related to the local anaesthetic action of tramadol after its administration, an effect produced by a different mechanism of action from its binding to μ receptors. The studies reported in the literature have not provided data that allow any definitive conclusions as to the influence of gender on the effects of tramadol. Nevertheless, due to the reduced number of patients analysed, new studies with a larger sample should evaluate whether the observed trend is significant.

Conclusions

Preoperative local submucosal administration of 50 mg tramadol for mandibular molars with SIP significantly improved the anaesthetic effect of IANB using 4% articaine with 1:100 000 epinephrine during access cavity preparation for treating root canals in comparison with a placebo, and produced a longer-lasting anaesthetic effect in male patients than female patients.

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Conflict of interest

The authors have stated explicitly that there are no conflict of interests in connection with this article.

References


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