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Citation for final published version:

Mousavi, S.A., Sadaghiani, L., Shahnaseri, S., Zandian, A., Farnell, D. J. J. and Vianna, M.E. 2020. Effect of magnesium sulphate added to lidocaine on inferior alveolar nerve block success in patients with symptoms of irreversible pulpitis: a prospective, randomized clinical trial. *International Endodontic Journal* 53 (2) , pp. 145-153.  
10.1111/iej.13186

Publishers page: <https://doi.org/10.1111/iej.13186>

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**Effect of magnesium sulphate added to lidocaine on inferior alveolar nerve block success in patients with symptoms of irreversible pulpitis: a prospective, randomized clinical trial**

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**Running title:** ID block with lidocaine plus magnesium sulphate.

**Key Words:** Inferior alveolar nerve block, Irreversible pulpitis, Magnesium sulphate

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## **Abstract**

**Aim** To investigate the effect of magnesium sulphate used as an adjuvant to lidocaine with epinephrine local anaesthetic on the success of inferior alveolar nerve blocks (IANB) in patients with irreversible pulpitis undergoing root canal treatment.

**Methodology** In a double-blind clinical trial, following power calculation, 124 patients with symptoms of irreversible pulpitis in mandibular molar teeth were selected and initial pain data was collected using a Heft-Parker (Heft & Parker 1984) visual analogue scale. The first group (control) received IANB with 1.8 mL of a local anaesthetic solution containing 1.8% lidocaine with 1:88,000 epinephrine whilst the second group (test) received IANB with 1.8 mL of an anaesthetic solution containing 1% magnesium sulphate, and 1.8% lidocaine with 1:88,000 epinephrine. Pain data was collected after access cavity and penetration of files in the canals using a Heft-Parker visual analog scale. Two patients were not included in the study as they did not consent and a further 54 patients were excluded as they did not report lip numbness within 15 minutes after IANB administration, thus the data presented in this study is related to 68 patients. The data were analyzed using chi-square and t- test ( $\alpha=0.05$ ).

**Results** The success of pulpal anaesthesia with IANB was 82% for the magnesium sulphate group and 53% for the control group. There was a significant difference in the effectiveness of the IANB between the 2 groups ( $P < .001$ ). There was no significant difference between the magnesium sulphate and control groups regarding gender ( $P = .598$ ) or age ( $P = .208$ ) or initial pain scores ( $p = .431$ ).

**Conclusions** The addition of 1% magnesium sulphate to 1.8% lidocaine with 1:88,000 epinephrine resulted in a positive impact for the success of IANB in patients with a diagnosis of irreversible pulpitis related to mandibular molar teeth undergoing root canal treatment. Thus magnesium sulphate may be used as adjuvant for achieving profound pulpal anaesthesia in challenging cases. However, more studies with larger sample size and different concentration doses must be carried out to establish an appropriate conclusion before its routine clinical use.

## Introduction

The inferior alveolar nerve block (IANB) is the most frequently used injection technique for inducing pulpal anaesthesia for endodontic procedures in posterior mandibular teeth (Malamed 2013). Clinical studies in patients with irreversible pulpitis in mandibular posterior teeth have reported 44%-81% failure in achieving adequate anaesthesia by IANB (Matthew *et al.* 2009, Parirokh *et al.* 2014, Shadmehr *et al.* 2017). Therefore, considerable ongoing research is directed at enhancing the success rate of IANB in patients with irreversible pulpitis, by introducing alternative injection techniques (Goldberg *et al.* 2008, Click *et al.* 2015), anaesthetic solutions (Shadmehr *et al.* 2017), supplemental injections (Parirokh *et al.* 2014, Shetty *et al.* 2015, Saatchi *et al.* 2016, Rodriguez *et al.* 2016), pre-medication before performing the IANB (Prasanna *et al.* 2011), and addition of an adjunct to local anaesthetic formulations (Youssef *et al.* 2017). The most likely explanation for the decrease in efficacy of local anaesthesia in inflamed pulps is proposed to be the activation effect of inflammation on the peripheral free terminals of nociceptive neurons and the associated central mechanisms (Chaudhary *et al.* 2001, Hargreaves & Keiser 2002, Goodis *et al.* 2006, Aggarwal *et al.* 2014). Central sensitization which is responsible for secondary hyperalgesia, the spread of tenderness or enhanced pain sensitivity outside of an area of injury, and tactile allodynia, pain in response to light touch, is a common component of both inflammatory and neuropathic pain (Woolf *et al.* 2007). Central sensitization has been found to be a manifestation of activity-dependent plasticity, due to an increase in synaptic strength, driven to a substantial extent, by N -methyl-D -aspartic acid glutamatergic receptors (Woolf & Thompson 1991). Therefore, magnesium ions, a non-competitive blocker of N-methyl-D-aspartate receptor (NMDA) with antinociceptive effects (Yentis & Hirsch 2013), could be of great importance in facilitating anaesthesia.

Magnesium has been shown to have the ability to block voltage dependent ion channels, a property which can contribute to its anti-nociceptive effect (Mayer *et al.* 1984, Iseri & French 1984). Magnesium sulphate is not used as a primary analgesic itself, but as an adjuvant agent

for enhancing the analgesic actions of the more established analgesics.

The role of magnesium sulphate for perioperative analgesia has been investigated during general anaesthesia as well as spinal anaesthesia. Magnesium sulphate has been reported to be effective in perioperative pain treatment and in blunting somatic, autonomic and endocrine reflexes provoked by noxious stimuli (Kara *et al.* 2002, Levaux *et al.* 2003).

Various studies have shown a beneficial effect on postoperative pain outcomes with a variety of magnesium sulphate pretreatments. Magnesium sulphate has been used intravenously, intrathecally as well as epidurally for pain relief (Mirkheshti *et al.* 2012, Bansal 2015, Jarahzadeh *et al.* 2016).

Recently the application of magnesium sulphate as an adjuvant to block anaesthesia for example in neuraxial, epidural, femoral and paravertebral blockades has been investigated. The results show positive impact in terms of increased duration and enhanced quality of the anaesthesia (Lee *et al.* 2012, Shruthi *et al.* 2016, ELShamaa *et al.*, Hassan & Mahran 2015).

Despite the evidence supporting the use of magnesium sulphate in anaesthetic solutions no study has yet investigated the anaesthetic efficacy of magnesium sulphate added to the routinely used 2% lidocaine with 1:80,000 epinephrine for IANB. Therefore, the purpose of this prospective, randomized controlled, double-blind study was to compare the anaesthetic success of a prepared anaesthetic solutions containing 1% magnesium sulphate and 1.8% local anaesthetic lidocaine with epinephrine 1:88,000 compared to 1.8% lidocaine with 1:88,000 (as control), used in inferior alveolar nerve blocks (IANB) in patients with symptomatic irreversible pulpitis.

## **Materials and Methods**

This study was reviewed and approved by the Ethics Committee of the School of Dentistry, Isfahan University of Medical Science, Isfahan, Iran (registration number 396169) and registered with the National Clinical Trials (ClinicalTrials.gov; number NCT03262857). All procedures were in accordance with 1964 Helsinki declaration and a written informed consent was obtained from all individuals included in the study.

Power calculations suggested that a sample size of 76 (two groups of 38 subjects) would be needed to detect a difference of 30% (60% versus 30% or 90%) in the success rate using a two-tailed test. A significance level of 5%, a power of 80%, and a continuity correction to the normal approximation of the discrete distribution were assumed. The calculation was carried out using the “power twoprop” command in STATA software (StataCorp. 2013, College Station, TX: StataCorp LP).

Patient recruitment and treatment took place between July and November 2017. A total of 124 patients who had been referred to the Dental Clinic of the Endodontics Department of Isfahan; University of Medical Sciences, Iran were screened by one clinician who also obtained consent from patients enrolled in the study. All patients were diagnosed with irreversible pulpitis related to a mandibular molar tooth (diagnosis made by the clinician who also undertook the treatment subsequently- clinician 2) based on the pain history and lingering pain following thermal testing. The pain history was assessed according to Heft-Parker visual analog scale (HP-VAS). Each patient rated their initial pain on this scale that is a 170-mm marked line divided into 4 categories with various terms describing the level of pain. No pain, mild pain, moderate pain, and severe pain were indicated by 0 mm, 1- to 54-mm, 55- to 113- mm, and 114- to 170-mm divisions, respectively. Patients exhibiting moderate to severe initial pain were included in the study.

The current and previous medical and dental histories were obtained and compliance with the inclusion and exclusion criteria was established.

The inclusion criteria consisted of adult patients aged 18 to 60 years old and physical status I according to classification of the American Society of Anesthesiologists (ASA) (Fitz-Henry 2011). Patients taking beta-blockers or being medicated with any opioids preoperatively, drug abusers, subjects who were on antidepressant medication, pregnant or nursing mothers, those with a contraindication for the use of magnesium or sulphate, those known to be allergic to any of the study medications and those with orofacial infection (facial abscess) were excluded.

The dental inclusion criteria were: 1) mandibular molars with pulps having symptoms of irreversible pulpitis, (2) moderate to severe pain, (3) lingering response to cold test, with prolonged response after the removal of the Endo-Ice cold spray stimuli (Hygenic Crop, Akron, OH, USA), and (4) no radiographic alterations of the periodontal ligament space and fully formed roots (revealed by an intra-oral periapical radiograph).

The dental exclusion criteria were: (1) absence of mandibular posterior teeth with symptoms of pulpitis, (2) pain symptoms not indicative of irreversible pulpitis or no pain (3) mandibular posterior teeth responding normally to cold test, and (4) presence of alterations of the periodontal ligament space (e.g. enlargement of PDL space and/or presence of periapical radiolucencies). All the excluded patients received the appropriated treatments but were not included in the study. After exclusion of 2 patients who did not consent to be included in the study, and a further 54 cases due to the lack of profound lip numbness following the administration of an IANB, a total of 68 patients from the initial 124 potential participants were included (Figure 1). These patients aged 19-43 years old with mean age of 35.4 years (SD: 12.19); comprising 42 females and 26 males. The trial was a double-blinded with operator and patients not aware of the allocated groups. Randomization of groups (using a table of random numbers) and preparation of the anaesthetic solutions were performed by the same clinician who took the consent (clinician 1).

### **The anaesthetic solution preparation**

The solutions were prepared by clinician 1 immediately before its administration by clinician 2 (endodontist). Briefly, under sterile conditions, 0.18 mL from a 1.8 mL cartridge of 2% lidocaine with 1:80,000 epinephrine was drawn from plastic plunger of the carpule (Persocaine, Darou Pakhsh, Tehran, Iran) using a 100 IU insulin syringe (BD Micro-Fine Plus®, Becton, NJ, USA) and replaced with 0.18 mL of a 10% magnesium sulphate solution (Magnesium sulphate 7H<sub>2</sub>O, 10% weight/volume, 0.81 mOsmol/mL, Pasteur Institute®, Tehran, Iran), giving a final concentration of 1% of magnesium sulphate, 1.8% lidocaine and 1:88,000 epinephrine within the cartridge (for administration to the test group). The cartridge was inverted 5 times to mix the solution, and no precipitation was created. For the non-magnesium sulphate LA solution (control group), 0.18 mL from a 1.8 mL cartridge of 2% lidocaine with 1:80,000 epinephrine was drawn and replaced with 0.18 mL of sterile distilled water giving a final concentration of 1.8% lidocaine and 1:88,000 epinephrine within the cartridge.

### **Anaesthetic solution Injections and data collection**

The injections (using the solutions detailed in the section above) were administrated using the standard mandibular nerve block, with aspiration being performed before depositing the anaesthetic solution. The administration of IANB was performed slowly (over 100 seconds, de Souza Melo *et al.* 2015) by clinician 2 (endodontist) who also performed the root canal treatments. The endodontist was not aware of group distributions (blinded injections). All the injections were performed using a 27-G, 1.5-inch needle (Septoject®; Septodont, Saint-Maur-des-Fossés, France) attached to a standard aspirating dental injection syringe.

Profound lip numbness within 15 minutes of IANB administration was considered as the criterion for IANB success (Shahi *et al.* 2018). If lip numbness was not profound, the IANB was indicated as missed, and the patient was excluded from the study. Fifteen minutes after the injection, the teeth were isolated with a rubber dam, and access cavities were prepared.



The patients were instructed to rate any pain felt during access cavity preparation and initial file placement (data was collected by clinician 1). If the patient felt pain, the treatment was immediately ceased, and the patient rated the discomfort using the HP-VAS. The success of pulpal anaesthesia was defined as the tooth without pain (HP-VAS score equal to 0 mm) or with mild pain (HP-VAS rating  $\leq 54$  mm) at any stage of the procedure.

### **Statistical Analysis**

Data on age, gender, initial pain, and the success of IANB ratings were analyzed statistically using the Statistical Package for the Social Sciences 22 (SPSS, IBM, NY, USA) at the significance level of 0.05. Comparisons between the magnesium sulphate and control group for the effectiveness of the IANB and gender differences were analyzed using the chi-square test. Age, and difference of initial pain in two groups were analyzed using independent/unpaired two sample t-test as the data was continuous and normally distributed.

### **Results**

Following the exclusion of 54 patients, and the refusal of a further 2 patients to take part in the study, a total of 68 individuals from the initial 124 potential participants were included in the study: 34 received IANB with 1.8% lidocaine/ 1:88,000 epinephrine (control) and 34 with 1% magnesium sulphate, 1.8% lidocaine/ 1:88,000 epinephrine (test group). The age, gender and initial pain data are presented in Table 1. There was no significant difference between the magnesium sulphate and control groups regarding gender ( $P > 0.999$ ), age ( $P = 0.208$ ) or initial pain ( $P = 0.311$ ).

Anaesthetic success for pulpal anaesthesia was 82% for the magnesium sulphate group according to HP-VAS scores [Mean 23.35(20.24)] and 53% for the control group [Mean 63.7(35.9)]. There was a significant difference in the success rates between the 2 groups ( $P < 0.001$ ).

## Discussion

The present study was designed to examine the effect of magnesium sulphate on the IANB produced by local anaesthetic to achieve profound pulpal anaesthesia in patients with symptoms of irreversible pulpitis. All the teeth included in this study were responsive to cold test and were found to have hyperaemic coronal pulp tissue on access to the pulp chamber.

Fifty-four patients (43%) were excluded from the study as the IANB was deemed to have failed based on the subjective assessment of profound lip numbness as reported by the patient, as described by Shahi *et al.* (2018). Although this is in line with success rate in the range of 30-97% for IANB in general, reported in the literature (Kanaa MD *et al.* 2006), this limitation is acknowledged and the fact that application of an objective method of assessment such as use of an electronic pulp tester would have provided more certainty. In that situation if the tooth responds positive, the anaesthesia should be considered as failed, and the patient excluded from the study. Lidocaine was selected as local anaesthetic for IANB for the present study as it is a commonly used anaesthetic solution (Nusstein *et al.* 1998, Tortamano *et al.* 2009, Saatchi *et al.* 2015, Aggarwal *et al.* 2019). Clinical studies have reported failure rates ranging from 30%–81% for IANB in mandibular posterior teeth with irreversible pulpitis (Nusstein *et al.* 1998, Tortamano *et al.* 2009, Saatchi *et al.* 2015; Webster *et al.* 2016). The finding of 53% success in achieving pulpal anesthesia in the control group is in line with this data. Failure to achieve profound anaesthesia may be due to the technical failure in delivering the anaesthetic solution to the target area, the pterygomandibular space where the inferior alveolar nerve enters the mandibular foramen (Argueta-Figueroa *et al.* 2012), or local causes such as inflammation in cases of irreversible pulpitis (Webster *et al.* 2016). The inflammation activates the capsaicin-sensitive transient receptor potential vanilloid type 1 and tetrodotoxin-resistant receptors, which reduce the efficacy of the commonly used local anaesthetic agents (Chaudhary *et al.* 2001, Stenholm *et al.* 2002). Alternative methods and anaesthetic agents have been introduced as an attempt to improve the success of pulpal anaesthesia in these circumstances, the addition of magnesium sulphate is one of the attempted strategies.

Magnesium is a N-methyl-D-aspartate (NMDA) antagonist that plays a role in moderating calcium influx into the neurons (Yentis & Hirsch 2013). Magnesium has been shown to decrease peripheral nerve excitability and to enhance the ability of lidocaine to raise the excitation threshold of A- $\beta$  fibers (Vastani *et al.* 2013). The results of the present study confirmed that the potential of magnesium sulphate in achieving more profound anaesthesia when compared to the control group.

Baseline variables such as age, gender, and initial pain were not significantly different between the two groups. The mean initial pain ratings of 141.50 mm for the magnesium sulphate group and 133.03 mm for the control group indicated severe pain on the HPS-VAS. This severe pain, combined with prolonged response to the cold test, and lack of radiographic signs of apical periodontitis was deemed to represent symptomatic irreversible pulpitis (Claffey *et al.* 2004, Matthew *et al.* 2009). The results of this trial are also in accordance with two studies which demonstrated that admixture of magnesium to prilocaine and ropivacaine for axillary brachial plexus block provided a pronounced sensory block without any adverse effects (Gunduz *et al.* 2006, Abd Elmawgoud *et al.* 2008). Although the long term evaluation of the IANB effect was not the aim of the present study, there were no reports in this study of complication following the administration of supplemented and non-supplemented anaesthetics (e.g. paresthesia).

In this study, the effectiveness of IANB (for achieving adequate pulpal anaesthesia) was assessed by measuring the pain levels during access cavity preparation and initial instrumentation using HP-VAS. The method for evaluating the success was based on the standard studies conducted by Aggarwal *et al.* (2011) and Simpson *et al.* (2011). The success of the IANB was defined as the tooth without pain (HP-VAS score equal to 0 mm) or with mild pain (HP-VAS rating  $\leq$ 54 mm).

The findings were also in agreement with Lee *et al.* (2012). In their study, interscalene nerve block was performed with 2 mL magnesium sulphate 10% added to 0.5% bupivacaine (M group) or 2 mL normal saline (saline group). Patients in the magnesium sulphate group had significantly decreased pain NRS scores at 12 hours (Lee *et al.* 2012).

The concentration of magnesium sulphate used in the present study was based on previous established reports (Goyal *et al.* 2008, El-Hamid *et al.* 2011, Lee *et al.* 2012, Mukherjee *et al.* 2014, Muthiah *et al.* 2016, Youssef *et al.* 2017) . All included doses of 150 mg magnesium or less as an adjuvant to induce nerve block and none reported adverse effect and all reported significantly increase in the success of anaesthesia.

There are no previous reports in the literature on the effect of magnesium sulphate used as adjunct to lidocaine, in IANB to achieve profound anaesthesia for root canal treatment of teeth with symptoms of irreversible pulpitis. However, magnesium sulphate USP 50% has been used in patients with symptomatic irreversible pulpitis 1 hour before administration of conventional IANB (Shetty *et al.* 2015). The authors reported the IANB effectiveness was significantly higher for magnesium sulphate group. The drawback of the Shetty *et al.* (2015) study was that patients received two injections, which may have its own potential risks and probable patient dissatisfaction. Therefore, the use of magnesium sulphate as adjuvants to local anaesthetics in the same injection for IANB would be advantageous in comparison.

Magnesium sulphate is inexpensive and safe to use while showing physical compatibility and chemical stability in combination with lidocaine hydrochloride (Houlihan *et al.* 2016). The biological basis for its potential NMDA receptor antagonism and calcium channel blocking effect is promising particularly in cases of prolonged nociceptive input of chronic inflammation that might cause increase in the number of NMDA receptors (hyperalgesia) resulting in reducing the intensity of stimuli necessary to initiate pain (allodynia) (Woolf & Thompson 1991, James 2009).

### **Conclusion:**

The addition of 1% magnesium sulphate to 1.8% lidocaine with 1:88,000 epinephrine resulted in a positive impact for the success of IANB in patients with a diagnosis of irreversible pulpitis related to mandibular molar teeth undergoing root canal treatment. Thus magnesium sulphate may be used as adjuvant for achieving profound pulpal anaesthesia in challenging cases.

However, more studies with larger sample size and different concentration doses must be carried out to establish an appropriate conclusion before its routine clinical use.

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## **Acknowledgements**

**Funding:** The work was supported by the Department of Endodontics, Isfahan University of Medical sciences, Isfahan, Iran, Research grant #396169.

**Conflict of Interest:** The authors confirm that there is no conflict of interest in relation to this study.

**Table 1.** Comparison of the effect of magnesium sulphate and control group in achieving anaesthesia using inferior alveolar nerve block in patients with symptomatic irreversible pulpitis.

	<b>Magnesium sulphate group (n=34)</b>	<b>Control group (n=34)</b>	<b>P value</b>	<b>95% confidence interval</b>
<b>Gender</b>	Female 21 (61.8%) Male 13 (38.2%)	Female 21 (61.8%) Male 13 (38.2%)	>0.999	
<b>Age</b> Mean ( $\pm$ Standard Deviation)	36.50 years ( $\pm$ 12.8)	40.82 years ( $\pm$ 15.099)	0.208	[-11.10, 2.46]
<b>Initial Pain</b> Mean ( $\pm$ Standard Deviation)	141.50 mm ( $\pm$ 15.71)	133.03 mm ( $\pm$ 12.07)	0.311	[-3.32, 10.27]
<b>Pain during access cavity or penetration of files</b>	23.35 mm( $\pm$ 20.24)	63.71 mm( $\pm$ 35.89)	P < .001	[-49.59, -30.76]

**Figure 1.** Flow diagram summarizing the study methodology.

