



# Post-operative analgesia of 2% lignocaine with or without magnesium sulfate for inferior alveolar nerve block in symptomatic mandibular molars - a randomized double blind controlled clinical trial

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**Background:** Single inferior alveolar nerve block is ineffective in achieving adequate pulpal anesthesia in 30-80% of patients due to anatomical variations, local tissue pH, central sensitization, and several factors. Various supplementary techniques and combination of adjuvants with lignocaine are used to overcome these failures. Magnesium sulfate (MgSO<sub>4</sub>), one such adjuvant, acts at the N-methyl-D-aspartate glutamate receptor resulting in effective anesthesia. The aim of this prospective, randomized, double-blind, clinical controlled trial was to evaluate the onset, anesthetic efficacy, duration and post-operative analgesia of 2% lignocaine with and without the addition of MgSO<sub>4</sub> in patients with symptomatic irreversible pulpitis and apical periodontitis.

**Methods:** Forty-two patients were randomly divided into three groups: 2% lignocaine (group 1) and 2% lignocaine with MgSO<sub>4</sub> (75 mg) and (150 mg) in groups 2 and 3, respectively. Pre-operative vitals and Heft Parker-Visual Analogue Scale (HP-VAS) pain scores were recorded. The onset of anesthesia, anesthetic efficacy, and duration of anesthesia were evaluated post administration of the local anesthetic solution. The post-operative analgesia was examined at intervals of 2, 6, 12, 24, and 48 h.

**Results:** Administration of 150 mg MgSO<sub>4</sub> hastens the onset of anesthesia (1.29 min) and produces better anesthetic efficacy (3.29 HP-VAS) compared to group 2 (2.07 min and 9.14 HP-VAS) and group 1 (3.29 min and 35.79 HP-VAS), respectively. The duration of anesthesia was significantly higher in group 3 (247.07 min) compared to that of groups 2 and 1 (190 min and 110.21 min) with P < 0.05.

**Conclusion:** Combining 75 mg or 150 mg of MgSO<sub>4</sub> with lignocaine is more effective than 2% lignocaine and 75 mg of MgSO<sub>4</sub> is adequate for endodontic procedures.

**Keywords:** Anesthetic efficacy; Duration; Inferior Alveolar Nerve; Lignocaine; Magnesium Sulfate; Onset; Postoperative Pain.

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## INTRODUCTION

Achieving profound pulpal anesthesia during root canal treatment is very important in endodontics [1]. The success rate of the inferior alveolar nerve block (IANB)

routinely used to anesthetize the mandibular's posterior region is only approximately 75-90% due to the large surface area covered by the inferior alveolar nerve [2]. However, it becomes inadequate in inflamed tissues, where the success rate is approximately 30-80% in patients with symptomatic irreversible pulpitis, which is

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challenging [3].

This lower success rate of local anesthetics (LA) could be attributed to anatomical variations, local tissue pH, acute tachyphylaxis, effect of nociceptors, central sensitization, psychological reasons, and more [1]. To overcome such failures, various supplementary anesthetic techniques such as intraligamentary, intraosseous, and intrapulpal are used routinely [4]. However, the additional needle prick may have a negative effect on the patient's psychology. Instead, an adjuvant such as epinephrine, mannitol, or ketorolac added to the LA produces synergistic anesthetic effect [5]. A thorough review of the literature showed that only limited drugs that are potent inhibitors of N-methyl D-aspartate (NMDA) glutamate receptor are available that provide central sensitization and block pain perception.

Magnesium sulphate ( $MgSO_4$ ) is used as an adjuvant in various fields of general anesthesia (GA), as intra-operative analgesics in obstetrics, in cardiovascular surgeries, in cases of epilepsy, etc. [6]. Narang et al. (2008) evaluated the use of  $MgSO_4$  added to lignocaine as a single dose in intravenous regional anesthesia for upper limb surgery and concluded that  $MgSO_4$  had better anesthetic and analgesic effects [7]. In dentistry, Shetty KP et al. (2016) showed that administering pre-injection of  $MgSO_4$  before giving IANB increased the anesthetic efficacy [8]. However, this requires two needle pricks for the patient, which may be a psychological deterrent. There are no clinical studies evaluating  $MgSO_4$  combined with lignocaine as a single dose. Hence, the aim of our prospective randomized, double-blind, controlled clinical trial was to combine  $MgSO_4$  with 2% lignocaine in two different concentrations (75 mg and 150 mg) to evaluate the onset, duration and anesthetic efficacy, and post-operative analgesia during routine root canal treatment in patients with symptomatic irreversible pulpitis and symptomatic apical periodontitis. The null hypothesis proposed was that the addition of  $MgSO_4$  to 2% LA will not have any effect on the above mentioned parameters.

## METHODS

The study protocol was presented to and ethical approval was obtained from the Institutional Review Board and Ethical Committee of the SRM Dental College, Ramapuram, Tamil Nadu, India. The trial was registered with the Clinical Trials Registry of India before commencement of the trial. (CTRI/2018/01/011569) (September 2016 to 2019). The study consisted of three groups: 1.5 ml of 2% LA only (Loxicard 2%; 50 ml; Neon; Mfg. Lic. No. KD/2632- A, Mumbai, India) (group 1), 1.5 ml of 2% LA with 0.15 ml of  $MgSO_4$  (Magneon, Neon Laboratories, Mumbai, India) containing an osmolar concentration of approximately 4.060 mosmol/ml that is equivalent to 75 mg of  $MgSO_4$  (group 2). Group 3 consisted of 1.5 ml of 2% LA with 0.3 ml of  $MgSO_4$  equivalent to 150 mg of  $MgSO_4$ . Patients classified under the American Society of Anesthesiologists (ASA) categories I and II, within the age groups of 20 to 60 years were screened in the study. After thorough clinical and radiographic examination along with sensitivity tests, those who were diagnosed with symptomatic irreversible pulpitis and symptomatic apical periodontitis of mandibular molar teeth were recruited into the study. Study protocol was explained to the patients and informed consent was obtained from those willing to participate. The maximum dosage used here is lesser than the adverse range and is safer for endodontic procedures as adverse drug reactions occur only when the serum magnesium level exceeds 6-7 mmol/kg.

Patients with pain of moderate-to-severe intensity (American association of endodontists guidelines) (85 to 170 Heft Parker-Visual Analogue Scale (HP-VAS) pain score) in the mandibular posterior teeth and those who were able to understand the pain scale and respond immediately to electric pulp testing were included in the study. Exclusion criteria included ASA category III and above, patients with any prior medications, those allergic to LA, pregnant, and lactating women.

This study was designed as a randomized controlled

trial with the evaluation of post-operative analgesia as the primary outcome and onset, duration and anesthetic efficacy as secondary outcome measures. Based on these primary and secondary outcomes, a non-blind pilot study was conducted to determine the sample size using six patients in each group. On basis of the results of the pilot study and individual power calculation, 11 subjects per group (N = 33) would provide a minimum of 90% power in all categories. Considering 20% drop-outs, the total sample size was calculated to be 14 per group. The recruited 42 patients were randomly allocated to three groups using block randomization ([www.randomization.org](http://www.randomization.org)). The experimental solutions were freshly prepared by an anesthesiologist (operator 1) who maintained the master coded list of the patients with the respective solutions. The patients, endodontist (operator 2) who performed the treatment, and evaluator (operator 3) who recorded the pre and post-operative parameters were blinded to the anesthetic solution used.

Before starting the procedure, the evaluator recorded the baseline pain values using the HP-VAS pain score. The endodontist then injected the coded anesthetic solution prepared by the anesthesiologist, on the landmark of corresponding operating IANB quadrant on the affected site. After negative aspiration, the local anesthetic solution was slowly deposited at the rate of 1.5 ml over 60 seconds. The Electric pulp tester (EPT) is a device to determine the vitality of the pulp. The onset of anesthesia was evaluated by EPT for every 1 min until the corresponding vital tooth stopped responding.

Root canal treatment was initiated and access cavity preparation was done under rubber dam isolation. The anesthetic efficacy was calculated using HP-VAS pain score on placement of the first 10 size K file (Mani Inc., Japan). Cleaning and shaping of the root canal system was performed subsequently, sterile cotton pellet was placed, and closed dressing given using Cavit-G (3M ESPE, Germany). The duration of anesthesia was evaluated every 15 min using EPT till the adjacent normal tooth responded on the working side. In this study, none of the patients experienced pain during the procedure and

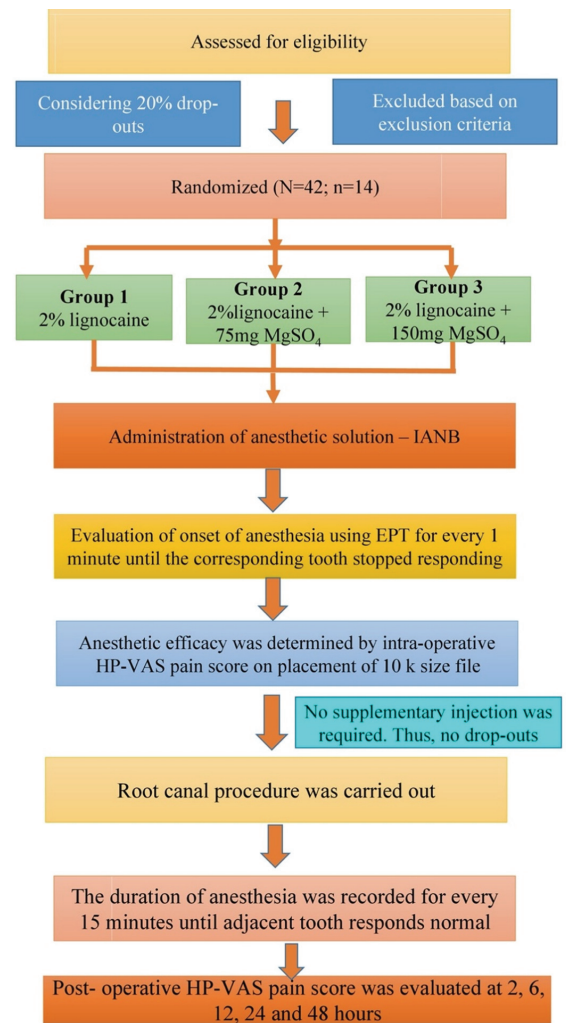


Fig. 1. CONSORT flowchart

thus no other supplementary injection was required in both groups. Post-operative analgesic efficacy was assessed up to 2 h after the procedure at the operating site. Subsequently, the patient was handed a HP-VAS pain scale and was requested to respond to our telephonic evaluation at 6, 12, 24, and 48 h. Figure 1 shows the Consort flow diagram of this randomized controlled clinical trial. Post-operative instructions were given to all the patients along with the prescription of an anti-inflammatory drug, to be consumed only if pain arises. On the subsequent visit, the endodontic therapy was completed.

### Statistical analysis

All the data were tabulated in excel sheet. Statistical

**Table 1.** Demographic data and pre-operative vital signs

	Group 1	Group 2	Group 3	Stat. analysis
Pulse rate	70.43 +/- 6.123	68.64 +/- 5.358	73.57 +/- 5.801	P > 0.05
Peripheral Oxygen saturation level (SpO <sub>2</sub> )	95.36 +/- 2.763	95.21 +/- 3.142	94.93 +/- 4.104	P > 0.05
Respiratory rate	12.36 +/- 1.008	12.07 +/- 0.917	12.14 +/- 0.535	P > 0.05
Blood pressure	97.5 +/- 5.801	97.14 +/- 5.789	99.29 +/- 2.673	P > 0.05
Gender distribution (M:F)	6:08	8:06	4:10	
Pre-operative EPT	2.57 +/- 1.222	2.29 +/- 0.994	2.57 +/- 1.222	P > 0.05
Pre-operative HP-VAS pain score	124.57 +/- 24.422	122.57 +/- 14.064	122.64 +/- 18.177	P > 0.05

EPT, electric pulp tester; HP-VAS, Heft Parker-Visual Analogue Scale

**Table 2.** Onset, duration and anesthetic efficacy of the 3 groups

Groups	Onset (Mins)	Duration (Mins)	Anesthetic efficacy (HP-VAS Pain score)
Group 1	3.29 +/- 0.994 <sup>a</sup>	110.21 +/- 37.559 <sup>a</sup>	35.79 +/- 33.598 <sup>a</sup>
Group 2	2.07 +/- 0.73 <sup>b</sup>	190 +/- 37.250 <sup>b</sup>	9.14 +/- 13.132 <sup>b</sup>
Group 3	1.29 +/- 0.611 <sup>b</sup>	247.07 +/- 26.339 <sup>c</sup>	3.29 +/- 8.352 <sup>b</sup>

Note: Different alphabetical superscripts indicate statistical significance between the groups (P < 0.05)

HP-VAS, Heft Parker-Visual Analogue Scale

**Table 3.** Comparison of post-operative analgesic efficacy at 2, 6, 12, 24, and 48 h intervals

Groups / Hours	2	6	12	24	48
Group 1	50.21 +/- 51.54 <sup>a</sup>	31.79 +/- 34.77 <sup>a</sup>	21.64 +/- 25.25 <sup>a</sup>	20.14 +/- 18.85 <sup>a</sup>	14.64 +/- 17.22 <sup>a</sup>
Group 2	25.36 +/- 35.78 <sup>a</sup>	24.64 +/- 35.89 <sup>a</sup>	13.64 +/- 32.62 <sup>a,b</sup>	4.21 +/- 11.01 <sup>b</sup>	1.64 +/- 6.14 <sup>b</sup>
Group 3	31.86 +/- 42.88 <sup>a</sup>	11.93 +/- 24.15 <sup>a</sup>	1.63 +/- 6.14 <sup>b</sup>	0.00 <sup>b</sup>	0.00 <sup>b</sup>

Note: Different alphabetical superscripts indicate statistical significance between the groups (P < 0.05)

analysis was performed with R statistical software (version 3.5.1). Since most of the data were ordinal in nature and non-normal in distribution as observed by the Shapiro Wilk test, non-parametric test was used to test the statistical significance within and between the groups. Kruskal Wallis and Dunn Post hoc tests were employed to determine the statistical significance in onset, duration, and efficacy of anesthesia among the three groups. Post-operative analgesia at 2, 6, 12, 24, and 48 h within the group was analyzed using Friedman test followed by Dunn post hoc test. Multiple comparisons were made at a significance level of P < 0.05, 95% confidence interval, and power set at 90%.

## RESULTS

The patients' demographic data is shown in Table 1. The patients were equally distributed between the groups

and show no significant difference. The mean and standard deviation of onset, duration and anesthetic efficacy of the three groups are mentioned in Table 2. Both experimental groups showed a significant difference in the onset, duration, and anesthetic efficacy compared to the control group. There was no significant difference between groups 2 and 3 in terms of the onset and anesthetic efficacy, but a significant difference was observed in the duration of anesthesia.

The mean HP-VAS scores of post-operative analgesic efficacy at different time points for all the three groups are given in Table 3. Friedman non-parametric test showed significant reduction in pain from the 12<sup>th</sup> hour in the experimental groups.

## DISCUSSION

Pain is a complex and multidimensional phenomenon

that requires comprehensive and ongoing assessment for an effective management. In the peripheral nervous system, the nociceptive message is transmitted from the periphery to the central nervous system via the axon of primary afferent nociceptors. There is a correlation between the intensity of stimulus and frequency of nociceptor discharge. In symptomatic irreversible pulpitis, voltage gated sodium channels are responsible for the transmission of pain. These are stimulated under physiological conditions by the excitable cells causing depolarization of the neurons and activation of the sodium channels subsequently transmitting the pain signals to the brain. Substances such as bradykinin and prostaglandin E<sub>2</sub> are released from the inflamed tissue to activate or sensitize the nociceptor at the neurons. In case of pulpal pain, the sensitization of pulpal nociceptors exhibits an increased resistance to local anesthetics. Inflammation also changes the synthesis of several neuropeptides and thus influences at the nociceptor level [9,10]. A probable assumption for local anesthetic failure during inflammation is an increase in the anesthetic-resistant subpopulation of sodium channels [1].

In this study, patients diagnosed as symptomatic irreversible pulpitis with symptomatic apical periodontitis were included because inflamed pulp causes pain, but once the inflamed pulp is treated, the pain progressively subsides. Whereas, in case of symptomatic apical periodontitis, the inflammatory mediators that are present increase the neuropeptides such as prostaglandins E<sub>2</sub> and bradykinin and can cause exaggerated central sensitization even in the presence of a small stimulus. This results in more post-operative pain [1].

For IANB, 1.5 ml of 2% lignocaine without methylparaben and adrenaline was used in this study. This is to standardize the anesthetic solution, rule out hypersensitivity reaction in patients, avoid any interaction between methylparaben and MgSO<sub>4</sub>, and avoid the influence of adrenaline on the heart rate and blood pressure, respectively [11,12]. Literature states that even 1.0 ml of 2% lignocaine is an effective volume for obtaining clinical success in IANB [13]. Usual regimens

of MgSO<sub>4</sub> administered as intravenous injection were a dose of 30–50 mg/kg followed by a continuous dose of 6–20 mg/kg/h till the end of surgery. According to the literature, 150 mg is the lowest concentration used in regional anesthesia for plexus block [14]. Since the inferior alveolar nerve is a peripheral nerve without a multiple plexus of nerves, a smaller dose of 75 mg was also chosen along with 150 mg of MgSO<sub>4</sub> in this randomized controlled clinical trial. The experimental anesthetic solution was freshly mixed to retain the chemical properties of the drug. However, Houlihan S et al. earlier observed that freshly mixed anesthetic solution showed no precipitation for up to 168 days when stored at 25°C and 40°C [15].

Though there are various forms of IANB techniques, the conventional form of injecting the solution is still considered to be effective and a gold standard. Since IANB has a failure rate of approximately 0–48.6%, a well experienced single operator administered the block for maximum effectiveness and standardization [16].

There was no significant difference in the demographic data and pre-operative vitals, indicating a random and an even distribution of subjects between the three groups (Table 1). This is in accordance to the statement of Wolff (1940) and Mumford (1965) who stated that the perception of pain is independent of age and sex [17,18].

The results of this study show that 150 mg of MgSO<sub>4</sub> when added to lignocaine provided faster and longer duration of anesthesia, maximum anesthetic efficacy, and better post-operative analgesia as compared to 2% LA. Hence, the null hypothesis was rejected. In addition, 75 mg of MgSO<sub>4</sub> also showed better results comparable to those of 150 mg MgSO<sub>4</sub>, though there was a significant difference between the 2 experimental groups in terms of the anesthetic efficacy.

In a study by Koinig et al. (1998), peri-operative administration of 50 mg/kg MgSO<sub>4</sub> reduced the analgesic requirements both intra- and post-operatively [19]. In addition, it was proved that adding 50 mg/100 mg of intrathecal MgSO<sub>4</sub> had a significant increase in the duration of anesthesia and analgesia that had a dose

related linear relationship [20].

Magnesium is a natural physiological calcium antagonist at different voltage gated channels, which has an important role to play in anti-nociception. The addition of  $Mg^{2+}$  blunts NMDA receptor activation, which obstructs the excitatory postsynaptic currents and diminishes the stimulation of C-fibers.  $MgSO_4$  abolishes hypersensitization by obstructing the activation of NMDA receptor in the dorsal horn of the brain via the amino acid transmitters, notably glutamate and aspartate, thus reducing central sensitization [21]. Magnesium has analgesic effects by itself and it also enhances the actions of established analgesics when used as an adjuvant [22].

This study also proves that the addition of  $MgSO_4$  to 2% LA has a dose dependent increase in the onset, duration, anesthetic efficacy, and post-operative analgesia. From the results of the study, we can extrapolate that 75 mg  $MgSO_4$  is sufficient in endodontics, since the duration of anesthesia with this group was found to be 190 +/- 37.250, which is more than adequate for the endodontic procedure to be completed.

It was further observed that the patients of the control group had lesser pain relief at 2 and 6 h compared to groups 2 and 3, though not statistically significant. Siqueira JF and Barnett F stated that the highest peak of post-operative pain was present at the 6<sup>th</sup> hour due to the action of the inflammatory mediators as a result of the local immune response [23]. It can be inferred that action of  $MgSO_4$  on the NMDA receptor and calcium channel blockers progressively reduced the post-operative pain and also proved to be effective at the 6<sup>th</sup> hour time point in Table 3.  $MgSO_4$  in both concentrations proved to be effective in post-operative analgesia at 12, 24, and 48 h with significant reduction in pain compared to group 1.

However, contradictory results were reported in the literature by few authors who showed that  $MgSO_4$  has limited or no effect on post-operative pain in patients undergoing abdominal hysterectomy and caesarean delivery [24,25]. Tramer MR and Glynn CJ also observed that the pre-treatment of  $MgSO_4$  for ambulatory

ilioinguinal hernia repair or operation of varicose vein had no effect on postoperative analgesia because of the heterogeneous populations and dose variation [26]. In our study, the pre-serum values of  $Mg^{2+}$  was not taken into consideration, although they may have an influence on the results.

To conclude, this clinical trial shows that both 75 mg and 150 mg of  $MgSO_4$  in combination with LA are more effective than 2% LA alone. The anesthetic duration achieved with 75 mg of  $MgSO_4$  is more than adequate for most of the dental procedures. Pertaining to the post-operative analgesia, both 75 mg and 150 mg did not have significant difference from 24 h onwards. Hence, considering the dental procedure that requires only half the duration compared to general surgery, a lower concentration or dose should be more than adequate for most dental procedures.

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**Mahalaxmi Sekar:** Conceptualization, Formal analysis, Supervision, Validation, Writing - review & editing

**Mary Nancy S:** Investigation, Supervision, Validation

**DECLARATION OF INTERESTS:** The authors declare that they have no conflict of interest

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