Original Article

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Addition of 2 mg dexamethasone to improve the anesthetic efficacy of 2% lidocaine with 1:80,000 epinephrine administered for inferior alveolar nerve block to patients with symptomatic irreversible pulpitis in the mandibular molars: a randomized double-blind clinical trial

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Introduction: This clinical trial aimed to evaluate the anesthetic effect of the addition of 2 mg (4 mg/ml) of dexamethasone to 2% lidocaine (plain or with 1:80,000 epinephrine). The solutions were injected for a primary inferior alveolar nerve block (IANB) to provide mandibular anesthesia for the endodontic treatment of mandibular molars with symptomatic irreversible pulpitis.

Methods: In a double-blinded setup, 124 patients randomly received either of the following injections: 2% lidocaine with 1:80,000 epinephrine, 2% lidocaine with 1:80,000 epinephrine mixed with 2 mg dexamethasone, or plain 2% lidocaine mixed with 2 mg dexamethasone, which were injected as a primary IANB. Ten minutes after injection, patients with profound lip numbness underwent electric and thermal pulp sensibility tests. Patients who responded positively to the tests were categorized as "failed" anesthesia and received supplemental anesthesia. The remaining patients underwent endodontic treatment using a rubber dam. Anesthetic success was defined as "no pain or faint/weak/mild pain" during endodontic access preparation and instrumentation (HP visual analog scale score < 55 mm). The effect of the anesthetic solutions on the maximum change in heart rate was also evaluated. The Pearson chi-square test at 5% and 1% significance was used to analyze anesthetic success rates.

Results: The 2% lidocaine with 1:80,000 epinephrine, 2% lidocaine with 1:80,000 epinephrine mixed with 2 mg dexamethasone, and plain 2% lidocaine mixed with 2 mg dexamethasone groups had anesthetic success rates of 34%, 59%, and 29%, respectively. The addition of dexamethasone resulted in significantly better results ($P < 0.001$, $\chi^2 = 9.07$, $df = 2$).

Conclusions: The addition of dexamethasone to 2% lidocaine with epinephrine, administered as an IANB, can improve the anesthetic success rates during the endodontic management of symptomatic mandibular molars with irreversible pulpitis.

Keywords: Anesthesia; Dexamethasone; Irreversible Pulpitis; Lidocaine; Mandible.

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INTRODUCTION

Mandibular molars with symptomatic irreversible pulpitis are often difficult to anesthetize [1]. A common anesthetic technique for providing anesthesia to the mandibular molars is the use of an inferior alveolar nerve block (IANB). However, the IANB has a relatively lower success rate than that of maxillary anesthesia [2–4]. The presence of any preoperative pain further reduces the success rate to 23% [2,5]. Various theories have been proposed to explain this high failure rate. The most widely accepted phenomenon is the activation/modulation of nociceptors due to localized inflammation [1,6–8]. Inflammation can be caused by bacterial invasion of the pulp, leading to the formation of prostaglandins and related compounds via the cyclooxygenase (COX) pathway [9,10]. The COX enzyme occurs as different isoforms in the body [9]: COX-1 regulates the cytoprotective effects of prostanoids and maintains normal cell functions under basal conditions [10–14] and COX-2 is inducible by tissue injury and mediates inflammatory reactions [14].

A plausible method to enhance the anesthetic efficacy of IANB is to reduce inflammation and its effect on pain conduction. A variety of pharmaceutical agents, including non-steroidal anti-inflammatory drugs (NSAIDs) and synthetic corticosteroids, have been evaluated as adjuncts or primary local anesthetic agents. Aksoy et al. [15] reported that submucosal administration of dexamethasone increased the duration of the anesthetic effect compared with that of tramadol or articaine [15]. Another study evaluated the use of dexamethasone as a preoperative periodontal injection and reported that dexamethasone significantly increased the success rate of IANB administered with 2% lidocaine [16]. Other studies have shown that administration of preoperative dexamethasone, either via the oral route or via buccal infiltration, can increase the anesthetic efficacy of IANB [17,18]. Regarding the use of NSAIDs, various systematic reviews and meta-analyses have shown that preoperative administration of NSAIDs can improve the success of mandibular anesthesia [19–21]. However, some randomized clinical trials have reported conflicting results [22].

The inflammation caused by pulpitis can lead to peripheral, as well as, central sensitization. Preoperative use of anti-inflammatory agents can be a viable option to increase the efficacy of IANB. A major limitation of their use is the mandibular buccal infiltration in the presence of a thick cortical plate. Another option is to mix dexamethasone solution with lidocaine solution and inject it for a primary nerve block. Few studies have evaluated the effectiveness of dexamethasone mixed with 2% lidocaine in symptomatic mandibular molars. Another possible use of this mixture is exclusion of epinephrine from the anesthetic solution. The addition of dexamethasone with plain 2% lidocaine in IANB increases the duration of anesthesia [23]. However, dexamethasone mixed with plain 2% lidocaine has not been evaluated for the management of symptomatic mandibular molars.

This prospective, randomized, double-blinded clinical trial aimed to comparatively evaluate the anesthetic success rates of IANB with either 2% lidocaine with 1:80,000 epinephrine, 2% lidocaine with 1:80,000 epinephrine mixed with 2 mg dexamethasone, or plain 2% lidocaine mixed with 2 mg dexamethasone. The effects of these injections on heart rate were also evaluated. The null hypothesis was stated as "no difference in the anesthetic success rates of these three anesthetic agents."

METHODS

The clinical trial was planned and completed as a randomized, double-blinded, controlled trial with an active control group (Fig. 1). This study was approved by the Institutional Research Review Committee (FOD/XXX/05/2019/F2). Patients reporting a painful mandibular molar and signs or symptoms of symptomatic

irreversible pulpitis were included in the trial. The pulpal diagnosis was made by an endodontist who was not involved in other clinical steps of the trial. Written informed consent was obtained after explaining the procedures to all prospective participants. Patients were enrolled between February 2020 and August 2021. The sample size was calculated priori and based on the primary and secondary outcomes. The primary outcome was the anesthetic success rate, and the secondary outcome was the change in heart rate after the administration of IANB. The anesthetic procedure was categorized as successful if the clinician was able to instrument the root canals with no or mild pain (pain score < 55 on the Heft Parker visual analog scale [VAS]) [2,24]. It was estimated that 36 patients per group would provide 80% power to detect a 30% difference in anesthetic success rates. Type I α and type II β errors were maintained at 5% and 1−0.8 respectively. The assumed proportions of patients in the control and experimental groups were based on data from a previous study [2]. The sample size for heart rate was 32, considering a resting heart rate of 77 ± 14 BPM and an estimated increase of 10 beats per minute [25].

Based on the sample size calculation, 124 patients were included in the trial. The inclusion criteria were as follows: the presence of a symptomatic mandibular first or second molar with irreversible pulpitis (diagnosed with prolonged response to thermal and electric tests), ASA class I or II medical histories, and ability to use pain scales. The exclusion criteria were as follows: absence of a vital coronal pulp during access opening, known allergy or contraindication to the use of dexamethasone (conditions of diabetes mellitus, occlusal herpes simplex, renal impairment, uncontrolled hypertension, myasthenia gravis, osteoporosis, psychotic tendencies, active tuberculosis, and acute or long-standing infections) or any content of local anesthetic solution, pregnant / breastfeeding women, pain in more than one tooth, and teeth with fused roots.

Before starting treatment, the pain scales were explained to the patients. The pain scale used was the Heft-Parker-combined VAS. The patient was instructed to mark the pain on a 170 mm-long line, and the mm markings were hidden. To assist the patient in marking, the pain scale had six categories: faint, weak, mild, moderate, severe, and intense. Anesthesia was considered successful if the patient had pain less than 55 mm, which corresponded to no pain and faint, weak, or mild pain.

All patients underwent intracutaneous tests before the administration of anesthetic injections to rule out sensitivity to the injection solutions (2% lidocaine and dexamethasone). Briefly diluted solutions were injected on the extensor surface of the arms using an insulin syringe, and the area was marked and evaluated for signs of allergic reaction. Patients were randomly allocated to three treatment groups with the help of an online random generator using a permuted block randomization protocol (randomization.com). The strata used for randomization included sex and type of anesthetic injection. An alphanumeric list of 240 possible participants was prepared to cover all the possibilities. Anesthetic injections were prepared by a dental intern; three solutions were used. The control group received 2% lidocaine with 1:80,000 epinephrine along with 0.5 ml normal saline (to blind the operator). To add dexamethasone to 2% lidocaine with and without epinephrine, 0.5 ml of dexamethasone (4 mg/ml) was administered (Dexona injection 4 mg, Zydus Fortiza, Mumbai, India) using an insulin syringe. The solution was added to a 5-ml disposable syringe and 2 ml of 2% lidocaine (plain or with 1:80,000 epinephrine, Lignox 2 %, Indoco Remedies, Gujarat, India) was added to this solution. All syringes contained 2.5 ml solutions. The syringes were prepared immediately before injection and given an alphanumeric code. The operator and the patient were blinded to the syringe content. The standard IANB was administered to all patients using intraoral and extraoral landmarks via a direct Halsted approach. After the target area was reached, the solution was deposited over 100 s after confirming the negative aspiration. Heart rate measurements were taken before and after the injections at 15-s intervals for 5 min using a finger-tip

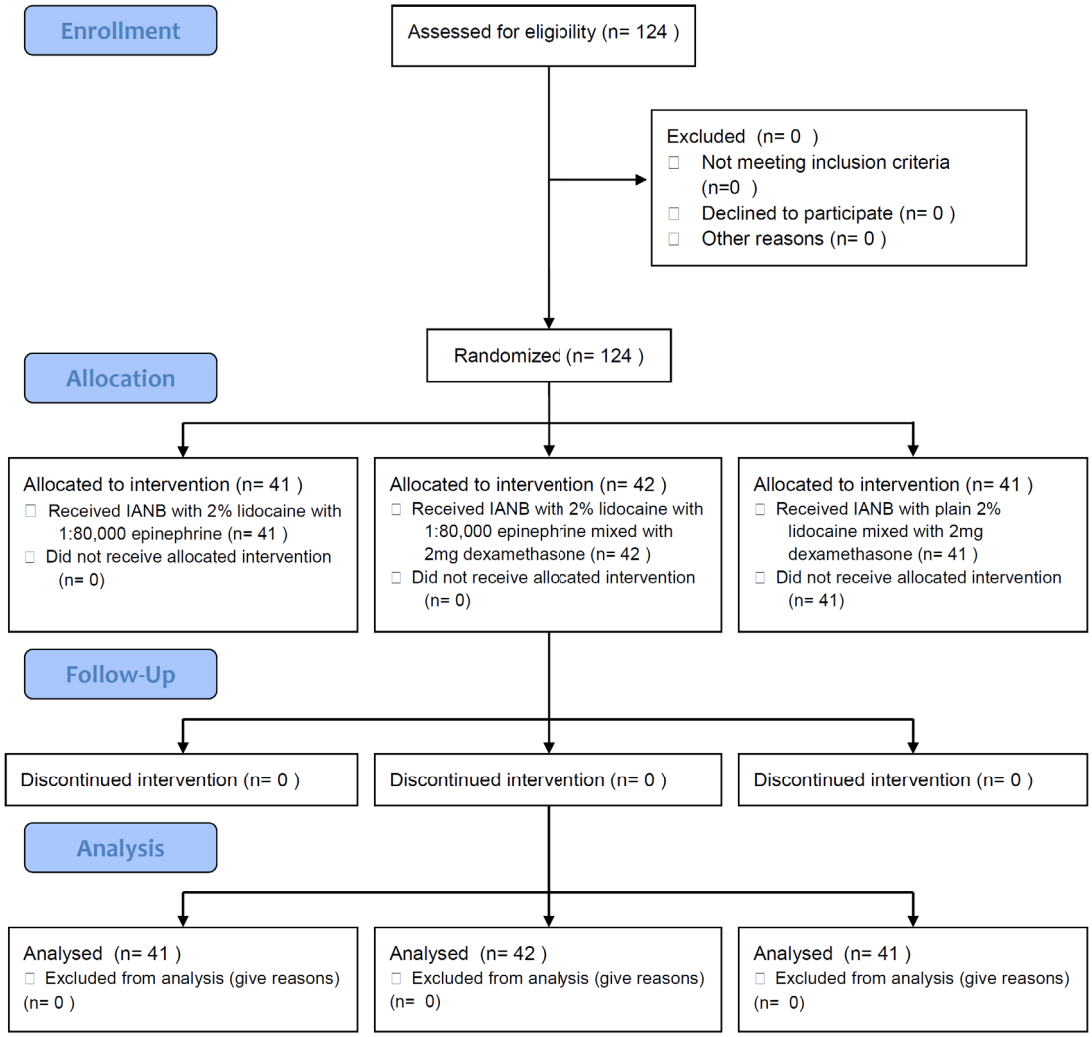

Fig. 1. CONSORT (Consolidated Standards Of Reporting Trials) Flow Diagram.

pulse oximeter. After 10 min of IANB, lip numbness was confirmed. In the absence of lip numbness, patients were excluded from the trial and were administered supplementary injections. Patients with profound lip numbness were subjected to thermal and electric pulp sensibility tests. If the patients responded positively to any test, the anesthesia was categorized as having "failed" and the data were included in the final analysis. In the case of a negative response, endodontic treatment was initiated after the placement of a rubber dam. In case of any pain, patients marked the pain on the HP VAS. In cases of failed anesthesia (pain score > 54), supplementary periodontal injections were administered. Data were recorded for the treatment stage at which "failure" was noted (electric pulp-testing stage, dentin penetration, and root canal instrumentation).

Age and changes in heart rate were analyzed using a one-way ANOVA. Differences in sex were analyzed using the chi-square test. Anesthetic success was statistically analyzed using the Pearson chi-square test at 5% and 1% significance levels.

RESULTS

A total of 124 patients were included, with a distribution of 41 patients in the 2% lidocaine with 1:80,000 epinephrine and plain 2% lidocaine mixed with

Table 1. Comparison of age, gender, type of tooth and success rates

	2% lidocaine with 1:80,000 epinephrine	Plain 2% lidocaine mixed with 2 mg dexamethasone	2% lidocaine with 1:80,000 epinephrine mixed with 2 mg dexamethasone	P value
Age	28 years ± 12 years, range- 18-51 years	30 years ± 11 years, range- 19-57 years	37 years ± 8 years, range- 18-59 years	0.43
Gender	23 males 18 females	21 males 20 females	21 males 21 females	0.8, χ^2 = 0.345, df = 2
Type of tooth	First molar = 32 Second molar = 9	First molar = 33 Second molar = 8	First molar = 30 Second molar = 12	0.6, χ^2 = 1.02, df = 2
Successful anesthesia	14 out of 41 patients (34%)	12 out of 41 patients (29%)	25 out of 42 patients (59%)	P = 0.009, χ^2 = 9.07, df = 2

There were no significant differences between the age, sex, and type of teeth. There were significant differences between the anesthetic success rates.

Table 2. Group-wise comparison of the anesthetic success rates

	vs.	Difference in success rates	P value	95% confidence intervals of difference in success rates	Chi square, degree of freedom (X^2, df)
2% lidocaine with 1:80,000 epinephrine	Plain 2% lidocaine mixed with 2 mg dexamethasone	5.0%	P = 0.63	-15% to 24%	0.235, 1
	2% lidocaine with 1:80,000 epinephrine mixed with 2 mg dexamethasone	25%	P = 0.02	3.5% to 43%	5.1, 1
Plain 2% lidocaine mixed with 2 mg dexamethasone	2% lidocaine with 1:80,000 epinephrine mixed with 2 mg dexamethasone	30%	P = 0.006	8.6% to 48%	7.48, 1

Table 3. Comparison of unsuccessful anesthesia based on the stage of treatment

		Number of cases with failed anesthesia
During post injection electric pulp testing/ dentin penetration	2% lidocaine with 1:80,000 epinephrine	12 out of 27
	Plain 2% lidocaine mixed with 2 mg dexamethasone	14 out of 29
	2% lidocaine with 1:80,000 epinephrine mixed with 2 mg dexamethasone	8 out of 17
During canal instrumentation	2% lidocaine with 1:80,000 epinephrine	15 out of 27
	Plain 2% lidocaine mixed with 2 mg dexamethasone	15 out of 29
	2% lidocaine with 1:80,000 epinephrine mixed with 2 mg dexamethasone	9 out of 17

2 mg dexamethasone groups and 42 in the 2% lidocaine with 1:80,000 epinephrine mixed with 2 mg dexamethasone group. All patients with profound lip numbness were included in the study. The values of age/sex and type of teeth were not significantly different (Table 1). The anesthetic success rates among the different groups were significantly different ($P < 0.001$, $\chi^2 = 9.07$, df = 2); thus, the null hypothesis was rejected. The group receiving 2% lidocaine with 1:80,000 epinephrine mixed with 2 mg dexamethasone presented with a 59% success rate, which was significantly higher than the rest of the groups ($P < 0.001$). The groups of 2% lidocaine with 1:80,000 epinephrine and plain 2% lidocaine mixed with 2 mg dexamethasone resulted in success rates of 34% and 29%, respectively, with no significant differences between them (Table 2). Table 3 presents the distribution of teeth with failed anesthesia according to the stages of treatment. Table 4 represents the preoperative and maximum postoperative heart rates (within 5 min of injections). All injections led to an increase in the heart rate. However, the increase was non-significant at a 1% significance level in the plain 2%

Table 4. Pair-wise comparison of the change in heart rates before and after injections

	Mean of heart rates at baseline	Mean of maximum heart rate after injections	Difference post-injection vs. Pre-injection	95% confidence intervals		T score, P value
				Lower bound	Upper bound	
2% lidocaine with 1:80,000 epinephrine	74.1	81.3	7.2	4.8	9.6	T = 5.9 P = 0.001 Significant at 5% and 1% df = 40
Plain 2% lidocaine mixed with 2 mg dexamethasone	75.4	78	2.7	0.5	2.4	T = 2.5 P = 0.03 Significant at 5% and Non-significant at 1% df = 40
2% lidocaine with 1:80,000 epinephrine mixed with 2 mg dexamethasone	75.2	80.8	5.59	3.6	7.9	T = 4.6 P < 0.001 Significant at 5% and 1% df = 41

lidocaine mixed with 2 mg dexamethasone group.

DISCUSSION

The non-significant difference in the 2% lidocaine with 1:80,000 epinephrine and plain 2% lidocaine mixed with 2 mg dexamethasone groups is an important finding. In simple words, plain lidocaine mixed with dexamethasone presents similar success rates to that of solutions containing epinephrine. Epinephrine is an alpha and beta receptor stimulant [26] and acts as a chemical tourniquet by causing local peripheral vasoconstriction via alpha-adrenergic receptors [27]. It is added to dental anesthetic solutions to decrease the absorption and increase the duration of anesthetic agents. Although it is a useful additive in dental anesthetic solutions, some questions have been raised regarding the safety of epinephrine-containing solutions, especially in patients with cardiac disorders [28]. It should be noted that a single injection of a dental anesthetic solution with epinephrine poses minimal risk [29]; however, this risk increases during the administration of multiple injections and may affect the treatment of patients with cardiac disorders or those taking medications that interact with epinephrine. Plain lidocaine solutions have a very short duration of anesthesia [30]. As stated before, epinephrine increases the duration of anesthesia but also induces significant cardiac stimulation. A study evaluated the cardiovascular effect of injecting three cartridges of 2% lidocaine with 1:100,000 epinephrine. The authors reported an increase in circulating epinephrine levels and cardiac output [31]. Similarly, another study reported an increase in systolic blood pressure, heart rate, and cardiac index after injection of 2% lidocaine with 1:80,000 epinephrine [32]. Literature suggests the use of low-dose (1:200,000) epinephrine with 2% lidocaine [30]. Studies have also reported that increasing epinephrine content beyond 1:200,000 does not increase the anesthetic success of nerve blocks. One study evaluated the anesthetic success of three different concentrations of epinephrine (1:50,000, 1:80,000, and 1:200,000) in 2% lidocaine in uninflamed pulps [33]. The authors reported no significant differences in the success rates. Another study evaluated two concentrations of epinephrine (1:80,000 vs. 1:200,000) with 2% lidocaine on IANB success rates and reported no significant difference between them [34]. Similar data have been reported for epinephrine-containing solutions in maxillary infiltrations [35]. However, increasing the concentration of epinephrine improved the success rates of supplementary intraligamentary injections after a failed primary IANB block [36]. A recent study reported that plain lidocaine solutions had very low anesthetic success rates compared to those of lidocaine solutions with epinephrine [35]. Considering the (slight) cardiac stimulating effect of

epinephrine, it would be beneficial to find a way to increase the anesthetic success of plain lidocaine solutions. In the present study, adding dexamethasone to the plain lidocaine solution resulted in success rates similar to those of lidocaine solutions with epinephrine. The data are similar to those of a study evaluating the anesthetic efficacy of 2% lidocaine combined with either dexamethasone or adrenaline during an oral surgical procedure [23]. The authors concluded that the presence of dexamethasone increases the action duration of 2% lidocaine and can be used in patients with contra-indications to adrenaline. An animal study comparing the use of lidocaine, dexamethasone, lidocaine-dexamethasone, and lidocaine epinephrine administered as epidural injections reported that lidocaine with dexamethasone resulted in a longer duration of anesthesia than that of other groups [37]. However, it should be noted that dexamethasone alone has no local anesthetic effect [37].

The anesthetic success rate of 2% lidocaine with 1:80,000 epinephrine was 34%. This low success rate is similar to that reported in studies evaluating 2% lidocaine for the management of symptomatic mandibular molars with irreversible pulpitis [2,5]. Various adjuncts have been evaluated to improve the success rates of 2% lidocaine solutions. The most commonly studied adjuvant drugs are dexamethasone, ketamine, tramadol, mida-zolam, hyaluronidase, dexmedetomidine, clonidine, and opioids [38]. A meta-analysis evaluated the effect of perineural dexamethasone as an adjunct to a local anesthetic solution for brachial plexus nerve block. The authors reported that the addition of dexamethasone prolonged the analgesic effect of the local anesthetic solutions [39]. Dexamethasone also increased the duration of motor blocks. A Cochrane systematic review evaluated the efficacy and safety of perineural dexamethasone in peripheral nerve block [40]. The data suggest that the addition of dexamethasone may increase the duration of sensory block and is effective in reducing postoperative pain. An animal study evaluated the use of liposomal dexamethasone along with liposomal bupivacaine in sciatic nerve blocks [41], which suggested that the co-delivery of liposomal dexamethasone increased the efficacy of liposomal bupivacaine.

In the present study, the addition of dexamethasone to 2% lidocaine with epinephrine significantly increased the anesthetic success rate compared with that of 2% lidocaine with epinephrine. Dexamethasone has been shown to increase the duration of nerve block [40,42]. The mechanism of action of dexamethasone in anesthetic solutions remains unclear. One study suggested that the vasoconstrictor properties of corticosteroids may increase the duration of anesthetic agents [42]. The peripheral vasoconstrictive properties of topical corticosteroids have been well described in literature [43]. Corticosteroids exert their vasoconstrictive properties via glucocorticoid receptors [44]. Dexamethasone also induces postoperative anesthesia. However, this property may be due to systemic absorption rather than peripheral effects [45]. In endodontics, dexamethasone has been administered via buccal infiltration [18], the oral route [17], intraosseous injections [46], and intraligamentary injections [16]. A systematic review suggested that the adjunct use of oral dexamethasone can improve the anesthetic success rates of dental nerve blocks [21]. A possible limitation of the present study was the slight dilution of the 2% lidocaine solution owing to the addition of dexamethasone/saline.

In conclusion, the addition of dexamethasone to 2% lidocaine with epinephrine, administered for an IANB, can improve anesthetic success rates during the endodontic management of symptomatic mandibular molars with irreversible pulpitis.

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