Original Article - Comparative Study

Role of addition of dexamethasone to lignocaine 2% with adrenaline in dental nerve blocks for third molar surgery: A prospective randomized control trial

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ABSTRACT

Context: Dexamethasone has been frequently used in oral surgical procedure and accepted by oral and maxillofacial surgeon community worldwide. However, this is the first clinical trial that used dexamethasone as adjuvant with lignocaine in dental nerve block (DNB). **Aims:** The purpose of this double-blind, randomized control trial (RCT) was to compare the effect of dexamethasone with normal saline (NS) in a lignocaine DNB. **Settings and Design:** This prospective, double-blind, RCT was carried out after obtaining approval from the Institutional Ethical Committee. **Subjects and Methods:** In forty patients, the present placebo-controlled clinical trial was conducted; allocated randomly into two groups: study group (SG) or control group (CG). The single-dose submucosal dexamethasone or NS injection was administered immediately after 2% lignocaine with epinephrine 1:2,00,000 nerves block during mandibular third molar surgery (TMS). Visual analog scale score, number, and exact time nonsteroidal anti-inflammatory drugs were administered were used to measure postoperative analgesia in 2nd and 7th days. **Statistical Analysis Used:** All the data were entered into the Spreadsheet (Excel, Microsoft) and Chi-square test, Mann–Whitney U-test, Student's paired and unpaired *t*-test, and Fisher exact test were used. **Results:** This study found maximum duration of DNB in SG was 248.88 min and in CG was 175.44 min, whereas minimum duration in SG was 197 min and in CG was 140.78 min. **Conclusions:** Dexamethasone prolongs the action of lignocaine 2% in DNB for TMS.

Keywords: Anesthesia, controlled release, dexamethasone, postoperative pain control, quality-of-life, third molar surgery

INTRODUCTION

The management of pain in dentistry encompasses a number of procedural issues, including management of surgical pain as well as other operative pain. Medical Expenditure Panel Survey 2009, approximately 11 percent of US population had reported at least one oral surgical procedure.[1] However, in this part of world like Nepal, percentage of oral surgical procedure has been reported quite high, it would be 50-60% of patient visiting in dentistry department. The reasons of high percentage of surgery could be many including lack of awareness, improper oral hygiene, cost of conservative treatment and reported at end stage of disease. Among those patients, many live with various untreated systemic diseases such as hypertension and cardiac disease where local anaesthetic agent with vasoconstrictors ie adrenaline are contraindicated or used with caution. Hence, perioperative pain

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management is the most common challenge for the clinicians in outpatient (Ambulatory) setting.

Pain is common and a normal response to the unavoidable trauma after surgery due to release of inflammatory mediator which sensitizes peripheral nociceptors, resulting in hyperalgesia. Pain score zero (patients achieving complete relief) depend on initial pain intensity after surgery.[2] Recent data suggest 80% of patients experience pain postoperatively[3] with between 11% and 20% experiencing severe pain.[3,4] Despite the availability of analgesics–including opioids–and national guidelines to manage pain, the incidence of postoperative pain has remained stable over the past decade.[5] Thus, acute pain associated with surgical and operative procedures is a common occurrence in the dental outpatient department and remains inadequately managed for many patients.

Most commonly surgical pain has been managed by clinician by blocking afferent nerve with local anesthetics (LAs). Many agents have been used for nerve blocks. Unfortunately, most of commercially available clinically active LA agents are short to intermediate acting. These agents are unable to provide good perioperative analgesia in surgery patients; hence, separate ultra-long LA injection has been used to control postoperative pain.[6,7] However, using two different LA agents, one for block and other for postoperative analgesia are not safe and economical.[7]

Good quality analgesia is a major concern.[8] The effective perioperative pain management decreases morbidity and mortality overall. Compromise or short duration of analgesia not only causes patient suffering and delays sense of well-being but also diminishes the ability to ambulate early.[9] Current practice involves using individual drugs or multimodal analgesic combinations to control surgical pain but it is not satisfactory. Hence, in search of better quality of perioperative analgesics, many research has been done, and it was found that LA provides good quality perioperative analgesia using controlled-release formulations[10-12] or co-encapsulating a second drug with single injection.[13] Last two decades, different agents have been used along with LA agent to increase the duration of locoregional nerve block such as neostigmine + lignocaine,[9] fentanyl, or tramadol + bupivacaine.[14,15]

The previous studies used dexamethasone plus LA agents in axillary nerve, brachial plexus, and sciatic nerve block and found significant prolongation of duration of nerve block.[10,11,16-21] Although different forms, dosage, and route of dexamethasone have been frequently used to control surgical pain and accepted by oral and maxillofacial surgeon community worldwide; combination of these two agents is not used yet. Based on pathophysiologic rationale, administering corticosteroid may be considered risky. However, multiple studies have shown the therapeutic safety of short-term corticosteroid exposures, and the drawbacks have not been shown to be clinically significant.[22] In addition, the submucosal injection method of dexamethasone delivery has shown efficacious, and best patient's compliance as well as reduces local and systemic side effect by concentrating drugs at proximity to surgical site.[23]

Pain after third molar surgery (TMS) has become the most frequently used in clinical trials because it is ideal for acute pain study.[23-30] As TMS is a most common procedure with pain frequently moderate or severe in intensity and with sufficient numbers of patients to make studies relatively easy to perform,[23] this clinical trial was conducted. The purpose of this research was to compare the effect of dexamethasone or normal saline (NS) on duration of 2% lignocaine dental nerve block (DNB) during TMS. It was hypothesized that single injection of submucosal dexamethasone might effectively prolong duration of DNB and provide good perioperative analgesia.

SUBJECTS AND METHODS

This prospective, double-blind, randomized control trial was carried out after obtaining approval from the Institutional Ethical Committee. The inclusion criteria were subjects between 20 and 41 years of age who were in good general physical health with no clinically significant and relevant medical history (the American Society of Anesthesiologists I and II). Subjects having at least one partially or fully bony impacted mandibular third molar and who could understand and were willing to take part in the study and likely to comply with all study procedure were included in this study.

The exclusion criteria were subjects who were on antibiotics and/or anti-inflammatory drugs within 2 weeks of the study entry, pregnant or lactating females, and subjects with any active medical illness. Subjects excluded also involved those in whom re-injection of LA solution was required to achieve profound block and subjects who used nontrial drugs during the study period.

The possible risks and benefits of the procedure were described to all the patients. Informed consent was obtained from subjects willing for this study on detailed consent form.

The forty subjects were allocated randomly into two groups: study group (SG) or control group (CG) through a permuted block randomization technique. A random-number table was used to generate a block randomization schedule chart specifying the group to which each subject would be assigned on the first come first basis. The blinding concept in clinical trial was adopted from study by Deo and Shetty, 2011.[23] Preoperative drugs, 30 ml vial of lignocaine 2% with epinephrine 1:2,00,000 (Xylocaine 2%, AstraZeneca, India), 2 ml ampoules NS (Zuche, New Delhi, India), and 2 ml of dexamethasone (Inj Dexona, Zydus Aliadac, India) were given to the nurses who were supporting the trial. On the day of surgery, nurses prepared either the test drug (2 ml of 4 mg/ml dexamethasone) for SG or the placebo (2 ml NS) for CG in identical 2 ml syringes according to a random table and documented the same in a chart. Now, 2 ml syringe contains clear solution X, either it could be SG or CG which was not known to surgeon or subjects.

The subject was prepared for TMS and laid down on dental chair comfortably. 2 ml of 20 mg/ml lignocaine in 0.005 mg/ml epinephrine local anesthesia (Xylocaine 2%, AstraZeneca, India) was used for the classical inferior alveolar nerve block, lingual, and long buccal nerve. Anesthetic-related complications, i.e., intravascular injections were monitored with pulse

oximeter (SPO_2), noninvasive blood pressure, and respiratory rate. Immediately after the completion of block, the solution X was injected submucosally preoperatively in same site of block injection as per randomization schedules chart. All the nerve blocks and solution X were administered by the same operator and under similar conditions to minimize operator variability. The onset of sensory blocks was assessed subjective and objectively. The patient was questioned regarding numbness of lip and tongue. In addition, the onset of lip numbness was assessed by asking the subjects to palpate the lip and report when lip numbness occurred. Objectively, nerve blocks were assessed every 2 min with application of cold spirit swabs in the lower lip and by response to atraumatic prick with the blunt instrument in a buccal and lingual mucoperiosteum in relation to the first molar and canine teeth. The time of complete nerve block was noted before starting surgical procedure. The blocks success was standardized that all patients would have profound lip numbness. If profound lip numbness was not recorded; then, the block was judged to be a failure. Such patient was eliminated from the study.

Routine impacted third molar surgical procedure with bone removal was performed by the same surgeon when complete anesthesia was achieved. The duration of the operation was recorded as the period between the anesthetic onset and the last suture placed. Detail of each procedure was recorded. Postoperative instructions were given to subjects. All the subjects were prescribed Amoxicillin 500 mg (Cap Aristomox 500, Aristo, India) per oral 3 times a day for 5 days and Ibuprofen 400 mg (Fc-tab Brufen400, Abbott, India) per oral as required as "rescue" analgesia. They were asked to report to the outpatient setting on the 2nd and 7th postoperative day (POD).

As the patients were operated in ambulatory setting; hence, patients were instructed to record postoperative data's. All the subjects were given two sheet; one sheet to document and other 10 cm visual analog scale (VAS) (no pain 0–1, mild pain 2–3, moderate pain 4–5, severe pain 6–7, and very severe pain 8–9); instructed about the rating. Postoperative pain was rated on a 10 cm VAS anchored by the verbal description "no pain" (0) and "very severe pain (9)" on daily basis for a week. When the patients began to experience moderate pain (VAS 4–5); it was considered that the analgesic effect of the drugs (LA agent + dexamethasone or Ibuprofen 400 mg) was terminated. Then, patients were prescribed analgesic on demand. The subjects were instructed to not to take any other analgesic drugs. They were asked to document the time at which the first analgesic was taken after postoperative and also total number of analgesics consumed until 7th POD. Again, patients were instructed to palpate the lower lip and tongue every 20 min to determine numbness (no feeling) until it returned to normal sensation and asked to note time. However, in this study, the duration of DNB or analgesia was considered the time between the start of operation, i.e., incision to the first analgesic taken.

Data analysis

All the demographic details, baseline data, and postoperative data were recorded in the case report form over the course of the study. All the data were entered into the Spreadsheet (Excel, Microsoft) and Chi-square test, Mann–Whitney U-test, Student's paired and unpaired *t*-test, and Fisher's exact test were used for analysis of the data.

RESULTS

Forty subjects aged 20–41 (mean 24.93) years were selected on the basis of inclusion and exclusion criteria. Two subjects having bilateral impacted third molars were operated on after a time gap of 4 weeks and hence were regarded as four additional subjects. The flow chart in Figure 1 describes the final subjects enrolled in this study.

Data from the 30 (19 male - 60%, 11 female - 40%) subjects were included in the study and analyzed. An individual statistical analysis demonstrated no statistically significant differences between SGs with regard to the subject age, smoking, class of impaction, depth of impaction, spatial relation of teeth, and number of roots. Table 1 showing minimal analgesic was received by patients of both groups while comparing between the groups, the SG (9.21 ± 2.66) was consumed statistically similar number of analgesic that of CG (10.81 ± 2.75). However, SG (181.57 ± 25.93 min) and CG (118 ± 17.33 min) was the time the first analgesic was taken after TMS, which was statistically very highly significant difference between the two groups ($P < 0.001$) [Table 1].

In this study, the duration of analgesia, i.e., duration of DNB was calculated by the sum of operative time, and time of first analgesic taken after TMS. The maximum duration of DNB in SG was 248.88 min and in CG was 175.44 min, whereas minimum duration in SG was 197 min and in CG was 140.78 min [Figure 2].

The VAS score for pain assessment showed progressive reduction in pain intensity from 1st to 7th PODs in both groups [Table 2]. The rate of decrease in VAS score was somewhat similar in both the groups.

Our subjective assessment of tingling and numbness of lip or tongue showed in Figure 3. At the time of 1st analgesic taken, 73.7% of SG felt numbness and tingling, whereas CG felt 45.5% and 54.5% numbness and tingling of lip and tongue, respectively. Some of subjects, 26.3% SG and 54.5% and 45.5% CG reported the same "1–2 days" over postoperative week. None of the subjects from both groups reported more than 2 days numbness and tingling of lip and tongue [Figure 3].

DISCUSSION

The local anesthesia is mostly preferred in ambulatory setting practice. However, it bears 3 principal challenges: inadequate duration of action, systemic toxicity, and adverse local tissue reaction. Past few decades have seen increased research into alternative in LA drugs and nerve block techniques. To provide better intra- and post-operative pain relief, control-release formulation[10,12,13] or combinations of drugs[9,14,17,19,21] have been successfully tried to prolong effect of LA drugs. Similarly, in this study, researcher believed that single injection of submucosal dexamethasone might effectively prolong duration of DNB and provide good perioperative analgesia in TMS. Many previous

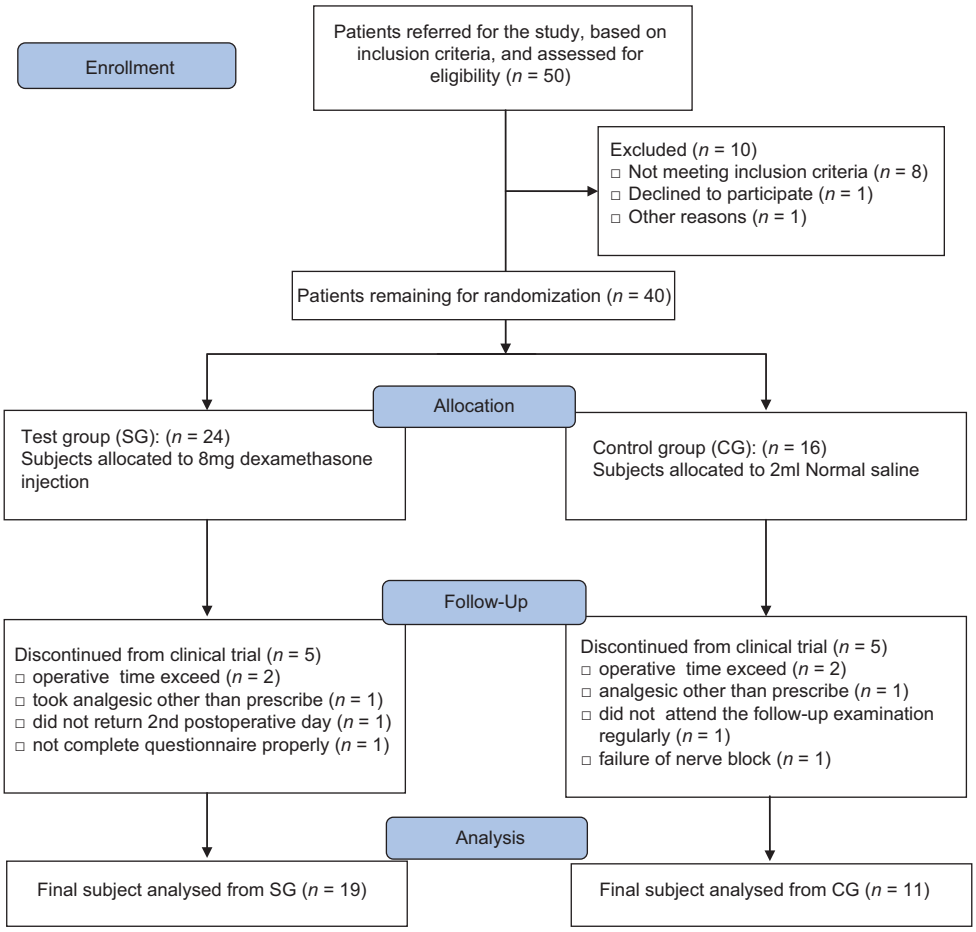

Figure 1: CONSORT diagram detailing patient recruitment and follow-up in this randomized control trial

studies used dexamethasone plus LA agents in axillary nerve, brachial plexus, and sciatic nerve block and found significant prolongation of duration of nerve block.[10,11,16-21] In intraoral nerve block or DNB, this combination has not been reported yet. Faithful comparisons with the previous studies are quite challenging but researcher tried to minimize all methodological flaws. Prolongation of nerve block was found in the past studies using dexamethasone adjuvant with LA agents, similarly in this study, dexamethasone was deposited submucosally as supplemental injection immediately after inferior alveolar, lingual, and long buccal nerve block (DNB). 2 ml of 20 mg/ml lignocaine in 0.005 mg/ml epinephrine local anesthesia (Xylocaine 2%, AstraZeneca, India) was used for DNB. An administration of submucosal dexamethasone in proximity to surgical site (retromolar area, etc.,) permits dexamethasone solution to diffuse around surrounding tissue spaces. At end of deposition, both solutions (dexamethasone and lignocaine) reach proximity to the nerve sheath of dental nerve.

The previous studies used long-acting LA which could mask the pharmacodynamic effect of dexamethasone or NS;[10,18,31] however, the methodological flaws were minimized by selecting short to intermediate acting LA, i.e., lignocaine. In addition, success rate of the primary DNB was assessed by 100% preoperative numbness and tingling sensation of lip and tongue; methods used in the present study were subjective and objective.

The study used valid and reliable tools to assess analgesia, i.e., VAS score and number of analgesic tablets, but response depended on patient's decision and a level of dissatisfaction with his/her pain at the moment. With some exception, past studies did not found statistically significant VAS while using dexamethasone during TMS.[27,28] Similar result was found in this study. Many authors have recorded a significant reduction in pain (VAS) 4–6 h postoperatively; however, not later,[29,30] this could be reason for insignificant VAS in this study and other studies.[24-30] In past studies which found significant VAS score; most of the studies have assessed VAS hourly at least first POD.[9,14,17,21] This study did not assess VAS score hourly because this measurement requires hospitalization for at least a day which was not done due to lack of resources and ambulatory setting of this study.

Many researches were carried out to study the effects of corticosteroid on perioperative analgesia.[22-30] Its safety and reliability to use in different form, dosages, and sites are well established.[22] but this study used dexamethasone proximity to nerve sheath which may raise some concerns.[32] In animal study, neurotoxicity was not found in repeated intrathecal injections of small dosage corticosteroids.[21,33,34] In addition, it has been used in the epidural space for epidural LAs.[35] Nerve injury has not reported complication of dexamethasone injection but rarely, it may occur in the context of needle trauma. In fact, the use of dexamethasone as an adjunct to local anesthesia for nerve blocks

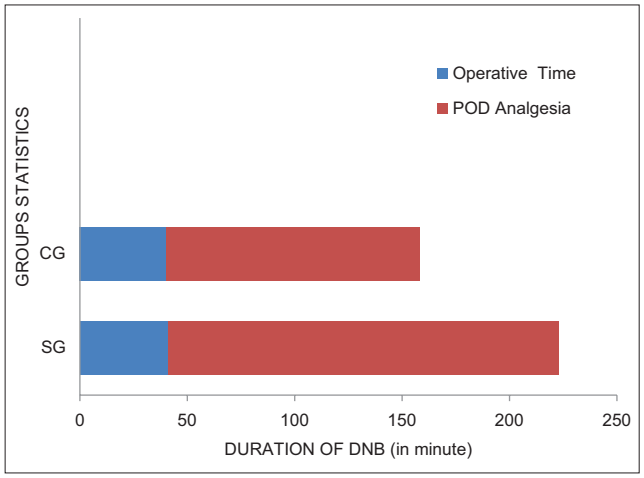

Figure 2: Comparison of duration of dental nerve block with 2% lignocaine between groups: Total duration of block was calculated by sum of operative time and average duration of analgesia after third molar surgery, here time at which 1st analgesia taken was considered as postoperative day analgesia

Table 1: Duration and number of analgesic consumption after TMS Data present mean with stander deviation between groups

	SG	CG	*P*
1st analgesic taken TMS in min	181.57±25.93	118±17.33	<0.001
Number of analgesic taken	9.21±2.66	10.81±2.75	0.124

Table2: Comparison postoperative of VAS Score between groups Data present mean and stander deviation between groups in 10 cm VAS scale

VAS Scores	SG	CG	*p*
1 POD	6.16± 1.01	6.45±1.50	0.52
2 POD	6.15±1.17	6.00±1.73	0.76
3 POD	4.84±1.64	3.90±1.04	0.10
4 POD	2.84±1.50	3.73±1.79	0.16
5 POD	2.00±1.86	2.36±1.36	0.56
6 POD	1.21±2.07	1.45±0.69	0.71
7 POD	0.68±2.08	0.36±0.67	0.63

is discussed in prominent textbooks. It has long history of safe use in all routes and systemic toxicity from a single dose of 8 mg dexamethasone is unlikely and probably reliable and effective pharmacological dose.[36] More recently, submucosal injection of dexamethasone was found effective to control perioperative pain and analgesia.[20,26-30] Similarly, this study found statistically very highly significant postoperative analgesia, i.e., time at 1st analgesic taken [Table 1].

Although many studies have been conducted to see the effect of dexamethasone on intra- or post-operative analgesia in a different setting but the mechanism of prolonging analgesia was not clearly defined. The proposed mechanisms are many in the previous literature.[37-39] These are classified in to three main mechanisms: (1) Systemic, (2) local vasoconstriction, and (3) local C-fibers blockade. An analgesic property of corticosteroids was well mentioned in literature through systemic effect. It has been used an adjuvant to general anesthesia, demonstrated beneficial in reducing pain during ENT surgery,

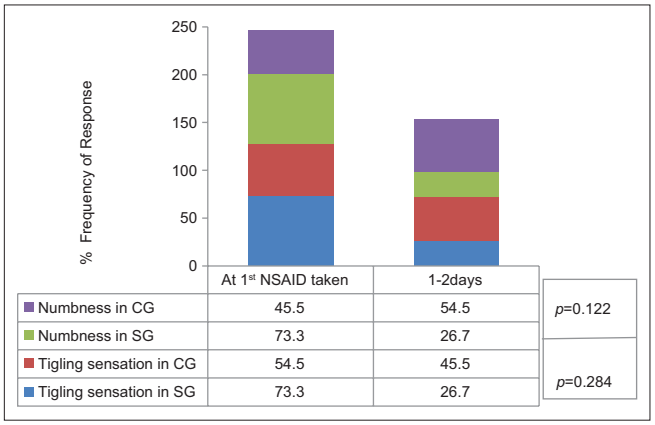

Figure 3: Percent of patients reporting tingling and numbness of lips or tongue after third molar surgery

general surgery, dental surgery, and orthopedic surgery.[40] In ambulatory TMS setting, corticosteroids have been used in oral surgical procedure for many decades; various route of administration of dexamethasone was found for postoperative analgesia.[29] While other studies have not corroborated same result. The effect was more effective when combined with a nonsteroidal anti-inflammatory.[41] Mechanism of analgesia in above studies was stated as anti-inflammatory effect or the action on corticosteroid receptor present in brain. However, this study canceled possibility of above mechanism because submucosal injection did not lead to systemic absorption.

Hence, preferred mechanism for this study would be 2nd and 3rd mechanisms. Dexamethasone causes vasoconstriction on topical application through nongenomic path of action. This pathway does not require *de novo* protein synthesis and acts by modulating the level of activation and responsiveness of target cells, such as monocytes, T cells, and platelets and also leads to peripheral vasoconstriction which further increases local drugs concentrations.[42] Other mechanism postulated in literature are blockade of transmission transmission in nociceptive C-fibers but not in A and B fibers or altering potassium channel of peripheral nerve.[17] More interestingly, when dexamethasone was used alone in regional blocks, the blockade was not produced. Hence, it is obvious that dexamethasone might bring this effect by altering the function of potassium channels in the excitable cell membrane and the effect was reversible.[43] Thereby, synergistic action with LAs block occurred in other studies as well as this study. In brief, the prolongation of DNB after submucosal administration of dexamethasone may be secondary to a local action on nociceptive C-fibers mediated through glucocorticoid receptors and the upregulation of the function of potassium channels in excitable cells.

Extraoral in peripheral nerve block with LA, 8 mg dexamethasone was found to significantly prolong the duration of sensory and motor blockade and improved the quality of analgesia.[9,44,45] However, most of these studies showed varying degree of success. Similarly, this study used submucosal dexamethasone in intraoral DNB and duration of block was found to be SG (181.57 ± 25.93 + 41.38 min) while comparing with CG (118 ± 17.33 + 40.11 min) was statistically significant. It was moderately shorter than other works [Figure 2].[9,21,22]

This finding could be a new development in local anesthesia in dentistry; however, further studies would be needed. Future clinical trials should be considered in the flowing areas-; sample size and immediate postoperative assessment data such asVAS score every hour till first 10 h, then 3 hourly till 24 h as well subjective and objective measurement of numbness of lip and tongue. It would be advisable to triple blind the clinical trial. Further studies are needed to determine the optimal dose, onset, and duration of LA prolongation in DNB. The development of better methodology to use dexamethasone and LA agents, as well as the mechanism of action, would be new advancement in field of local anesthesia in dental practices.

Limitation of this study is not to evaluate the postoperative anesthesia objectively as well as onset time DNB. However, the positive point of this study is analgesia assessment by patient perception which is more clinically relevant patient outcome measure, probably was not assessed in the previous studies. Further studies are needed with well-defined objective end-points and standardized care programs.

CONCLUSIONS

The submucosal injection of dexamethasone gives good perioperative analgesia by single injection due to prolongation duration of dental sensory nerve block during TMS. The advantages include patient comfort and satisfaction, earlier mobilization, faster recovery with less likelihood of the development of neuropathic pain, and reduced cost of care. This combination can be used in patients where adrenaline is contraindicated specially heart diseases. However, dexamethasone may not be indicated for some patients. In addition, requirement of postoperative nerve block or supplementary injection is diminished.

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Conflicts of interest

There are no conflicts of interest.

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