Does dexmedetomidine combined with levobupivacaine in inferior alveolar nerve blocks among patients undergoing impacted third molar surgery control postoperative morbidity?

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Background: Postoperative analgesia (POA) is an important determinant of successful treatment. Dexmedetomidine (DEX) has recently gained attention as a promising adjuvant to local anesthetics (LA). The present study aimed to evaluate the efficacy and safety of levobupivacaine (LB) as an adjuvant during inferior alveolar nerve block (IANB) in the extraction of lower impacted third molars (LITM).
Methods: A prospective, randomized, placebo-controlled, triple-blind, parallel-arm, and clinical study was performed on 50 systemically healthy participants who required removal of an asymptomatic LITM. Using a 1:1 distribution, the participants were randomized into two groups (n = 25). Group L (control group) received 1.8 mL of 0.5% LB and 0.2 mL normal saline (placebo) and Group D (study group) received a blend of 1.8 mL of 0.5% LB and 0.2 mL (20 μg) DEX. The primary outcome variable was the duration of POA and hemodynamic stability, and the secondary variable was the total number of analgesics required postoperatively for up to 72 h. The participants were requested to record the time of rescue analgesic use and the total number of rescue analgesics taken. The area under the curve was plotted for the total number of analgesics administered. The pain was evaluated using the visual analog scale. Data analysis was performed using paired students and unpaired t-test, Mann−Whitney U test, Chi-square test, and receiver operating characteristic analysis. Statistical significance was set at P < 0.05.
Results: The latency, profoundness of anesthesia, and duration of POA were statistically significant (P < 0.05). The differences between mean pain scores at 6, 12, 24, 48, and 72 h were found to be significant (each P = 0.0001). Fewer analgesics were required by participants in group D (2.12 ± 0.33) than in L (4.04 ± 0.67), with a significant difference (P = 0.0001).
Conclusion: Perineurally administered LA with DEX is a safe, effective, and therapeutic approach for improving latency, providing profound POA, and reducing the need for postoperative analgesia.

Keywords: Analgesia; Dexmedetomidine; Impacted Mandibular Third Molars; Inferior Alveolar Nerve Block; Levobupivacaine; Local Anesthesia.

INTRODUCTION

Excision of the third molar is a commonly performed procedure in the daily clinical practice of dentistry. It is always associated with variable tissue insult, resulting in moderate to severe pain and other inflammatory complications, such as edema and trismus [1]. The

importance of effective control of postoperative pain is paramount and results in positive emotional and physiological outcomes projecting greater satisfaction, faster recovery, and early return to daily activities; thus, enabling a good quality of life for the participant [2]. Local anesthetic (LA) is the critical tenet of pre-emptive analgesia in dental procedures; however, it has the disadvantage of a finite duration of action that falls short of the duration of postoperative pain [3]. Levobupivacaine (LB), an enantiomer of bupivacaine, demonstrates a dose-dependent prolonged duration of action with minimal cardiac toxicity and has emerged as the preferred long-acting LA.

Dexmedetomidine (DEX) is a selective $\alpha2$ agonist used to control anxiety and pain and to induce sedation. DEX was primarily intended to be used as a sedative for short procedures in intensive care settings. DEX demonstrates analgesic properties via selective $\alpha2$ adrenergic receptor agonist activity and anti-inflammatory and anti-oxidative pathways [4]. Its systemic analgesic effect has been validated by numerous studies as it has emerged as a preferred analgesic for pain control in acute postoperative settings [5, 6]. Recently, DEX as an adjunct to LA has evoked special interest in locoregional pain control [7, 8]. Perineurally administered DEX has a latency shorter than 5 min and reaches a peak effect within 15 min. Apart from longer duration of postoperative analgesia (POA), controlled hypotension (by its peripheral and central sympatholytic activity) minimal suppression of the respiratory drive, ease of administration, fewer side effects whilst preserving adequate perfusion of the vital organs has led to its utility in the maxillofacial procedures [9–16]. Blends of LB and DEX in peripheral nerve blocks have demonstrated encouraging results in transverse abdominis and brachial plexus blocks with consistently superior results; however, their efficacy in LITM surgery is a matter of investigation [17–21].

Hence, the present study was designed to analyze and compare the efficacy and safety of LB with or without DEX in LITM surgery with the hypothesis that the addition of DEX to LB may prove to be a beneficial

therapeutic strategy over LB alone for POA in an acute postoperative setting. The primary outcome variables were the duration of POA and hemodynamic stability, while the requirement of the number of analgesics and occurrence of adverse effects were the secondary outcome variables.

METHODS

To address the research intention, a prospective, randomized, triple-blind, parallel-arm study was conducted on patients who reported the removal of asymptomatic LITM to our Outpatient Department of Oral and Maxillofacial Surgery at Sharad Pawar Dental College and Hospital, Sawangi (M), Wardha between October 2019 and October 2021. The study protocol of the randomized controlled trial was approved by the Institutional Ethics Committee of the Datta Meghe Institute of Medical Sciences (Wardha). The study adhered to the recommendations of the Declaration of Helsinki and the Consolidated Standards of Reporting Trials statement [22] (Fig. 1) (Ref. No. DMIMS (DU)/IEC/Sept-2019/8508).

The sample size for the present study with 95% confidence interval and 80% power of the study was derived using the formula:

$$N = (Z_{\alpha/2} + Z\beta)\ 2\ x\ 2\ x\ \sigma^2\ /\ d^2$$

Where "$Z_{\alpha/2}$" is the critical value of the normal distribution at $\alpha/2$ (for a confidence level of 95%, α is 0.05 and the critical value is 1.96), "$Z\beta$" is the critical value of the normal distribution at β (power of 80%, β is 0.2 and the critical value is 0.84), "σ^2" is population variance, and "d" is the difference you would like to detect.

$$N = 25$$

Fifty systemically healthy participants (ASA class I status) aged between 18 and 40 years with the presence of at least one asymptomatic LITM devoid of any
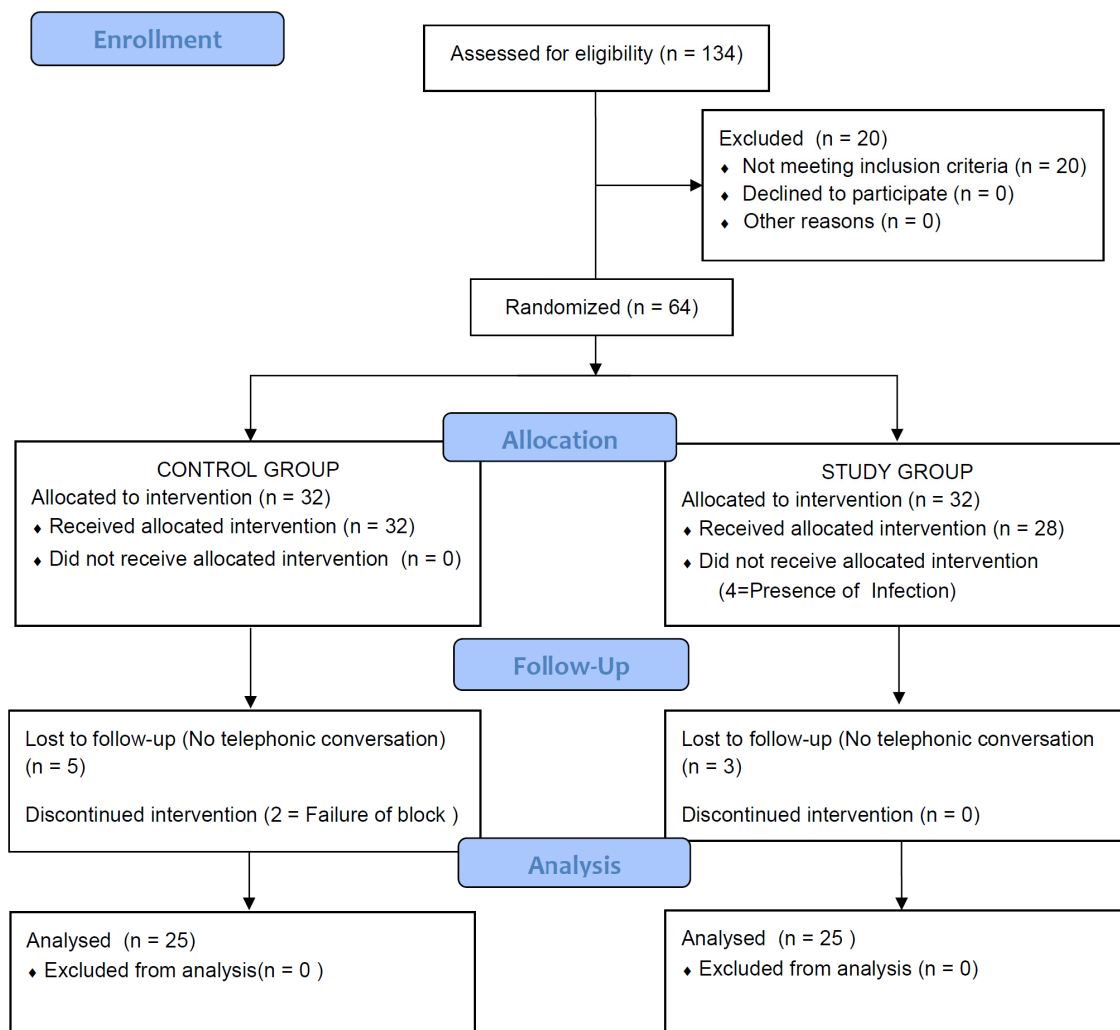
Fig. 1. CONSORT Consolidated Standards Of Reporting Trials) 2010 Flow Diagram

pathologies with similar angulations/orientations (Class II B Winter [23] and Pell and Gregory [24]) were included in the study. Participants with a history of drug abuse, immunocompromised status, comorbidities, presence of any local infection, women on oral contraceptives or pregnant and nursing mothers, allergy to the LA used in the study, and radiologic evidence of inferior alveolar canal approximation of the roots of the third molar were excluded from the study.

Participants were explained in detail about the study protocol and the visual analog scale (VAS) [25] and their right to withdraw from the study at any time without any prejudice. After obtaining written informed consent, thorough hematological, clinical, radiological, and intra-dermal sensitivity tests were performed. Randomization was performed using a table of random numbers, irrespective of age, sex, and site of impacted teeth. Randomization was ensured by an independent researcher who was not involved in data collection, analysis, and interpretation of statistical results. Sealed opaque envelopes containing the codes were opened and decoded to prepare a blend of anesthetic solutions. The control group (Group L) was administered a blend of 1.8 mL LB and 0.2 mL normal saline (Levo-Anawin®, Neon pharmaceuticals, India) whereas the study group (Group D) was injected with a blend of 1.8 mL LB and 0.2 mL (20 μg) DEX (Dextomid®, Neon pharmaceuticals, India).

The study was triple-blind in nature, wherein the

Table 1. Patient characteristics based on age, gender, physical class

Variables	Group L (N = 25)	Group D (N = 25)	P value
Age	30.24 ± 4.12	32.50 ± 8.04	NS
Gender	M : 16, F : 9	M : 14, F : 11	NS
Weight	52 ± 2.5	48 ± 3.6	NS
Height	148.0 ± 4.2	162.0 ± 2.5	NS
BMI	20.2 ± 2.4	21.5 ± 3.5	NS
ASA PS class	class I : 25	class I : 25	NS

ASA, American Society of Anesthesiologists; BMI, body mass index; F, female; M, male; SD, standard deviation.

Table 2. Latency (seconds) between the two groups

Variable	N	Group L Mean ± SD	Group D Mean ± SD	P - value
Latency period	50	203.6 ± 17.7	119.92 ± 8.44	0.0001

SD, standard deviation.

Table 3. Profoundness of anesthesia between the two groups

Variables	N	Group L Mean ± SD	Group D Mean ± SD	P - value
Incision	50	0 ± 0	0 ± 0	
FLAP Reflection	50	0 ± 0	0 ± 0	
Bone Guttering	50	0.12 ± 0.33	0.04 ± 0.2	0.3
Tooth / Root Sectioning	50	0 ± 0	0.08 ± 0.27	0.15

SD, standard deviation.

participant, operator, and evaluator were masked to the blend of the anesthetic solution. Post-inclusion omission criteria included participants experiencing a VAS pain score ≥ 4 at any point in the procedure, duration of surgery exceeding ≥ 60 min, and presentation with prolonged numbness along with the IAN ≥ 12 h. Additionally, participants with a sudden drop in pulse/heart-rate < 60/min or BP < 100 mmHg systolic and 60 mmHg diastolic were given immediate treatment and were excluded from the study.

To ascertain homogeneity, all interventions (nerve blocks and surgical procedures) were performed by a single experienced surgeon in a standardized manner under a similar controlled operatory. An IANB was considered successful when the participant experienced numbness along the IAN. All vital parameters (heart rate, oxygen saturation, systolic blood pressure, and diastolic blood pressure) were recorded preoperatively and periodically as per the study protocol using a multi-parameter monitor. The sedation level was assessed and monitored periodically using the eight-point modified Ramsay sedation (MRS) score [26]. The profoundness of anesthesia was evaluated using the 10 point VAS during incision, flap elevation, ostectomy, odontectomy, and/or tooth elevation.

All the participants were provided with the same standard postoperative instructions. Participants were requested to record the time of rescue analgesic intake and note the total number taken thereafter. The duration of analgesia was recorded from the point of securing the knot of the last suture to the point when the first increment in pain was experienced. The participants were asked to

consume rescue analgesics only when they could grade their pain score to ≥ 4 on the VAS. This information, along with any adverse effects experienced, was retrieved from the participants during the follow-up visit.

Statistical analysis was conducted using descriptive and inferential statistics, including the chi-square test, Student's t-test, repeated measures ANOVA with post hoc pairwise comparison, and the Statistical Package for Social Sciences (IBM SPSS Statistics 27.0, IBM Co., NY, USA). Statistical significance was set at P < 0.05.

RESULTS

The study population comprised two groups (n = 25 each) with a mean age of 31.40 ± 7.01 years ranging from 22 to 48 years, who underwent elective extraction of LITM (Table 1). The latency to anesthesia was significantly shorter in group D than that in group L (P = 0.0001) (Table 2). The profoundness of anesthesia was significantly greater (P = 0.0001) in Group D than that in Group L, which was assessed by measuring pain severity preoperatively using VAS (Table 3). The hemodynamic parameters (heart rate, blood pressure, and oxygen saturation) were assessed preoperatively at specified time intervals. No significant hemodynamic

Table 4. Heart rate (beats/min) at specified intervals between the two groups

Variables	N	Group L Mean ± SD	Group D Mean ± SD	P − value
Baseline	50	74.24 ± 6.81	75.2 ± 7.34	0.63
15 min	50	75.36 ± 4.46	73.84 ± 3.26	0.17
30 min	50	75.92 ± 3.48	75.68 ± 3.24	0.80
60 min	50	76.8 ± 4.65	77.68 ± 4.26	0.48
90 min	50	75.52 ± 4.55	74.72 ± 4.68	0.54
120 min	50	76.08 ± 3.18	75.92 ± 3.23	0.86

SD, standard deviation.

Table 5. Systolic and diastolic blood pressure (BP) (mmHg) at specified intervals between the two groups

Variables	N	Systolic BP Group L Mean ± SD	Systolic BP Group D Mean ± SD	P - value	Diastolic BP Group L Mean ± SD	Diastolic BP Group D Mean ± SD	P - value
Baseline	50	113.36 ± 7.65	119.2 ± 8.3	0.05	74.04 ± 6.88	75.36 ± 7.15	0.87
15 min	50	113.68 ± 6.96	116.48 ± 5.6	0.12	74.48 ± 5.86	73.12 ± 4.69	0.37
30 min	50	114.16 ± 6.75	115.6 ± 6.48	0.44	72.96 ± 6.56	73.12 ± 6.24	0.93
60 min	50	115.28 ± 7.04	116.8 ± 6.37	0.42	73.04 ± 6.73	71.84 ± 6.45	0.52
90 min	50	115.36 ± 6.57	115.76 ± 6.2	0.82	72.88 ± 6.32	72.72 ± 5.19	0.92
120 min	50	114.4 ± 6.35	116.32 ± 5.85	0.27	73.52 ± 5.89	73.36 ± 3.72	0.90

SD, standard deviation.

Table 6. SpO$_2$ levels (%) at specified intervals between the two groups

Variables	N	Group L Mean ± SD	Group D Mean ± SD	P − value
Baseline	50	98.2 ± 1.32	97.96 ± 1.17	0.50
15 min	50	98.2 ± 1.19	98.2 ± 0.95	1.00
30 min	50	98.16 ± 1.31	98.24 ± 0.92	0.80
60 min	50	98.12 ± 1.2	98.28 ± 0.97	0.60
90 min	50	98.2 ± 1.15	98.16 ± 0.85	0.89
120 min	50	98.2 ± 1.44	98.28 ± 0.93	0.81

SpO$_2$, peripheral capillary oxygen saturation; SD, standard deviation.

Table 7. Duration of Post operative analgesia between the two groups

Variable	N	Group L Mean ± SD	Group D Mean ± SD	P - value
Duration of post operative analgesia	50	487.2 ± 34.49	776.4 ± 10.59	0.0001

SD, standard deviation.

changes were observed during or after the procedure (P > 0.05) (Tables 4, 5, 6). The sedation level was assessed using the MRS score, wherein none of the participants experienced or reported a sedation score > 1 [26] with an insignificant difference (P > 0.05). The difference in the mean duration of POA was found to be significant (P = 0.0001), with participants in Group D experiencing prolonged analgesia in comparison with Group L (Table 7). The mean pain scores at 6, 12, 24, 48, and 72 h (P = 0.0001) were found to be significant (Fig. 2). The mean number of analgesics taken in the postoperative period up to 72 h was lower in Group D (2.12 ± 0.33) than in Group L (4.04 ± 0.67), and the differences were found to be statistically significant (P = 0.0001) (Table 8).
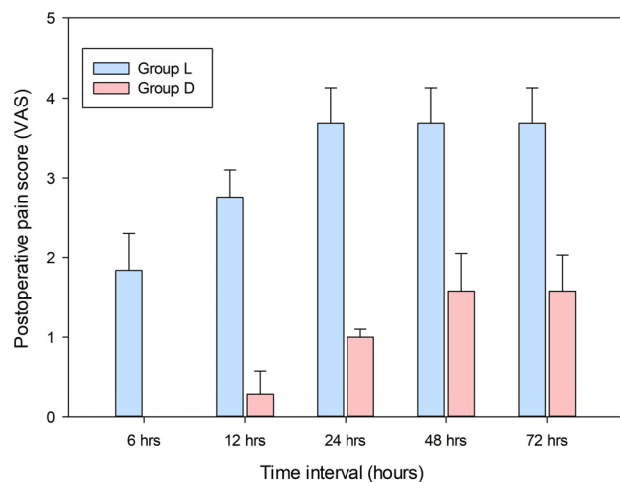
Fig. 2. The postoperative pain scores (mean ± SD) of two groups at 6, 12, 24, 48, and 72 h. P = 0.0001 (repeated measures ANOVA)

DISCUSSION

Pain control after LITM has been a challenge because of the variable inflammatory response [27]. The dental impaction pain model is a versatile and predictable study model to study the efficacy and safety of any LA and analgesic, as it has a predictable assay sensitivity, rapid recruitment of participants, and cost-effectiveness [28]. There is a continual burgeoning search for pharmacological agents with optimal therapeutic efficacy and minimal side effects. DEX is a promising pharmacologically active dextro-isomer of medetomidine that exhibits specific and selective $\alpha 2$ adrenoceptor agonism. Clinically, it not only prolongs the duration of anesthesia but also helps reduce anxiety and induce arousable sedation and analgesia. When used as an adjunct to LA, it shortens the latency period and prolongs the duration of LA, maintains homeostasis, induces hemostasis, and helps provide better patient satisfaction [29]. The present study aimed to compare and evaluate the anesthetic efficacy and safety of LB with or without DEX in IANB for the surgical removal of LITM.

In the present study, we selected a homogenous sample with well-controlled determinants of postoperative pain and inflammation in the extraction of LITM, viz: age, sex, asymptomatic, similarly oriented LITM, surgeon's

Table 8. Total number of analgesics consumed between the groups

Variable	N	Group L		Group D		P - value
		Mean ± SD		Mean ± SD		
Total number of analgesic tablets consumed	50	4.04 ± 0.67		2.12 ± 0.33		0.0001
Range		3 to 5		1 to 3		

experience, and the quantity of LA used.

The results of the present study demonstrated that the addition of DEX to LB significantly shortened the latency. This is in congruence with other studies that reported similar observations of rapid onset of anesthesia [9–11,13,15]. This could be due to the synergistic action of the individual drugs. The shorter latency observed in group D can be attributed to the blockage of presynaptic $\alpha 2$ receptors by DEX, which inhibits the release of norepinephrine, ultimately terminating the propagation of pain signals and prolonging hyperpolarization, which prevents the nerve from returning to the resting membrane potential [30].

During the entire maneuver at all points in time, participants in both groups withstood the procedure well without any pain (VAS $\leq$ 2) and discomfort barring a few participants (24%, n = 6) in group L, who reported mild discomfort during bone guttering and odontectomy. The overall difference in both groups during the procedure was statistically significant (P < 0.05). Similar observations were made by others, who noticed an increase in pain threshold values when combining DEX with lignocaine [11,16].

We evaluated pain as an individual unit and did not associate it with other perceptions such as temperature, proprioception, and pressure; therefore, the total duration of anesthesia and time to pain onset during the postoperative period were not comparable. In the present study, the differences in mean VAS scores between groups postoperatively at 6, 12, 24, 48, and 72 h were .found to be significant (P = 0.0001 for each. The mean number of analgesics taken by participants in group D was 2.12 ± 0.33, and group L was 4.04 ± 0.67, with a significant difference (P = 0.0001), indicating that participants in group D had a prolonged time to pain onset and required fewer

analgesics than those in group L. These results indicate the analgesic potency and prolonged duration of action of DEX, which can be attributed to its anti-inflammatory and local vasoconstriction effects, respectively. Studies have demonstrated that DEX acts centrally by inhibiting the discharge of substance P by activating $\alpha 2$ receptors at the locus coeruleus [31]. However, in another independent study, no significant difference was observed between the DEX and placebo groups in pain control and the number of analgesic tablets used [32].

Hemodynamic parameters, such as heart rate and blood pressure, have a multifactorial influence. In the present study, all nerve blocks and surgical procedures were performed by the same surgeon in a well-controlled operatory using a standard protocol; the pre-, intra-, and post-operative and vital parameters such as heart rate, systolic and diastolic blood pressure, and oxygen saturation did not vary significantly ($P > 0.05$) at any time point between groups D and L from their baseline values. None of the participants in either group experienced a sedation score > 1 at any specified time point. Perineurally administered DEX at various doses caused minimal hemodynamic alterations. These alterations are significantly affected by the route of administration, dose of the drug, and rate of drug delivery. A recent meta-analysis concluded that perineural doses ranging from 2 to 50 μg and intravenous doses up to 3 μgm/kg do not influence the hemodynamic response [33]. These results imply that hemodynamic stability is a complementary advantage of DEX administration.

To our knowledge, no previous studies have attempted to evaluate the effects of DEX and LB on POA in LITM surgery. The combination of DEX and LB provided prolonged and profound POA with fewer analgesic tablets required in the acute postoperative period up to 72 h. The study has some limitations. A split-mouth study design would have been ideal to evaluate pain and analgesia. This study was conducted with a finite study population. The study cannot recommend the use of DEX in patients with hypertension and cardiovascular disorders as participants with these conditions were excluded from the study population. Pain is an individual response that may vary from person to person and at different times within the same person. There is a possibility of interpreting pain and its correlation with the VAS score.

In conclusion, when used as an adjunct to a long-acting LA such as LB, DEX enhances the latency and profoundness of anesthesia. It prolongs the duration of POA with minimal cardiovascular and neurocognitive actions. This, in turn, leads to decreased consumption of analgesics in the postoperative period, thereby avoiding the undesirable side effects of the commonly used analgesics. It can be concluded that DEX in a single IANB block with LA may be effective and advantageous in providing adequate anesthesia, prolonged duration of POA, and fewer analgesic requirements with minimal side effects. Multi-centric trials involving larger numbers of participants and greater power are required to support the conclusions of the present study.

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CONFLICT OF INTEREST: The authors declare that they have no conflict of interest.

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