Original Article

Comparison of Intranasal Versus Intravenous Dexmedetomidine to Attenuate Haemodynamic Response of Laryngoscopy and Endotracheal Intubation in Elective Lumbar Spine Surgery: A Randomized Controlled Study

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Abstract

Background: In general anaesthesia, hemodynamic alterations during endotracheal intubation are vital concerns. The efficacy of intranasal and intravenous Dexmedetomidine (DEX) in decreasing the stress response generated by laryngoscopy and endotracheal intubation was investigated in this study.

Methods: Seventy adults were randomised into two groups in this prospective, randomised, double-blind study: Group DIV (n=35) and Group DIN (n=35). Dexmedetomidine (DEX) infusion (0.5 µg /kg) was administered intravenously over 40 minutes to the DIV group and intranasally (1 µg /kg) to the DIN group 40 minutes before induction.

The primary outcome was to compare the mean arterial pressure (MAP) between the two groups starting 40 minutes before induction and continuing every 10 minutes until induction of anaesthesia, at the time of intubation, and then every minute afterwards until 5 minutes, 7 minutes, and 10 minutes following intubation. Comparisons of heart rate (HR), systolic (SBP) and diastolic blood pressure (DBP), sedation and any adverse effects were the secondary outcomes.

Results: The two groups had no statistically significant difference in MAP, HR, SBP and DBP. The DIV group's preoperative sedation score before induction was significantly higher than the DIN group's (P = 0.014).

Conclusion: This study demonstrates that dexmedetomidine administered intravenously is equally efficient as intranasal dexmedetomidine in attenuating hemodynamic response during laryngoscopy and intubation.

Keywords

laryngoscopy, intubation, dexmedetomidine, premedication, spine surgery.

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Introduction

The augmented cardiovascular responses in the form of tachycardia, hypertension, and even myocardial infraction brought about by the noxious stimulus of laryngoscopy and intubation may be detrimental for patients with cardiovascular and cerebrovascular diseases.[1]

Adequate premedication is necessary for stable haemodynamics during laryngoscopy and intubation, which is an integral component of general anaesthesia.

A perfect premedication should be anxiolytic, sedative, analgesic, and antisialagogue. It should have a brief duration of action, a rapid onset, be administered non-

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parenterally, and have no adverse hemodynamic or respiratory effects[2]

Dexmedetomidine (DEX) is a highly selective, short-acting, alpha 2-adrenoreceptor agonist used for conscious sedation, and analgesia perioperatively. The intranasal mode of administration of dexmedetomidine has advantage over the intravenous mode in respect to ease of administration.

There needs to be more literature regarding comparison of the efficacy between intranasal (IN) and intravenous (IV) DEX as a premedication to attenuate haemodynamic response during laryngoscopy and endotracheal intubation in lumbar spine surgery.

So, this study intends to compare the efficacy of IN dexmedetomidine and IV dexmedetomidine for the prevention of haemodynamic surges during laryngoscopy and endotracheal intubation in patient undergoing lumbar spine surgery.

Materials and Methods

A double-blind, randomised control study was conducted in a teaching institution of tertiary care after approval of the Institutional Ethical Committee (RMC/IHEC/2021/93) and the informed consent of the participants.

Seventy adults, 18 to 60 years of age, ASA (American Society of Anaesthesiologists physical status) I and II, undergoing elective lumbar spine surgery under general anaesthesia with endotracheal intubation, were included in this study.

Excluded from this study were patients who refused to participate, had a known allergy or hypersensitivity to dexmedetomidine, had severe cardiac and respiratory disease, and were predicted to have a difficult airway. All patients were assessed for intranasal pathology during the preoperative visit. Patients with nasal ulcers, nasal polyps, or nasal septum deviation were precluded from the study. Individual patients underwent a comprehensive pre-operative evaluation and any necessary investigations. Both groups of patients fasted for six hours and received ranitidine (150 mg) and alprazolam (0.5 mg) the night before surgery as premedication.

The randomization was based on a computer-generated random number table. This randomisation schedule allowed for the assignment of patients in two equal groups (Group -D_{IV} and Group D_{IN}). The list was concealed in opaque, sealed envelopes that were numbered and unsealed sequentially after obtaining patient consent.

On the day of the operation, all participants were moved to the preparatory area two hours beforehand. In the preoperative room, all standard monitors, including pulse oximetry, noninvasive blood pressure (NIBP), and electrocardiogram (ECG), were affixed, and baseline haemodynamic parameters were recorded. An 18G peripheral venous cannula administered 80ml/h of Ringer's lactate solution as maintenance fluid.

Group D_{IV} received intravenous DEX (0.50 µg /kg) over the course of 40 minutes before induction. The equivalent volume of NS was intravenously administered to the D_{IN} group.

Patients in Group -D_{IN}- received IN DEX (1 µg /kg) in its undiluted, parenteral formulation (100 g/ml) form. Intranasal medication was administered into both nostrils using a 1 ml syringe in the supine, head-down position approximately 40 minutes prior to induction. The equivalent volume of NS was intranasally administered to the D_{IV} group. All patients were instructed to avoid sucking and sneezing following intranasal drug administration. Neither the person administering the medication nor the patients were informed of their group assignment during the course of the study.

Heart rate (HR), mean arterial pressure (MAP), systolic blood pressure (SBP), diastolic blood pressure (DBP), and SpO2 were measured in the preoperative room at 10-minute intervals until induction of anaesthesia.

In the operating room, hemodynamic parameters were recorded during intubation, then every minute for the next five minutes, at seven minutes, and ten minutes after intubation. Using the Ramsay sedation scale (RSS), an observer evaluated the sedation status of both groups at baseline and 40 minutes after drug administration.

After transferring the patient to the operating room, general anaesthesia techniques were standardised for both groups. In the operating room, additional monitors, such as a neuromuscular monitor and an $ETCO_2$ monitor, were affixed, and monitoring continued until the end of the procedure. The monitoring of hemodynamics was maintained throughout the perioperative period. After 3 minutes of preoxygenation with 100% oxygen, all patients were induced with propofol (2 mg/kg) and fentanyl (1 µg /kg) administered intravenously. The administration of intravenous rocuronium bromide (1 mg/kg) facilitated tracheal intubation. When the train of four (TOF) count was zero, an experienced anesthesiologist performed laryngoscopy with a Macintosh laryngoscope blade and endotracheal (ET) intubation with an appropriate size cuffed-disposable armoured ET tube. The laryngoscopy & intubation time limit was 15-20 seconds. If laryngoscopy & intubation were not completed within 15 to 20 seconds, the data were excluded from the study analysis. No surgical procedure was permitted until 10 minutes after intubation. Anaesthesia was maintained with (40% O_2 and N_2O with sevoflurane) and repeated intermittent bolus doses of rocuronium in both

groups. All patients were ventilated utilising volume-controlled ventilation with a closed circuit to maintain an $EtCO_2$ level between 35 and 40 mm Hg. The timing of extubation was determined by neuromuscular surveillance (TOF watch).

The primary outcome was to compare the mean arterial pressure (MAP) between the two groups starting 40 minutes before induction and continuing every 10 minutes until induction and at the time of intubation, and then every minute afterwards until 5 minutes, 7 minutes and 10 minutes following intubation. Comparisons of heart rate, systolic and diastolic blood pressure, sedation, and other adverse effects were the secondary outcomes.

During the study period, episodes of hypotension (MAP 20% of baseline), bradycardia (HR 50/min), and hypoxia (SPO_2 90%) were recorded and treated accordingly.

Infusions of neostigmine (0.05 mg/kg) and glycopyrrolate (0.01 mg/kg) were administered intravenously to reverse neuromuscular block after surgery. After extubation, the patient was transferred to the recovery area. When the patient's Aldrete score was > 9, he was transferred to the ward and his vital signs were monitored for 12 hours.

A pilot study was conducted to ascertain the sample size based on the 15-mmHg standard deviation difference between the two groups post-intubation MAP. It was determined that 35 subjects per group were required to detect a 10-mmHg difference in MAP with 80% power and 5% type-1 error probability. The sample size calculation was performed by the nMaster 2.0 programme. [Biostatistics Department, CMC Vellore].

Statistica version 6 [Tulsa, Oklahoma: StatSoft Inc., 2001] and GraphPad Prism version 5 [San Diego, California: GraphPad Software Inc., 2007] were utilised for statistical analysis. Except for the Ramsay Sedation Score and SpO2 values, all numerical variables in the descriptive statistics were normally distributed (Kolmogorov-Smirnov goodness-of-fit test). The RSS score of 2 (awake, oriented, and cooperative) was deemed adequate for statistical analysis. Student's unpaired t-test for normally distributed data and Mann-Whitney U test for skewed data were used to evaluate comparisons of numerical variables between two groups. If the data were normally distributed, repeated measures analysis of variance (ANOVA) was followed by Tukey's test as a post hoc test; if the data were skewed, Friedman's analysis of variance (ANOVA) was followed by Dunn's test as a post hoc test. A P value of 0.05 was deemed statistically significant.

Statistical Analysis

The collected data was coded and saved within the MS Excel spreadsheet program. SPSS v23 (IBM Corp.) was utilized for information analysis. The continuous variables were analyzed by descriptive statistics and were elaborated in the form of medians/IQRs and means/standard deviations. The categorical variables were elaborated in the percentages and frequencies. To compare proportions, inferential statistics were used by using the Fisher's exact or Chi-square test. The student's t-test and Mann-Whitney U test were used for the comparison of means in the two groups as applicable. The paired t-test was used for the comparison of continuous variables at two points in time. Multiple logistic regression analysis was used to document independent predictors of desired outcomes.

Results

A total of 70 patients were analysed. Consort flow diagram is shown in (Figure 1). All the demographic data on patient's characteristics like age, height, weight, BMI and sex were comparable between the two groups (Table 1). In both the groups, the HR was decreased from the baseline value during the preoperative period, but in Group D_{IV} the decrease in the HR was more (19.75% at 30 min and 23.50% at 40 min) than in Group D_{IN} (15.16% at 30min and18.18% at 40 min). During intergroup comparison, a statistically significant difference in HR was shown at 30 and 40 minutes after the study drugs administration (p-value of 0.044 and 0.015 respectively). None of the patients in both groups has clinically significant bradycardia (Table 2). At 40 min intervals, 57.1% of patients in the DIN group remain in RSS stage II, whereas 77.14% of patients in the D_{IV} group remain in RSS stage III, 77.14%. The D_{IV} group's preoperative sedation score before induction was significantly higher than the D_{IN} group's (P = 0.014). SBP, DBP and MAP were gradually decreased from baseline values from 20 min onwards in both the groups, but it was more prominent in IV group than IN group. During intergroup comparison, they found no statistically significant difference. (Maximum decrease of SBP at 40 min 11.45% in Group D_{IN} and 11.9% in Group D_{IV}. Similarly maximum fall of DBP at 40 min 12.28% in Group D_{IN} and 15.20% in Group $D_{IV.}$ Maximum fall of MAP at 40 min for Group D_{IN}14.8% and Group D_{IV}13.20% (Table 3). It was found that the maximal increase in HR and BP occurred during laryngoscopy and endotracheal intubation, and then it gradually came down to normal limits within 10 min in both groups. The maximal increase in heart rate was 23.7% in Group D_{IN} and 20.84% in D_{IV} during laryngoscopy and endotracheal intubation. During intergroup comparison, there was no statistically significant difference in HR was found during and up to

10 mins after intubation. (Table 4). Similarly, maximal increase in MAP occurred during laryngoscopy and endotracheal intubation, then it gradually came down to the normal limit within 10 min in both the group. The increase in MAP was 19% in Group D_{IN} compared to 12.5% for MAP in Gr D_{IV} during laryngoscopy and

Table 1: Demographic characteristics of the patients in two groups.

Demography and other parameters of patients	Group D_{IN} (n=35) Mean±SD	Group D_{IV} (n=35) Mean±SD	P-value
Age (in year)	40.71±10.91	42.03±12.50	0.641
Sex(M/F)	22/13	19/16	0.642
Weight (in kgs)	60±6.894	61.03±7.350	0.548
Height (in meter)	1.623±0.075	1.625±0.065	0.892
BMI (in $kg/m^{2)}$	22.75±1.7	23.10±2.388	0.980

Table 2: Comparison of heart rate between two groups at different time pointsa

Time in mins	Group D_{IN} Mean±SD	Group D_{IV} Mean±SD	P-value
Basal	87.06±11.337	82.43±8.462	0.057
10min	82.31±10.715	78.80±8.213	0.128
20min	76.80±10.238	73.09±7.358	0.086
30min	73.86±9.372	69.86±6.722	0.044
40min	71.23±9.481	66.60±5.553	0.015

Table 3: Pre operative SBP, DBP and MAP at different time points

	Group	Basal	10min	20min	30min	40min
	D_{IN}	128.20±11.749	125.03±11.449	120.20±11.483	117.26±12.793	113.54±12.181
SBP	D_{IV}	126.94±10.519	123.71±9.057	118.89±10.417	116.23±10.672	111.80±9.710
	p-value	0.639	0.596	0.618	0.716	0.510
	D_{IN}	79.74±7.590	75.29±7.458	71.89±7.940	68.91±8.424	66.00±6.962
DBP	D_{IV}	78.74±8.965	75.97±9.596	72.91±9.441	70.60±8.247	66.77±7.628
	P-value	0.616	0.740	0.623	0.401	0.660
	D_{IN}	94.63±8.128	90.83±8.624	87.00±8.888	84.20±9.333	81.06±7.673
MAP	D_{IV}	93.06±9.365	90.37±9.340	86.94±9.175	84.57±7.868	80.74±7.913
	P-value	0.456	0.832	0.979	0.858	0.867

Table 4: Intraoperative heart rate at different time points

Time in min	Group D_{IN} Mean±SD	Group D_{IV} Mean±SD	P-value
Intubation	84.40±9.435	79.03±5.874	0.090
1min	82.06±8.734	80.54±6.487	0.413
2min	79.74±9.082	77.94±6.063	0.333
3min	78.54±9.936	76.29±5.453	0.243
4min	77.94±10.833	75.60±5.325	0.256
5min	76.46±9.669	74.63±5.325	0.331
7min	76.09±9.633	75.09±5.883	0.602
10min	76.71±9.164	76.09±5.404	0.728

Table 5: Intraoperative MAP (mm of Hg) at different time points

Time in min	Group D_{IN} Mean±SD	Group D_{IV} Mean±SD	P-value
Intubation	93.63±7.080	90.91±8.336	0.147
1min	91.97±7.833	91.26±6.853	0.682
2min	88.83±6.853	88.17±7.812	0.709
3min	86.89±7.696	86.40±7.531	0.790
4min	86.23±6.787	85.20±7.304	0.544
5min	85.49±7.089	83.97±6.640	0.360
7min	85.54±6.630	83.71±6.090	0.234
10min	83.26±5.617	84.66±7.557	0.382

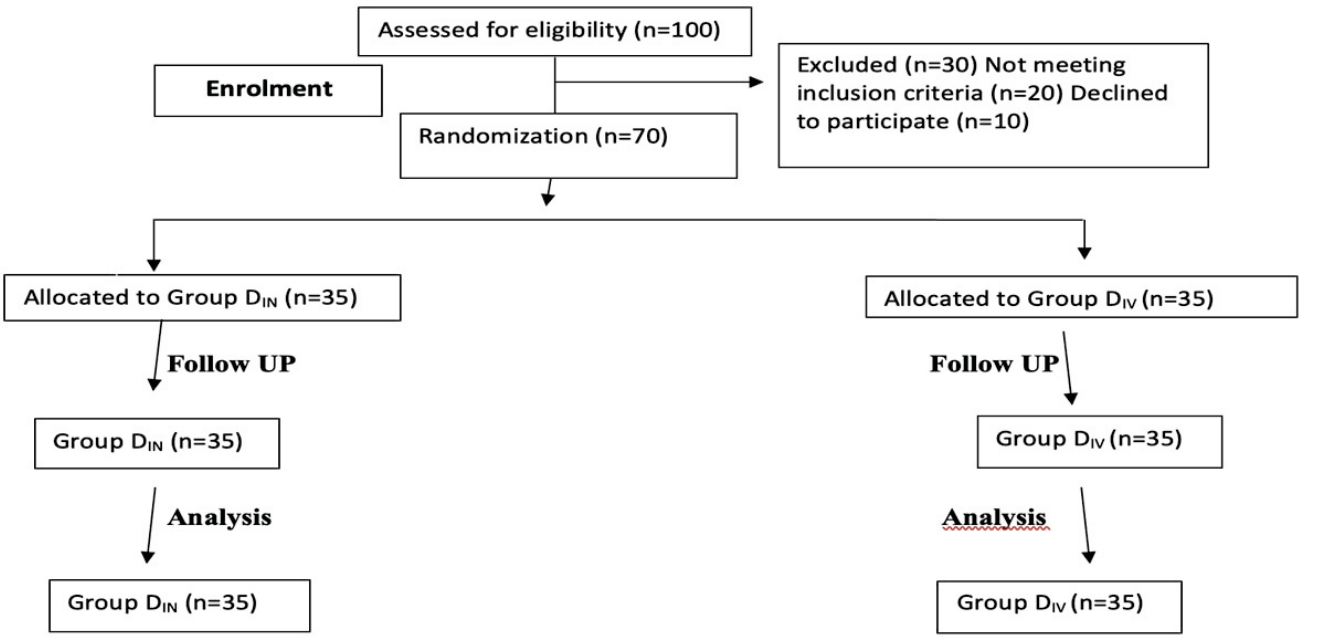

Figure 1 : Consort Diagram

Discussion

This study demonstrates that intranasal DEX administered 40 minutes before intubation is as efficacious as intravenous DEX in reducing laryngoscopic stress responses. In both groups, all hemodynamic parameters (HR, SBP, DBP, MAP) remain within the permissible range during the preoperative and intraoperative phases. Preoperative sedation was substantially greater in the D_{IV} group than in the D_{IN} group. Laryngoscopy and endotracheal intubation are the two most consistent procedures leading to significant increase in heart rate and blood pressure. This has been attributed to a sympathetic response as evidenced by increased circulating catecholamine levels.[3] These changes are found to be greatest 60 seconds after intubation and may even last for 5-10 min post-intubation. The haemodynamic changes brought about by laryngoscopy were first described by Reid and Brace Proper use of premedication may decrease this stress response.[4] Numerous pharmacological agents such as opioids (fentanyl), adrenergic blocking agents (esmolol), vasodilating agents (sodium nitroprusside), and local anaesthetics drugs (intravenous lidocaine) have been attempted to attenuate these haemodynamic effects, but none have been able to attenuate these responses completely.[5] Due to its unique sedative, hypnotic, anxiolytic, sympatholytic, antisecretory, and analgesic properties, DEX is widely utilised in intensive care units. The presynaptic activation of α-2 receptors in locus caeruleus inhibits noradrenaline release and causes sedation and hypnosis. Postsynaptic activation of α-2 receptors in central nervous system decreases sympathetic activity leading to bradycardia and hypotension.

Dexmedetomidine, a centrally acting α 2 agonists, offers a unique pharmacological profile with sedation, sympatholysis, analgesia, cardiovascular stability and with greater advantage in avoiding respiratory depression.

All this characteristics of DEX are highly attributable as an ideal premedication agent.[6,7]

Lakshmi et al found that Intranasal dexmedetomidine is a better premedication agent in morbidly obese patients than oral alprazolam.[8] DEX can be administered via intravenous,[9] intramuscular,[10] intranasal,[11] and intraoral[12] routes. Intranasal administration is more convenient because it is innocuous, odourless, and requires no intravenous infusion. Intranasal administration of a substance allows it to cross the blood–brain barrier and reach the central nervous system directly [13]. Because of the increased vascularity of the nasal mucosa, medications can gain rapid access to the venous blood of the systemic circulation, thereby bypassing first-pass metabolism in the liver.[14]

Various clinical studies with intravenous DEX show that IV DEX can effectively attenuate the stress responses.

Till now intravenous DEX is most popularly used as premedication. However, it is documented that the sedative effect of IV DEX is more pronounced than the analgesic effect, accompanied by profound bradycardia and hypotension. Moreover, IV DEX may induce biphasic MAP oscillations, which are undesirable in anaesthesia.

A study by Bloor BC et al on intravenous Dexmedetomidine[15] revealed that in spite of mild hypercapnia and hypoventilation intravenous dexmedetomidine was useful in providing perioperative sedation and analgesia without significant respiratory depression.

A clinical study by Sebastian B. et al documented that 0.75 μg/kg is the optimal IV dose for attenuation of stress response to laryngoscopy and endotracheal intubation without any haemodynamic disturbances.[16]

There is some clinical studies where intranasal DEX has been administered as a premedication especially in paediatric patients. In a study, Yuen VM, et al.[17] did a randomised comparison of two intranasal dexmedetomidine doses (1 μg /kg and 2 μg /kg) as premedication in children. They concluded that both doses produced a similar level of satisfactory sedation in children with no adverse haemodynamic effects in any of the groups. In this study, to avoid any untoward side effects, we used the lower safe dose of 1 μ/kg.

Nasal premedication with midazolam and Dexmedetomidine has also been studied as alternative to oral premedication with comparable results[18] Intranasal route has been successfully used as a sedative in children for magnetic resonance imaging, CT scan and for burn dressing.[19]Noon et al found Intranasal administration of 1.5 μg/kg atomized dexmedetomidine is effective, convenient, and safe as a sedative for patients undergoing third molar extraction.[20]

A recent study by Iriola T et al,[21] documented that the peak concentration of intranasal DEX was achieved with a median time range 38-45 min later. So, in our study, we administered intranasal DEX 40 mins before induction.

In our study, preoperative HR was gradually decreased in both groups of patients and this decrease was more in the IV group than intranasal group. A similar finding was found in a study by Cheung et al.[22]

In our study, in both the group preoperative SBP, DBP and MAP, all gradually decreased from baseline value up to 40 min after study medication. However, these decreases were more marked in intravenous group than the intranasal group which was statistically significant differences. None of these patients, however, developed clinically significant decreases that required

vasopressor or anticholinergics support.

In our study, the maximal increase in HR, SBP, DBP and MAP were occurred during laryngoscopy and endotracheal intubation; then it gradually came down to the normal limit within 10 min in both the group. Though the intranasal group had slightly higher values of SBP, DBP and MAP, they were not statistically significant during intergroup comparison.

Conclusion

This study demonstrates that, dexmedetomidine administered intravenously is equally efficient as intranasal dexmedetomidine in attenuating hemodynamic response during laryngoscopy and intubation. Additionally, during the preoperative phase, intravenous dexmedetomidine induces higher sedation than intranasal method. To control haemodynamic response during laryngoscopy and endotracheal intubation, intranasal dexmedetomidine can be utilised as a safer alternative premedication in patients undergoing general anaesthesia for lumbar spine surgery.

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Conflict of Interest

There are not conflict of interest.

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