

Original Research Article

PREOPERATIVE NEBULIZED DEXMEDETOMIDINE FOR ATTENUATION OF THE HAEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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ABSTRACT

Background: Laryngoscopy and endotracheal intubation provoke a sympathoadrenal stress response that can precipitate myocardial ischaemia or cerebrovascular events in vulnerable patients. Nebulized dexmedetomidine has been proposed as a non-invasive premedication that may attenuate this response with fewer haemodynamic side effects than the intravenous route. We evaluated the efficacy and safety of preoperative nebulized dexmedetomidine for attenuating the haemodynamic response to laryngoscopy and endotracheal intubation.

Materials and Methods: In this prospective, randomized, double-blind, placebo-controlled trial, 110 adult patients of ASA physical status I-II undergoing elective surgery under general anaesthesia were randomized to Group D (nebulized dexmedetomidine 1 µg/kg, n=55) or Group S (nebulized 0.9% saline, n=55), administered 20 minutes before induction. Heart rate (HR), systolic (SBP), diastolic (DBP) and mean arterial (MAP) blood pressures were recorded at baseline, after nebulization, and at 1, 2, 4, 6, 8 and 10 minutes after laryngoscopy. Perioperative adverse events were recorded.

Results: Baseline characteristics and haemodynamics were comparable between groups (all $p > 0.05$). Following laryngoscopy, Group S showed marked increases in all four parameters, whereas Group D showed a substantially attenuated response. HR peaked at 96.96 ± 7.11 bpm in Group S versus 90.64 ± 10.97 bpm in Group D; SBP, DBP and MAP remained near or below baseline in Group D throughout. Between-group differences were significant from 1 minute after laryngoscopy onward ($p < 0.001$ from 2 minutes for all parameters). Hypotension occurred in 12.7% of Group D versus 1.8% of Group S ($p = 0.07$, all transient); no bradycardia occurred in either group. PONV and postoperative sore throat rates were not significantly different between groups.

Conclusion: Preoperative nebulized dexmedetomidine (1 µg/kg) effectively and safely attenuates the haemodynamic stress response to laryngoscopy and endotracheal intubation, without bradycardia, supporting its use as a non-invasive premedication strategy.

Keywords: Nebulized dexmedetomidine; laryngoscopy; endotracheal intubation; haemodynamic response; general anaesthesia

INTRODUCTION

Endotracheal intubation is a routine step in general anaesthesia, but the direct laryngoscopy required to secure the airway triggers a marked sympathoadrenal stress response manifested by transient increases in heart rate (HR) and blood pressure (BP).^[1-4] While generally well tolerated in healthy adults, this pressor response can precipitate myocardial ischaemia, arrhythmia, or cerebrovascular events in patients with underlying cardiovascular risk. Several pharmacological strategies, including opioids, β -blockers, calcium-channel blockers and α 2-adrenergic agonists, have been used to blunt this response, but each carries specific limitations related to dose-dependent side effects.^[3,5] Dexmedetomidine, a highly selective α 2-adrenergic agonist with sedative, analgesic, anxiolytic and sympatholytic properties, has emerged as an attractive option because it attenuates the stress response without causing clinically significant respiratory depression.^[6] Intravenous dexmedetomidine has been extensively studied for this indication, but its use is limited in some patients by dose-dependent bradycardia and hypotension.^[3] Nebulized dexmedetomidine has recently been proposed as a non-invasive, needle-free alternative that exploits the drug's high bioavailability across the nasal, buccal and respiratory mucosa, achieving gradual systemic absorption that may reduce haemodynamic side effects while retaining efficacy.^[7-9] Head-to-head comparisons suggest that the nebulized route can match intravenous administration in blunting the pressor response, with a lower incidence of bradycardia and hypotension.¹ However, evidence specific to Indian surgical populations remains limited, and data on associated perioperative adverse events, namely hypotension, bradycardia, postoperative nausea and vomiting (PONV), and postoperative sore throat (POST), are sparse.^[8,9] We therefore conducted a randomized, double-blind, placebo-controlled trial to evaluate whether preoperative nebulized dexmedetomidine (1 μ g/kg), administered 20 minutes before induction, attenuates the haemodynamic response to laryngoscopy and endotracheal intubation compared with nebulized normal saline, and to characterize its perioperative adverse-event profile, in adult patients undergoing elective surgery under general anaesthesia.

MATERIALS AND METHODS

Study design and setting: This prospective, randomized, double-blind, placebo-controlled trial was conducted in the Department of Anaesthesiology, Sri Lakshmi Narayana Institute of Medical Sciences and Hospital, Puducherry, India, from March 2024 to August 2025, following approval by the Institutional Ethics Committee (approval no. IEC/C-P/43/2024, dated 8 February 2024). The trial

was not prospectively registered with the Clinical Trials Registry of India (CTRI) or any other clinical trials registry before enrolment of the first participant; this is acknowledged as a limitation of the study. A total of 110 adult patients scheduled for elective surgery under general anaesthesia with endotracheal intubation were enrolled after written informed consent.

Participants: Eligible patients were of American Society of Anesthesiologists (ASA) physical status I or II, of either sex, aged 18-60 years, with body mass index below 30 kg/m², scheduled for low- to moderate-risk elective surgery lasting 2-3 hours. Patients were excluded for anticipated difficult airway (modified Mallampati class III/IV), intubation requiring more than one attempt or longer than 20 seconds, use of antihypertensive medication, chronic smoking, asthma or chronic obstructive pulmonary disease, pregnancy or lactation, hepatic, renal or cardiac disease, or known dexmedetomidine allergy.

Sample size: Sample size was calculated from a previous study's HR data at baseline (78.13 $\pm$ 13.73 bpm) and 1 minute after intubation (70.00 $\pm$ 11.77 bpm), a mean difference of 8.13 bpm, 80% power, and a two-sided α of 0.05, giving a required 104 patients; this was rounded up to 110 (55 per group) to allow for dropouts.

Randomization and blinding: Patients were randomized 1:1 to Group D (nebulized dexmedetomidine 1 μ g/kg diluted in 4 mL 0.9% saline, total 5 mL) or Group S (nebulized 0.9% saline, 5 mL) using a computer-generated sequence, with allocation concealed in serially numbered, sealed, opaque envelopes opened only in the preoperative holding area. Patients and outcome assessors were blinded to group allocation; the nebulized solution was administered by an independent investigator not otherwise involved in the study.

Procedures: The study drug was nebulized via a compressor-driven face-mask nebulizer (Eco Smart, Saify Healthcare and Medi Devices, India) over approximately 15 minutes, 20 minutes before induction of anaesthesia. General anaesthesia was induced with intravenous ondansetron 4 mg, midazolam 1 mg, fentanyl 2 μ g/kg, and propofol 2 mg/kg; laryngoscopy was performed 180 seconds after vecuronium 0.08 mg/kg. Anaesthesia was maintained with sevoflurane in 50% oxygen-nitrous oxide, with vecuronium for muscle relaxation. Laryngoscopy and intubation were performed by an experienced anaesthesiologist.

Outcome measures: HR, SBP, DBP and MAP were recorded at baseline (pre-nebulization), 1 minute after nebulization, and at 1, 2, 4, 6, 8 and 10 minutes after laryngoscopy. The primary outcome was the effect of nebulized dexmedetomidine on HR and SBP response to laryngoscopy and intubation; secondary outcomes were DBP and MAP response, and perioperative adverse events (hypotension, bradycardia, PONV, POST).

Statistical analysis: Continuous variables are expressed as mean $\pm$ SD and were compared between

groups using independent-samples parametric tests; categorical variables are expressed as n (%) and were compared using Fisher's exact test. A two-tailed p value <0.05 was considered statistically significant.

RESULTS

All 110 enrolled patients completed the study protocol; none were excluded after randomization. The two groups were comparable for age, BMI, sex distribution and ASA physical status (all $p>0.05$; Table 1), and baseline HR, SBP, DBP and MAP did not differ between groups (all $p>0.05$; [Table 1]), confirming adequate randomization; values remained similar at 1 minute after nebulization, indicating that nebulization itself did not alter baseline haemodynamics.

Following laryngoscopy and intubation, both groups showed a rise in all four haemodynamic parameters, but the increase was consistently and significantly smaller in Group D [Table 2, Figure 1]. HR rose to a peak of 96.96 ± 7.11 bpm in Group S versus 90.64 ± 10.97 bpm in Group D at 2 minutes ($\Delta+18.87$ vs $\Delta+11.00$ bpm from baseline); the between-group difference was significant from 1 minute after

laryngoscopy onward ($p=0.01$ at 1 min, $p=0.001$ at 2 min, $p<0.001$ from 4-10 min).

SBP increased to a peak of 134.05 ± 6.51 mmHg in Group S at 2 minutes, while Group D remained close to its own baseline (117.22 ± 10.14 mmHg); differences were significant at every post-laryngoscopy time point ($p<0.001$). DBP followed a similar pattern, rising to 80.13 ± 12.19 mmHg in Group S at 2 minutes versus 73.11 ± 8.29 mmHg in Group D ($p<0.001$ from 1 minute onward). MAP showed the most pronounced divergence: Group S peaked at 98.82 ± 5.67 mmHg at 2 minutes while Group D progressively declined to 76.49 ± 5.56 mmHg by 10 minutes (all post-laryngoscopy $p<0.001$).

Perioperative adverse events are shown in Table 3. Hypotension occurred more often in Group D (12.7%) than Group S (1.8%), a numerical but not statistically significant difference ($p=0.07$); all episodes were transient and responded to intravenous fluids without vasopressor use. No bradycardia occurred in either group. PONV occurred in 3.6% of Group D and 1.8% of Group S ($p=1.00$). POST, the most common adverse event, occurred in 30.9% of Group D versus 18.2% of Group S ($p=0.18$). No serious or life-threatening adverse events were recorded in either group.

Table 1: Baseline Demographic, Clinical and Haemodynamic Characteristics

Variable	Group D (n=55)	Group S (n=55)	p-value
Age (years)	39.51 ± 12.91	39.07 ± 14.94	0.87
BMI (kg/m ²)	25.62 ± 3.52	26.78 ± 3.23	0.08
Sex, M:F	41.8% : 58.2%	56.4% : 43.6%	0.18
ASA status, I:II	50.9% : 49.1%	49.1% : 50.9%	1.00
Heart rate, bpm	79.64 ± 9.68	78.09 ± 8.49	0.375
Systolic BP, mmHg	117.49 ± 8.92	117.82 ± 7.10	0.832
Diastolic BP, mmHg	73.60 ± 7.65	73.69 ± 5.86	0.944
Mean arterial pressure, mmHg	88.00 ± 7.88	89.67 ± 5.11	0.190

Values expressed as mean $\pm$ SD or percentage (%). $p<0.05$ considered statistically significant. ASA, American Society of Anesthesiologists; BMI, body mass index; BP, blood pressure.

Table 2: Serial Haemodynamic Parameters at All Time Points, Group D vs Group S

Time point	Group D (Mean $\pm$ SD)	Group S (Mean $\pm$ SD)	p-value
Heart rate (bpm)			
Baseline	79.64 ± 9.68	78.09 ± 8.49	0.38
1 min after nebulization	83.00 ± 9.58	80.96 ± 8.14	0.23
1 min after laryngoscopy	86.69 ± 11.77	92.02 ± 7.60	0.01*
2 min after laryngoscopy	90.64 ± 10.97	96.96 ± 7.11	0.001*
4 min after laryngoscopy	88.85 ± 11.99	95.73 ± 6.11	<0.001*
6 min after laryngoscopy	84.64 ± 10.79	92.56 ± 5.90	<0.001*
8 min after laryngoscopy	82.27 ± 11.74	89.31 ± 6.09	<0.001*
10 min after laryngoscopy	80.40 ± 11.48	85.82 ± 5.90	<0.001*
Systolic blood pressure (mmHg)			
Baseline	117.49 ± 8.92	117.82 ± 7.10	0.832
1 min after nebulization	118.29 ± 8.78	119.44 ± 6.39	0.436
1 min after laryngoscopy	119.00 ± 13.55	131.87 ± 9.34	<0.001*
2 min after laryngoscopy	117.22 ± 10.14	134.05 ± 6.51	<0.001*
4 min after laryngoscopy	111.44 ± 8.58	129.05 ± 17.38	<0.001*
6 min after laryngoscopy	106.93 ± 12.90	128.56 ± 15.82	<0.001*
8 min after laryngoscopy	105.27 ± 8.42	122.29 ± 7.02	<0.001*
10 min after laryngoscopy	104.09 ± 6.79	118.27 ± 7.06	<0.001*
Diastolic blood pressure (mmHg)			
Baseline	73.60 ± 7.65	73.69 ± 5.86	0.94
1 min after nebulization	73.76 ± 7.34	73.65 ± 5.70	0.93
1 min after laryngoscopy	74.11 ± 11.51	80.11 ± 7.35	<0.001*
2 min after laryngoscopy	73.11 ± 8.29	80.13 ± 12.19	0.001*
4 min after laryngoscopy	68.93 ± 7.82	78.60 ± 5.19	<0.001*

6 min after laryngoscopy	65.51 ± 9.72	74.78 ± 5.71	<0.001*
8 min after laryngoscopy	64.02 ± 6.14	70.20 ± 5.32	<0.001*
10 min after laryngoscopy	63.13 ± 6.02	66.56 ± 5.46	<0.001*
Mean arterial pressure (mmHg)			
Baseline	88.00 ± 7.88	89.67 ± 5.11	0.19
1 min after nebulization	89.00 ± 7.56	89.82 ± 4.82	0.50
1 min after laryngoscopy	89.09 ± 11.06	97.02 ± 6.76	<0.001*
2 min after laryngoscopy	87.58 ± 8.86	98.82 ± 5.67	<0.001*
4 min after laryngoscopy	82.85 ± 7.89	96.18 ± 5.30	<0.001*
6 min after laryngoscopy	79.20 ± 10.86	92.04 ± 5.13	<0.001*
8 min after laryngoscopy	77.31 ± 6.82	87.82 ± 5.51	<0.001*
10 min after laryngoscopy	76.49 ± 5.56	83.98 ± 5.67	<0.001*

Values expressed as mean ± SD. *p<0.05, statistically significant. bpm, beats per minute.

Table 3: Perioperative Adverse Events

Adverse event	Group D, n (%)	Group S, n (%)	p-value
Hypotension	7 (12.7%)	1 (1.8%)	0.07
Bradycardia	0 (0.0%)	0 (0.0%)	N/A
Postoperative nausea and vomiting	2 (3.6%)	1 (1.8%)	1.00
Postoperative sore throat	17 (30.9%)	10 (18.2%)	0.18

Values expressed as n (%). Fisher's exact test used for all comparisons. N/A, not applicable (zero events in both groups precluded comparative testing).

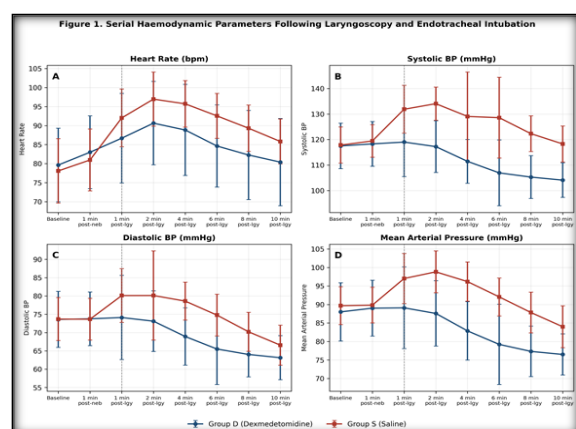


Figure 1: Serial Haemodynamic Parameters Following Laryngoscopy and Endotracheal Intubation

Panels A-D show mean heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure, respectively, at baseline, 1 minute after nebulization, and 1, 2, 4, 6, 8 and 10 minutes after laryngoscopy, in Group D (dexmedetomidine, blue) and Group S (saline, red). Error bars represent standard deviation; the dashed vertical line marks the point of laryngoscopy and intubation.

DISCUSSION

In this randomized, double-blind, placebo-controlled trial, preoperative nebulized dexmedetomidine (1 µg/kg), administered 20 minutes before induction, produced a consistent and clinically meaningful attenuation of the HR, SBP, DBP and MAP response to laryngoscopy and endotracheal intubation compared with nebulized saline, without a single episode of bradycardia in either group. Baseline demographic, clinical and haemodynamic characteristics were well matched between groups, confirming adequate randomization; similar baseline comparability with nebulized dexmedetomidine has been reported previously.^[8,9] Our HR findings are

consistent with Kumar et al,^[2] who reported markedly lower post-intubation HR with nebulized dexmedetomidine than with control. A recent systematic review and meta-analysis of randomized trials,^[10] confirmed significant HR attenuation with nebulized dexmedetomidine across pooled studies, corroborating our primary finding at the highest level of evidence currently available, although that analysis also noted considerable heterogeneity across the small number of included trials.

The SBP attenuation observed in Group D is consistent with the magnitude of unattenuated pressor responses described by Sebastian et al,^[3] with intravenous dexmedetomidine, and the comparable efficacy of the nebulized route relative to the intravenous route reported by Singh et al.,^[1] who found equivalent haemodynamic control with fewer adverse events after nebulized administration. DBP and MAP attenuation mirrored these findings and align with data reported for nebulized dexmedetomidine by Misra et al.⁸ and Shrivastava et al,^[9] and with intravenous dexmedetomidine in hypertensive patients reported by Ismail et al.^[4] These effects parallel findings by Lee and Kim.^[12] who demonstrated significant haemodynamic attenuation with preanaesthetic dexmedetomidine in elderly hypertensive patients, supporting the drug's efficacy across at-risk subgroups.

Notably, no bradycardia occurred in either group in our trial, whereas an incidence of 12-18% has been reported with the intravenous route in earlier series. This is consistent with the head-to-head comparison by Singh et al.,¹ who found a lower tendency toward bradycardia and hypotension with the nebulized route than with the intravenous route, with haemodynamics that were overall more stable. This supports the pharmacokinetic rationale that gradual mucosal absorption after nebulization avoids the high peak plasma concentration associated with intravenous bolus dosing,^[6,7] thereby reducing vagally-mediated bradycardia.

Hypotension was numerically more frequent in Group D (12.7% vs 1.8%) though the difference was not statistically significant, and all episodes were transient and fluid-responsive; this finding warrants monitoring but does not appear to compromise the overall safety profile of the technique. PONV incidence was low and comparable between groups, likely reflecting routine antiemetic prophylaxis. POST, although numerically more frequent with dexmedetomidine (30.9% vs 18.2%), did not reach statistical significance in our sample; this contrasts with lower POST rates reported with nebulized dexmedetomidine by Thomas et al,^[11] and may reflect our smaller sample size or the aerosol deposition pattern of the compressor-mask interface used, which may favour supraglottic rather than lower-airway deposition.

Clinically, these findings support nebulized dexmedetomidine as a simple, needle-free premedication strategy that can be incorporated into routine preoperative care to reduce perioperative cardiovascular stress, particularly relevant in resource-limited settings where continuous invasive monitoring during titrated intravenous infusions may not always be feasible.

Strengths of this trial include its randomized, double-blind, placebo-controlled design; standardized induction and monitoring protocol; complete 10-minute post-intubation observation window; and 100% protocol completion with no post-randomization exclusions, in a south Indian population under-represented in the existing literature. Limitations include the relatively modest, single-centre sample; the absence of plasma dexmedetomidine level monitoring, which precluded correlation between systemic drug exposure and haemodynamic or adverse-event outcomes; and the lack of prospective registration of the trial with the Clinical Trials Registry of India or an equivalent registry before enrolment began, which we disclose transparently as a methodological limitation.

Larger, multicentric trials with pharmacokinetic sampling, dose-ranging comparisons, and longer safety follow-up are warranted to refine the optimal nebulized dexmedetomidine regimen and to clarify its adverse-event profile, particularly for hypotension and POST, relative to the intravenous route.

CONCLUSION

Preoperative nebulized dexmedetomidine (1 µg/kg), administered 20 minutes before induction, effectively attenuated the haemodynamic stress response to laryngoscopy and endotracheal intubation across all measured parameters, without causing bradycardia

and with an acceptable adverse-event profile. These findings support nebulized dexmedetomidine as a safe, effective and non-invasive premedication strategy for haemodynamic stabilization during airway instrumentation in adult patients undergoing elective surgery under general anaesthesia.

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