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Research Article

Evaluation of the Effect of Nebulized Dexmedetomidine on Attenuating the Hemodynamic Response to Intubation during Entropy-Targeted Anesthesia

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ABSTRACT

Background: Laryngoscopy and intubation cause transient hemodynamic changes within thirty seconds after intubation. Dexmedetomidine, a selective alpha 2 adrenoceptor agonist, has been used to blunt this response via routes like intravenous, intranasal, and nebulization. The efficacy of nebulized dexmedetomidine in reducing the response to laryngoscopy and tracheal intubation with the additional benefit of reducing the propofol dose was evaluated during this study. Entropy monitoring was used to achieve adequate anesthetic depth.

Methods: This prospective, randomized, and comparative study was conducted on 120 ASA 1-2 patients. Patients were nebulized with dexmedetomidine 1 µg/kg body weight in 5 ml normal saline in group D and only 5 ml normal saline in group C twenty minutes before induction of anesthesia. Anesthesia was induced with an injection of propofol under entropy guidance. Hemodynamic parameters were noted at baseline, after nebulization, immediately after intubation, and up to 10 minutes. The incidence and severity of sore throat were noted in the postoperative period.

Results: Demographics were comparable. After laryngoscopy and intubation, the increase in heart rate and blood pressure was much lower in the dexmedetomidine group compared to the saline group. Furthermore, the requirement of propofol to achieve an entropy of 40–50 and the incidence and severity of postoperative sore throats in the dexmedetomidine group were significantly lower than in the normal saline group.

Conclusion: Administration of nebulized dexmedetomidine 1 µg/kg preoperatively effectively attenuates the hemodynamic response to laryngoscopy and intubation, with more stable hemodynamics and no side effects.

Introduction

Laryngoscopy for intubation is an unavoidable stimulation that incites a sympathoadrenal response, distinguished by an elevated arterial blood pressure and heart rate (HR) [1]. Many drugs, like lignocaine [2], clonidine [3], esmolol [4], and opioids, have been used to date in order to reduce this hemodynamic stress response. The most recent addition to this list is dexmedetomidine, a selective alpha 2 adrenoceptor agonist with sympatholytic, analgesic, hypnotic, anti-sialagogue, anxiolytic, and sedative properties that enhances the stability of cardiovascular and respiratory systems [5]. Dexmedetomidine has been used to blunt the hemodynamic response via the intravenous route; however, undesirable side effects like bradycardia and hypotension were associated with

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intravenous administration [6]; therefore, other routes like intranasal [7] and nebulization [5] were tried. The nebulization route is preferred over intranasal administration due to patient comfort.

Depth of anesthesia monitoring is traditionally done by hemodynamic response. Newer monitoring modalities include entropy and bispectral index (BIS), among others, to monitor depth. The Entropy module's basic concept involves using the increase in anesthesia depth to determine the level of anesthesia [8-9]. For administration and measurement of the optimal dose of propofol, our study was done under entropy monitoring.

Very sparse literature is available on the use of entropy as a guide to determine the depth of anesthesia. Hence, the current study was designed to assess the effectiveness of nebulized dexmedetomidine in lowering the hemodynamic response to laryngoscopy and intubation under entropy-guided anesthesia.

Methods

A prospective, randomized, double-blind, and comparative study was conducted over a span of nine months in our hospital after approval by the Institutional Ethics Committee (Project-2572) and registration with the Clinical Trial Registry of India (CTRI/2024/03/063949) dated 11/03/2024. A total number of 120 American Society of Anesthesiologists (ASA) I and II patients, aged 18 to 60 years and scheduled for surgeries requiring general anesthesia, were enrolled after obtaining written informed consent. Patients with a body mass index (BMI) > 35 kg/m², upper respiratory tract infection, hepatic insufficiency, renal insufficiency, a history of smoking, exposure to household smoke, patients taking medications affecting the heart and blood pressure, and obstetric patients were excluded. The study sample was calculated based on previous research done by Kumar NR et al. [10]. All statistical interpretations were done using Statistical Package for the Social Sciences software version 21 (SSPS Inc., Chicago, USA). Using a computer-generated random number table, two groups of 60 patients each were randomly selected from a total of 120 patients undergoing elective surgery under general anesthesia with endotracheal intubation. The assigned number of patients was then sealed in an opaque, coded envelope.

Group D: The patient was nebulized with dexmedetomidine 1 µg/kg body weight in 5 ml normal saline.

Group C: The patient was nebulized with 5 ml of normal saline.

The study procedure was explained to each patient. Patients were nebulized by an anesthesia resident who was not involved in this study. Nebulization with dexmedetomidine 1 µg/kg diluted with normal saline to reach a volume of 5 ml was given to Group D patients in a sitting position twenty minutes before induction with a nebulizer and a face mask along with 100% oxygen at 6 L/min for around 10 minutes. Patients in the control group were nebulized with normal saline.

On arrival in the operation room (OR), baseline monitors were attached along with end-tidal carbon dioxide (EtCO2), RE, and SE (Carescape 750, GE Healthcare Helsinki, Finland). Readings were recorded before induction of anesthesia. Both response and state entropy were targeted to a value of around 40-50.

All patients received intravenous injections of midazolam 0.04 mg/kg and glycopyrrolate 0.2 mg as premedication. After preoxygenation for three minutes, anesthesia was induced using nalbuphine 0.1 mg/kg, intravenous 2% lidocaine 1 ml to reduce pain on injection with propofol, and an injection of 60 mg of propofol was given, followed by 20mg boluses until both response entropy (RE) and state entropy (SE) record a value of around 40-50. Succinylcholine 1.5 mg/kg was used to facilitate tracheal intubation with direct laryngoscopy. The patient was not disturbed for a period of 10 min after intubation, and vital parameters like heart rate (HR), systolic blood pressure (SBP), diastolic (DBP), and mean arterial pressure (MAP), were noted by a doctor not involved in this study at the following time points: before nebulization (Tb), after nebulization (T0), immediately after induction (T1), and 1, 5, and 10 minutes after intubation. (T2, T3, T4), and at the end of surgery prior to extubation (T5).

Thirty minutes prior to the end of the surgery, patients were given 0.1 mg/kg ondansetron and 15 mg/kg paracetamol. On completion, patients were reversed and extubated using inj. glycopyrrolate and neostigmine and shifted to the post-anesthesia care unit, where they were assessed and graded for the presence or absence of postoperative sore throat [11].

Results

Out of 136 patients enrolled, 16 were excluded (10 did not meet the inclusion criteria, 3 refused to participate, and 3 patients had their surgery postponed (Figure 1). The remaining 120 patients were randomized and distributed among the two groups. Demographic data was comparable among the groups (Table 1). The average response and state entropy achieved in group C were 44.77±1.71 and 41.12±1.98, while those in group D were 44.90±1.77 and 40.93±1.94. This difference was statistically not significant (P value = 0.615 and 0.614) (Table 2).

The primary outcome of the study was to assess the effects of dexmedetomidine nebulization on hemodynamics during laryngoscopy and intubation. We observed that the heart rate in group D after nebulization, after induction, 1, 5, and 10 minutes after intubation, and at the conclusion of surgery was lower than in group C

with a P value< 0.05 (Table 3, Figure 2). The systolic, diastolic, and mean blood pressures in the dexmedetomidine group were lower than in the control group at the same time points, and the difference was statistically significant with a P value < 0.05 (Table 4) (Figures 3-5). The secondary outcome of our study was to assess the average propofol dose used and to know the incidence of POST among two groups. The average requirement of propofol in group C was 108±19.55 mg, whereas in group D it was 95.33±23.40. The difference between the two groups was statistically significant with a P value of 0.003 (Table 2). Postoperative sore throat was present in 34 out of 60 patients in the control group, while the incidence was 20 out of 60 patients in the dexmedetomidine group, which came out to be statistically significant with a P value = 0.01. The difference in severity of postoperative sore throat among the groups was also statistically significant (P value = 0.034) (Table 5).

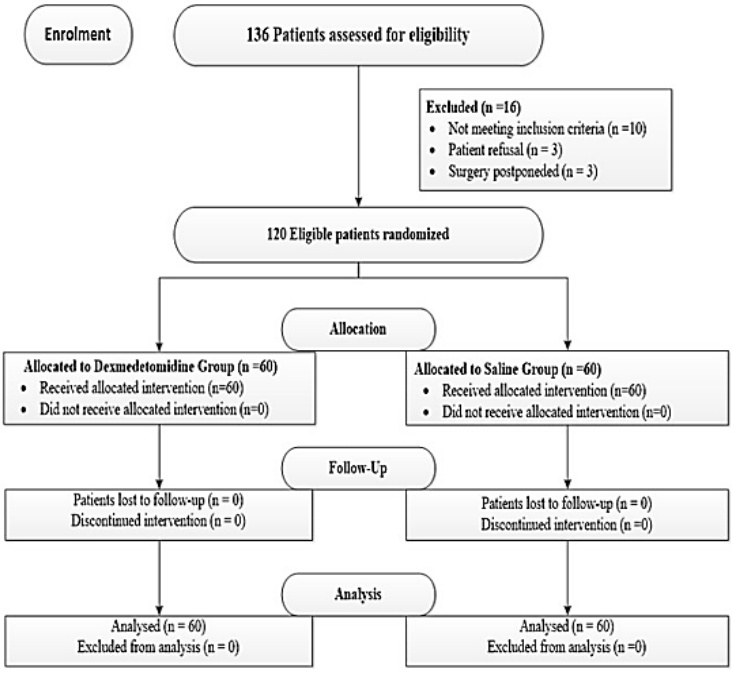

Figure 1- Consort Diagram

Table 1- Comparison of patient characteristics

	Group D	Group C	P value
Age (Years)	38.32±10.91	36.97±11.36	0.508
Sex (M/F)	26/34	26/34	1.000
Height (Meter)	1.63±0.09	1.63±0.08	0.779
Weight (Kg)	67.33±11.55	66.50±11.30	0.727
BMI (Kg/M^2)	25.16±2.08	24.81±2.05	0.274
ASA Grade I/II	28/32	22/38	0.267

Table 2- Comparison of state and response entropy achieved and dose of propofol required in each group.

	Group D	Group C	P value
Response Entropy	44.90±1.77	44.77±1.71	0.615
State Entropy	40.93±1.94	41.12±1.98	0.614
Dose of Propofol (mg)	95.33±23.40	108±19.55	0.003

Table 3- Comparison of heart rate among the groups:

Heart Rate (Bpm)	Group D	Group C	P value
Tb	85.77±6.75	85.57±4.78	0.891
T0	82.77±7.08	85.53±4.61	0.024
T1	76.48±7.27	85.67±4.61	0.001
T2	82.58±6.52	104.03±6.26	0.001

T3	79.23±6.43	88.85±3.96	0.001
T4	76.38±6.32	82.72±4.29	0.001
T5	77.38±5.83	80.7±4.29	0.001

Tb- Baseline, T0- After Nebulization, T1- After Induction, T2- 1 min After Intubation, T3- 5 min After Intubation, T4- 10 min After Intubation, T5- Before Extubation.

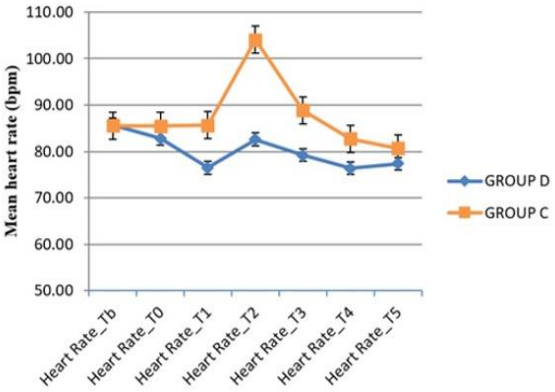

Figure 2- Comparison of heart rate among the groups

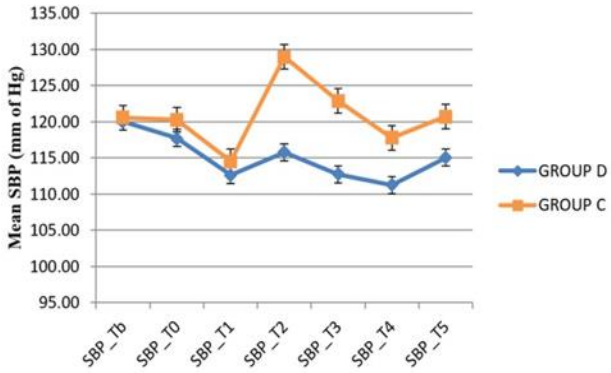

Figure 3- Comparison of systolic blood pressures

Table 4- Comparison of blood pressure among the groups

Parameter	Time	Group D	Group C	P value
Systolic Blood Pressure (mm of Hg)	Tb	120.03±10.91	120.52±10.88	0.799
	T0	117.73±10.46	120.28±9.73	0.194
	T1	112.67±11.57	114.55±9.42	0.392
	T2	115.73±11.33	129.02±9.51	0.001
	T3	112.70±6.18	122.90±8.62	0.001
	T4	111.28±6.18	117.77±9.01	0.001
	T5	115.03±7.23	120.72±7.52	0.001
Diastolic BP (mm of Hg)	Tb	76.53±8.14	78.05±8.68	0.277
	T0	74.47±8.30	78.00±8.02	0.025
	T1	70.90±8.15	73.48±7.74	0.087
	T2	74.03±7.74	86.05±8.22	0.001
	T3	71.27±5.58	82.43±8.02	0.001
	T4	70.42±4.76	75.72±7.38	0.001
	T5	74.03±6.08	77.58±7.06	0.003
Mean Arterial Pressure (mm of Hg)	Tb	90.30±9.02	92.02±9.09	0.264
	T0	88.89±8.73	92.09±8.37	0.039
	T1	84.82±9.01	87.17±8.07	0.153
	T2	87.93±8.73	100.37±8.44	0.001
	T3	85.08±5.90	95.92±7.96	0.001
	T4	84.04±4.96	89.73±7.70	0.001
	T5	87.70±6.14	91.96±6.81	0.001

Table 5- Comparison of incidence and severity of postoperative sore throat in the study groups:

Postoperative Sore Throat		Group D	Group C	P value
Incidence		33.3%	56.7%	0.010
Severity	0	66.7%	43.3%	0.034
	1	23.3%	36.7%	
	2	10.0%	20.0%	

Severity: 0- No Sore Throat, 1. The patient answered affirmatively when asked about a sore throat. 2. The patient complained of a sore throat on his/her own. 3. The patient is in obvious distress. Grading system from Rajan S, Malayil GJ, Varghese R, and Kumar L. Comparison of the usefulness of ketamine and magnesium sulfate nebulizations for attenuating postoperative sore throat, hoarseness of voice, and cough. Anesth Essays Res. 2017;11:287-93[11].

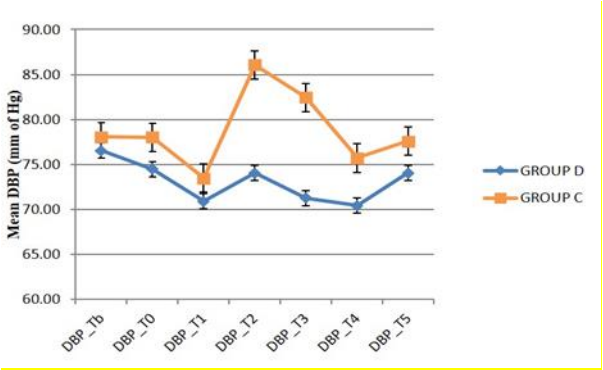

Figure 4- Comparison of diastolic blood pressures

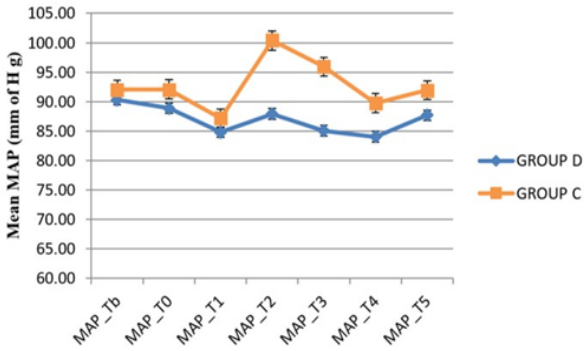

Figure 5- Comparison of mean arterial pressures

Discussion

It is well recognized that tracheal intubation and laryngoscopy are noxious stimuli that induce a stress response, leading to increased heart rate and BP and causing increased myocardial work and oxygen demand. The reason for this response is thought to be the stimulation of the mechanoreceptors present in the pharyngeal wall, epiglottis, and vocal cords. The response initiates within one minute and peaks within five minutes. The current study was conducted to evaluate the effects of dexmedetomidine nebulization on hemodynamic response to laryngoscopy and intubation during general anesthesia under entropy monitoring. Additionally, this study evaluated both the propofol-sparing effect of dexmedetomidine during induction and the incidence and severity of postoperative sore throat. According to our research, nebulization with dexmedetomidine keeps hemodynamics more stable during laryngoscopy, intubation, and throughout surgery. Patients who took dexmedetomidine showed a noticeably lower increase in SBP, DBP, and MAP at 1, 5, and 10 minutes following intubation. These outcomes are consistent with research by Shrivastava S et al., who likewise reported that the saline group required more propofol and a much greater rise in the hemodynamic measures than the dexmedetomidine group [12].

In a similar study by Kumar NR et al., a much lower increase in heart rate and BP was found in the dexmedetomidine group. They also found that dexmedetomidine resulted in a lower response entropy and state entropy and a lower requirement of propofol compared to the saline group [10].

In our study, a statistically significantly lesser rise in heart rate was observed in the dexmedetomidine group as compared to the saline group at T1, T2, T3, T4, and T5. These outcomes were similar to research by Singh V et al., who compared intravenous and nebulized dexmedetomidine and found that the intravenous group depicted a substantial decrease in heart rate and blood pressure after three minutes of treatment. Analgesic requirements and propofol consumption were comparable between the two groups. They concluded that nebulized dexmedetomidine improved hemodynamic stability and reduced the sympathetic response to laryngoscopy, although less than intravenous [13].

Misra S et al in a similar study, reported a lesser increase in heart rate at intubation and lesser doses of propofol and opioids in group D; however, unlike our study, not much difference was observed in the change in blood pressure during laryngoscopy among the two groups. This can be explained by the lower MAC of isoflurane used in the dexmedetomidine group as compared to the higher MAC in the saline group [14]. In our study, the requirement of propofol to achieve the target entropy in group C was 108±19.55 mg, whereas in group D, the average requirement came out to be 95.33±23.40 mg, which was significantly lower than group C (P value = 0.003). These findings were consistent with previously done studies [10, 12, 14].

Propofol is a commonly used inducing agent due to its safety, efficacy, and short action, but because of its inadequate analgesic qualities, a higher dosage may be required to maintain adequate depth. The addition of adjuvants in the anesthetic technique reduces the requirements of individual components and thus, their side effects. Alpha-2 agonist dexmedetomidine produces dose-dependent analgesia, sedation, anxiolysis, and sympatholysis without depressing the respiratory system. It can act as an excellent adjuvant to propofol for providing analgesia and increasing the depth of anesthesia.

In order to minimize the risk of intraoperative awareness or avoid the consequences of a propofol overdose, we have monitored the depth of general anesthesia using an Entropy monitor. Our research revealed that a substantially lower dosage of propofol was needed to provide the same level of anesthesia in individuals who received dexmedetomidine nebulization

(as measured by state and response entropy). Our findings aligned with the research done by Kumar NR et al. [10].

Walia et al. compared intravenous 1 µg/kg dexmedetomidine and 30 mg/kg magnesium sulfate with normal saline and found both these medications markedly lowered the propofol induction dose; however, the dexmedetomidine group's reduction in propofol need dose was greater, which supports the findings of the present study. The activation of alpha 2 adrenoceptors in the locus ceruleus is the cause of this reduction [15]. Kang et al. conducted a study in which they administered intravenous dexmedetomidine during general anesthesia under bispectral index monitoring. It was reported that the dexmedetomidine group had more stable hemodynamics and a much lower propofol infusion rate than the control group. These findings support the findings of the current study [16].

Both the incidence and severity of postoperative sore throat were significantly reduced in our study when comparing the dexmedetomidine group to the control group; this result is corroborated by other research [10, 14, 17].

1 µg/kg of dexmedetomidine given by nebulization reduces the chances of unwanted side effects such as bradycardia and hypotension. The nasal and buccal mucosa is responsible for the bioavailability of nebulized dexmedetomidine, which reaches up to 83%. 54 Dexmedetomidine is an extremely selective imidazole derivative that binds highly selectively to the alpha 2 receptors located in several structures, especially in the central nervous system. Dexmedetomidine causes a centrally mediated sympatholytic effect, which could possibly justify the long-lasting reduction in sympathetic tone even after a single dose [18].

Limitations

Cases with anticipated difficult airways were excluded; they were likely to have more airway manipulation and hence a greater sympathetic response. Patients with hypertension and cardiovascular diseases were excluded, who could benefit more from attenuation of the laryngoscopy response. The effect of dexmedetomidine on the requirement of drugs other than propofol, such as opioids and volatile anesthetic agents, was not assessed.

Conclusion

We conclude that administration of nebulized dexmedetomidine 1 µg/kg premedication effectively attenuates the hemodynamic response to laryngoscopy and intubation, with more stable hemodynamics during surgery, reduces the requirement of propofol to achieve entropy of 40-50, and reduces the incidence and severity of postoperative sore throat without undesirable side effects.

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