Evaluation of Nebulised Dexmedetomidine Given Pre-operatively to Attenuate Hemodynamic Response to Laryngoscopy and Endotracheal Intubation: A Randomised Control Trial

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Abstract

Background and aim
A variety of medications have been studied to reduce the hemodynamic response to laryngoscopy and intubation. Dexmedetomidine has been used intravenously in many studies to reduce the hemodynamic response to laryngoscopy and intubation. In high-risk patients, this pressor response can increase morbidity and mortality. As dexmedetomidine has a good bioavailability via the nebulisation route, we formulated this study to evaluate the effect of nebulised dexmedetomidine on the hemodynamic response to laryngoscopy and endotracheal intubation.

Methods
This is a prospective, randomised controlled trial conducted on 100 patients with the American Society of Anesthesiologists grade I and II. The primary objective of the study was to see if nebulised dexmedetomidine at a dose of 1 microgram/kg could reduce the stress reaction to laryngoscopy and intubation. The secondary objective was to study the dose sparing effect of nebulised dexmedetomidine on the amount of propofol used during induction of general anaesthesia. The study population was randomly divided into two groups: group A (n = 50) included patients nebulised with dexmedetomidine 1 microgram/kg and group B (n = 50) included patients nebulised with 5 ml saline 30 minutes before induction of anaesthesia in a sitting position.

Results
The demographics were similar in both groups. Following laryngoscopy and intubation, the systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate showed a significant increase in the control group B as compared to the treatment group A. In group A, there was attenuation in SBP (one minute = 113.2 ± 14.503, P < 0.001; five minutes = 109.86 ± 8.342, P < 0.001; 10 minutes = 114.24 ± 7.797, P = 0.010), DBP (one minute = 73.72 ± 10.986, P = 0.011; five minutes = 71.62 ± 9.934, P = 0.005; 10 minutes = 76.1 ± 8.006, P = 0.009), MAP (one minute = 86.80 ± 11.86, P = 0.001; five minutes = 84.44 ± 8.97, P = 0.006; 10 minutes = 88.72 ± 7.44, P = 0.018), and heart rate (one minute = 83.34 ± 12.325, P = 0.001; five minutes = 81.56 ± 13.33, P = 0.005; 10 minutes = 80.16 ± 14.086, P = 0.013) following laryngoscopy and intubation. Induction dose of propofol was significantly lower in the dexmedetomidine group (73 ± 19.509, P < 0.001).

Conclusion
Nebulised dexmedetomidine effectively blunts the hemodynamic response to laryngoscopy and intubation and also has a dose sparing effect on the induction dose of propofol.

Introduction
Direct laryngoscopy and intubation are associated with a hemodynamic response, which is characterised by an increase in blood pressure and heart rate. This response occurs within 30 seconds after intubation and lasts for less than 10 minutes [1]. These transient responses are normally harmless in healthy people, but they can be dangerous in patients with reactive airways, hypertension, coronary artery disease, myocardial insufficiency, and cerebrovascular disorders [2]. Numerous drugs such as opioids, beta-blockers, and intravenous lignocaine are used to attenuate this hemodynamic response.
Dexmedetomidine is an alpha-2 agonist with sedative, sympatholytic, amnestic, and analgesic actions [5]. Dexmedetomidine in various doses and routes, such as intravenous [4], intranasal [5,6], intramuscular [7], and nebulised [8,9], had been studied to reduce hemodynamic response to intubation. In paediatric patients, nebulised dexmedetomidine in doses of 1-2 microgram/kg has been found to be effective for premedication [10].

The nasal mucosa accounts for 65% of the bioavailability of nebulised dexmedetomidine, while the buccal mucosa accounts for 82% [11]. Intravenous dexmedetomidine has been associated with hypotension and bradycardia, so an alternative route of nebulisation was thought to be explored.

The primary outcome was to evaluate the role of nebulised dexmedetomidine 1 microgram/kg as a premedication in attenuating the stress response to laryngoscopy and intubation. The secondary objective was to study the dose sparing effect of nebulised dexmedetomidine on the amount of propofol used during induction of general anaesthesia.

**Materials And Methods**

This study was conducted after obtaining approval from the Institutional Ethics Committee, Rajendra Institute of Medical Sciences, Ranchi (letter number: 323). This trial was registered on the Clinical Trials Registry, India (CTRI/2021/08/035888).

**Inclusion criteria**

This study is a double-blinded randomised controlled trial. After taking informed written consent, 100 patients with the American Society of Anesthesiologists grade I and II and a normal airway undergoing elective surgery under general anaesthesia with endotracheal intubation were included in the study.

**Exclusion criteria**

Patients with anticipated difficult intubation and those requiring more than 15 seconds for intubation or more than one attempt at laryngoscopy, patients having an allergy to dexmedetomidine, taking medicines that affect the heart rate such as clonidine and beta-blockers, pregnant patients, and patients undergoing emergency surgeries were excluded from the study.

**Method**

A day before surgery, all patients were visited. They were fasted for the night before surgery and given tablet ranitidine 150 mg and tablet alprazolam 0.5 mg orally as pre-medication.

Patients were randomly divided into two groups (A and B) by computer-generated random numbers. The drug for nebulisation was prepared by an anaesthesiologist not involved in the study. Allocation concealment was done by using sequentially numbered opaque sealed envelopes, which were opened in the operating room by the anaesthesiologist who prepared the drug. Patients were taken to the operating table and all essential monitors were attached like blood pressure, heart rate, and pulse oximetry. All these parameters were continuously monitored during the nebulisation procedure. Group A received nebulisation with dexmedetomidine in the dose of 1 microgram/kg made to a total volume of 5 ml by mixing normal saline. Group B was nebulised with 5 ml 0.9% normal saline. An electric compressor nebuliser, which generated fine mist and turned the full volume to mist in 15-20 minutes, was used for nebulisation 30 minutes prior to induction of general anaesthesia in a propped up position at 45 degrees. Incidence of bradycardia, hypotension, or sedation was noted. Sedation was assessed by the Observer’s Assessment of Alertness/Sedation Scale [12]. Fall in systolic blood pressure (SBP) > 20% of the baseline was treated with an injection of mephentermine 3 mg bolus, and in case of bradycardia, i.e., heart rate < 50/minute, it was treated with IV atropine 0.6 mg bolus dose. In case of hypotension (SBP < 20% of baseline) or bradycardia (heart rate < 50/minute), nebulisation was stopped.

Application of bi-spectral index sensors was done before preoxygenation. All patients were preoxygenated for three minutes. After 1 mg midazolam and 2 microgram/kg fentanyl premedication, 1-2 mg/kg propofol was administered in 10 mg aliquots titrated to the loss of vocal responsiveness. After achieving adequate bag and mask ventilation, vecuronium 0.10 mg/kg was given, and ventilation was done with a bag and mask for three minutes. Depth of anaesthesia was achieved with isoflurane in 50% oxygen in the air to obtain a bi-spectral index of 50-60. End-tidal carbon dioxide monitoring was done and the value was maintained at 32-35 mmHg.

Anaesthesiologists with at least 10 years of experience in anaesthesia performed the intubation. Any intubation taking more than 15 minutes was excluded from the study. Direct laryngoscopy was performed and endotracheal intubation was done using an appropriate size endotracheal tube. Then controlled ventilation was started by connecting the patient to the ventilator. The patient was left undisturbed for 10 minutes and parameters such as SBP, diastolic blood pressure (DBP), mean arterial pressure (MAP), and pulse oximetry were recorded at the baseline, after nebulisation, and one, five, and 10 minutes after intubation by...
an anaesthesia resident who was not involved in the study. After the operation, all patients were given 1 gm paracetamol and 50 mg tramadol intravenously. At the end of the surgery, residual neuromuscular blockade was reversed with a 10 microgram/kg injection of glycopyrrolate and 0.05 microgram/kg neostigmine intravenously, and the trachea was extubated on meeting the extubation criteria.

Statistical testing was conducted using SPSS version 21.0 (IBM Corp., Armonk, NY). Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentages. The comparison of normally distributed continuous variables between the groups was performed using Student’s t-test. Nominal categorical data between the groups were compared using the chi-squared test or Fisher’s exact test as appropriate. P < 0.05 was considered statistically significant.

Sample size calculation
Using the statistical software G*Power version 3.1.9.2, the sample size for this investigation was computed. In a study by Sale and Shendage [13], IV lignocaine was compared to IV dexmedetomidine for attenuation of hemodynamic response to laryngoscopy and intubation. The difference in the mean of MAP from baseline (91.00 ± 7.80) and one minute after intubation (80.50 ± 7.09) was used to calculate the effect size in this study. The effect size was 0.6, the power was 90%, and the alpha error was 0.05. The sample size was determined to be 98 patients, 49 in each group.

Results
A total of 100 patients were randomised for the study, out of which 50 were nebulised with dexmedetomidine 1 microgram/kg made up to a volume of 5 ml by adding normal saline and the other 50 were nebulised with 5 ml saline.

**Mean age, mean weight, mean duration of surgery, and time for intubation**

It was observed that there was no significant difference in mean age (p = 0.920), mean weight (p = 0.377), mean duration of surgery (p = 0.645), and mean time for intubation (p = 0.709) between the two groups (Table 1).

|                        | Treatment group (n = 50) | Control group (n = 50) | P-value |
|------------------------|--------------------------|------------------------|---------|
| **Age (years)**        | 38.66 ± 13.907           | 39.28 ± 14.475         | 0.920   |
| **Weight (kg)**        | 52.2 ± 11.258            | 53.58 ± 9.305          | 0.377   |
| **Duration of surgery (hours)** | 2.1 ± 2.3               | 1.68 ± 0.728           | 0.645   |
| **Time for intubation (seconds)** | 12.26 ± 2.311          | 12.42 ± 1.95           | 0.709   |

**TABLE 1**: Comparison of mean age, mean weight, mean duration of surgery, and mean time for intubation between the two groups

**Gender distribution**

It was observed that there was no significant difference in the sex distribution of the patients when compared between the two groups (p = 0.075) (Table 2).
TABLE 2: Comparison of gender distribution

| Sex      | Treatment group | Control group | P-value |
|----------|-----------------|---------------|---------|
|          | Frequency | %  | Frequency | %  |         |
| Male     | 10       | 12% | 18        | 36% | 0.075   |
| Female   | 40       | 88% | 32        | 64% |         |
| Total    | 50       | 100% | 50        | 100% |         |

Comparison of systolic blood pressure

Table 3 shows that there is a statistically significant difference in the SBP of the two groups recorded before laryngoscopy (p = 0.019), after intubation (p = 0.007), after one minute of intubation (p < 0.001), after five minutes (p < 0.001), and after 10 minutes (p = 0.010) of intubation.

| SBP                   | Treatment group | Control group | P-value |
|-----------------------|-----------------|---------------|---------|
|                       | Mean ± SD       | Min - Max     |         |
| Baseline              | 121.96 ± 13.046 | 97 - 152      | 0.817   |
| After nebulisation    | 118.98 ± 10.281 | 94 - 147      | 0.314   |
| Before laryngoscopy   | 117.58 ± 9.609  | 100 - 143     | 0.019   |
| After intubation      | 117.42 ± 12.119 | 100 - 155     | 0.007   |
| After 1 minute of intubation | 113.2 ± 14.503 | 92 - 159     | <0.001  |
| After 5 minutes of intubation | 109.86 ± 8.342 | 92 - 125     | <0.001  |
| After 10 minutes of intubation | 114.24 ± 7.797 | 98 - 132     | 0.010   |

TABLE 3: Comparison of mean SBP at various time points between the two groups

SBP: systolic blood pressure; SD: standard deviation; Min - Max: minimum - maximum.

Comparison of diastolic blood pressure

Table 4 shows the comparison of mean DBP at various time points between the two groups under the study. It was further observed that there was a significant difference in mean DBP at time intervals before laryngoscopy (p < 0.001), after intubation (p = 0.034), after one minute (p = 0.011), after five minutes (p < 0.005), and after 10 minutes (p = 0.009) of intubation when compared between the two groups; however, at baseline, no significant difference was observed between the two groups (p = 0.201).
|                         | Treatment group         | Control group          | P-value |
|-------------------------|-------------------------|------------------------|---------|
|                         | Mean ± SD | Min - Max | Mean ± SD | Min - Max |         |
| Baseline                | 70.68 ± 8.702 | 51 - 93 | 73.32 ± 11.592 | 57 - 96 | 0.201 |
| After nebulisation      | 76.76 ± 5.854 | 63 - 86 | 74.58 ± 11.53 | 56 - 98 | 0.236 |
| Before laryngoscopy     | 76.76 ± 6.589 | 62 - 91 | 68.68 ± 12.011 | 51 - 102 | <0.001 |
| After intubation        | 75.2 ± 10.124 | 60 - 105 | 80.66 ± 14.752 | 54 - 104 | 0.034 |
| After 1 minute of intubation | 73.72 ± 10.986 | 55 - 101 | 79.18 ± 9.917 | 64 - 101 | 0.011 |
| After 5 minutes of intubation | 71.62 ± 9.334 | 48 - 86 | 77.48 ± 10.595 | 53 - 105 | 0.005 |
| After 10 minutes of intubation | 76.1 ± 8.006 | 63 - 93 | 81.38 ± 11.366 | 60 - 111 | 0.009 |

TABLE 4: Comparison of mean DBP at various time points between the two groups
DBP: diastolic blood pressure; SD: standard deviation; Min - Max: minimum - maximum.

Comparison of mean blood pressure

Table 5 shows the comparison of MAP at various time points between the two groups under the study. It was further observed that there was a significant difference in the MAP at time intervals before laryngoscopy (p < 0.047), after intubation (p = 0.042), after one minute (p = 0.001), after five minutes (p < 0.006), and after 10 minutes (p = 0.018) of intubation when compared between the two groups; however, at baseline, no significant difference was observed between the two groups (p = 0.081).

|                         | Treatment group         | Control group          | P-value |
|-------------------------|-------------------------|------------------------|---------|
|                         | Mean ± SD | Min - Max | Mean ± SD | Min - Max |         |
| Baseline                | 87.74 ± 9.29 | 66 - 112 | 88.82 ± 14.28 | 60 - 110 | 0.081 |
| After nebulisation      | 90.90 ± 6.48 | 73 - 100 | 90.26 ± 12.28 | 70 - 118 | 0.773 |
| Before laryngoscopy     | 90.40 ± 7.01 | 75 - 107 | 85.88 ± 12.27 | 67 - 119 | 0.047 |
| After intubation        | 89.28 ± 10.63 | 73 - 122 | 95.02 ± 16.56 | 48 - 130 | 0.042 |
| After 1 minute of intubation | 86.80 ± 11.86 | 67 - 120 | 94.82 ± 11.06 | 75 - 119 | 0.001 |
| After 5 minutes of intubation | 84.44 ± 8.97 | 63 - 98 | 90.18 ± 11.24 | 63 - 117 | 0.006 |
| After 10 minutes of intubation | 88.72 ± 7.44 | 75 - 106 | 93.52 ± 11.87 | 68 - 120 | 0.018 |

TABLE 5: Comparison of mean MAP at various time points between the two groups
MAP: mean arterial pressure; SD: standard deviation; Min - Max: minimum - maximum.

Comparison of heart rate

It was observed that the heart rate was attenuated in the treatment group in a statistically significant manner with the p-values before laryngoscopy (p = 0.015), after intubation (p = 0.024), after one minute (p = 0.001), after five minutes (p = 0.003), and after 10 minutes of intubation (p = 0.013) (Table 6).
| Heart rate          | Treatment group | Control group | P-value |
|---------------------|-----------------|---------------|---------|
|                     | Mean ± SD       | Min - Max     | Mean ± SD | Min - Max |         |
| Baseline            | 85.84 ± 13.764  | 55 - 111      | 89.72 ± 17.963 | 55 - 130 | 0.228   |
| After nebulisation  | 82.6 ± 11.759   | 59 - 105      | 88.74 ± 18.43 | 50 - 128 | 0.050   |
| Before laryngoscopy | 81.56 ± 11.348  | 60 - 102      | 88.28 ± 15.422 | 60 - 123 | 0.015   |
| After intubation    | 83.34 ± 12.146  | 66 - 104      | 89.22 ± 13.391 | 65 - 116 | 0.024   |
| After 1 minute      | 83.34 ± 12.325  | 58 - 105      | 91.94 ± 12.255 | 66 - 114 | 0.001   |
| After 5 minutes     | 81.56 ± 13.33   | 54 - 89       | 89.56 ± 12.591 | 65 - 118 | 0.003   |
| After 10 minutes    | 80.16 ± 14.086  | 52 - 104      | 87.4 ± 14.445  | 59 - 138 | 0.013   |

**TABLE 6: Comparison of mean heart rate at various time points between the two groups**

SD: standard deviation; Min - Max: minimum - maximum.

**Propofol used for induction**

Table 7 shows the comparison of mean propofol used for induction between the two groups. Under the treatment group, it was observed that the mean propofol used for induction was 73 ± 19.509 mg, while in the control group, the mean was 105.2 ± 14.741 mg.

|                      | Treatment group | Control group | P-value |
|----------------------|-----------------|---------------|---------|
|                      | Mean ± SD       | Min - Max     | Mean ± SD | Min - Max | Median (Q1-Q3) |         |
| Propofol used for induction (mg) | 73 ± 19.509 | 50 - 120 | 70 (60 - 90) | 105.2 ± 14.741 | 80 - 140 | 100 (100 - 120) | <0.001 |

**TABLE 7: Comparison of mean propofol used for induction between the two groups**

mg: milligram; SD: standard deviation; Min - Max: minimum - maximum; Q1 - Q3: lower quartile - upper quartile.

It was further observed that there was a significant difference in the mean when compared between the two groups (p < 0.001). Nebulised dexmedetomidine given pre-operatively significantly reduced the dose of propofol used for induction during general anaesthesia.

**Comparison of sedation**

There was no sedation in both the groups according to the Observer’s Assessment of Alertness/Sedation Scale. The level of sedation was noted in both groups after nebulisation was complete. All the patients responded readily to the name spoken in a normal tone, the speech was normal, facial expression was normal, and the eyes were clear with no ptosis. Hence, all patients in both the groups had a score of 5 on the Observer’s Assessment of Alertness/Sedation Scale after nebulisation in both the groups.

**Discussion**

In this prospective randomised study, we found significant attenuation of hemodynamic response to laryngoscopy and intubation in group A as compared to group B. There was no incidence of hypotension or bradycardia in either group A or B. This study was formulated to avoid the side effects of intravenous dexmedetomidine, i.e., hypotension and bradycardia, which are known adverse effects of intravenous dexmedetomidine.

Intubation and laryngoscopy can produce tachycardia, hypertension, laryngospasm, bronchospasm, increased intracranial pressure, and increased intraocular pressure [14]. Reid and Brace were the first to document the hemodynamic alterations that laryngoscopy and intubation cause [15]. The response begins within five seconds of laryngoscopy, peaks in one to two minutes, and recovers to normal in five minutes [14]. These alterations are normally transient, and healthy people bear them well. In patients with cardiovascular problems and cerebrovascular disease, these hemodynamic perturbations can lead to...
myocardial ischemia, ventricular dysrhythmias, ventricular failure, pulmonary oedema, as well as cerebrovascular accidents [14].

Dexmedetomidine is an alpha-2A receptor agonist. It acts on alpha-2A receptors located in locus coeruleus, the predominant noradrenergic nuclei of the upper brain stem, and it inhibits noradrenaline release. It has sedative, hypnotic, anxiolytic, sympatholytic, antiserotonergic, and analgesic properties. It has no respiratory depressant effect. Reduced sympathetic activity results from postsynaptic stimulation of alpha-2 receptors in the central nervous system, resulting in bradycardia and hypotension [16]. Atipamizole is the reversal drug for dexmedetomidine; it acts by increasing the central turnover of noradrenaline. Many studies have used intravenous dexmedetomidine to reduce the hemodynamic response to intubation; however, it has been found to cause hypotension and bradycardia [17]. Alternative routes for dexmedetomidine delivery are being investigated to avoid this. Intravenous dexmedetomidine in the doses of 0.5-1 microgram/kg has proved to be effective in various studies to decrease the intensity of hemodynamic response to intubation [18-20]. So this study was designed to study whether dexmedetomidine when given via nebulisation route can attenuate hemodynamic response to laryngoscopy and intubation or not. When given via the nebulisation route, the nasal mucosa accounts for 65% of dexmedetomidine bioavailability, whereas the buccal mucosa accounts for 82% [10].

Only two randomised controlled trials have been done to study the effect of nebulised dexmedetomidine on attenuation of hemodynamic response to laryngoscopy and intubation. The study done by Kumar et al. [8] concluded that nebulised dexmedetomidine decreases the hemodynamic response to laryngoscopy and intubation with no adverse effects. A low dose of propofol was required during induction in the treatment group.

Another study done by Misra et al. [9] concluded that nebulised dexmedetomidine decreased the increase in heart rate but not SBP during and after laryngoscopy and intubation. There was a considerable reduction in the dose of propofol required at induction of general anaesthesia in the treatment group. Misra et al. [9] found that intraoperative requirement of fentanyl and isoflurane also decreased significantly in the nebulised dexmedetomidine group.

There was significant attenuation of heart rate, SBP, DBP, and mean blood pressure at one minute, five minutes, and 10 minutes following intubation in the group of patients who received dexmedetomidine nebulisation in the present study. Nebulised dexmedetomidine has a dose sparing effect on the induction dose of propofol.

Conclusions
Nebulisation with dexmedetomidine 1 microgram/kg attenuates the hemodynamic response to laryngoscopy and intubation, without the incidence of hypotension and bradycardia. It is a new route of administration for reducing the hemodynamic response to laryngoscopy and intubation, so further research is required in this field. No sedation was observed in either group A or group B patients, according to the Observer’s Assessment of Alertness/Sedation Scale. Nebulised dexmedetomidine appears to be a promising drug to attenuate the hemodynamic response to laryngoscopy and intubation.

Additional Information
Disclosures
Human subjects: Consent was obtained or waived by all participants in this study. Institutional Ethics Committee, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand issued approval Letter number: 323. This research work was started after taking approval from the ethics committee. The Institutional Ethics Committee approved this research work on 27 July 2021 (letter number: 323). This research was registered on the Clinical Trials Registry, India (CTRI/2021/08/035888). Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that there are no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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