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Effect of Dexmedetomidine Nebulization on Attenuation of Haemodynamic Responses to Laryngoscopy: Randomized Controlled Study

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Abstract

Introduction: Dexmedetomidine is a potent and highly selective alpha (2)-adrenoreceptor agonist. It has sympatholytic and antinociceptive effects which allow hemodynamic stability during stressful condition e.g. Laryngoscopy and surgical stimulation. This study has been done to assess the efficacy of nebulization of Dexmedetomidine to obtund the sympathetic response of laryngoscopy and tracheal intubation. *Material and Methods:* The present study was conducted on 70 patients of ASA physical status I and II, aged between 18 and 50 years of either sex, scheduled for elective surgeries under general anaesthesia. The preoperative vitals of each patient [HR, SBP, DBP and MAP] was recorded in waiting room of operation theatre. The patients were randomly divided into two groups. In preoperative room/ waiting area, Group-N (Normal saline group) patients were nebulized with normal saline (5 ml) and in Group-D (Dexmedetomidine group) patients were nebulized with Dexmedetomidine solution (2 mcg/kg) 30 minutes prior the induction of anaesthesia. All patients were induced with Inj. Fentanyl 2 mcg/kg, Inj. Propofol 2 mg/kg and paralyzed with Inj. Vecuronium 0.1 mg/kg. After confirming adequate neuromuscular blockade HR, SBP, DBP and MAP were recorded; Laryngoscopy was done [keeping laryngoscopy timing < 15 seconds] & patients were intubated with standard/ adequate size endotracheal tube. Heart rate and blood pressure were recorded after intubation at 1minute interval for 5 minutes. During this time no other stimuli were given to the patient (e.g. surgical drape, catheterization, Ryle's tube etc.). The comparison was made between hemodynamic parameters obtained at pre-laryngoscopy and post laryngoscopy time period. *Result:* We found that in Group- D, the parameters were lower than the baseline value at 3 min time after intubation. However, hemodynamic variables never reached the baseline by 5 minutes time in case of Group- N. Neither bradycardia nor hypotension was observed in any of the patients. The sedation score was more in Group- D when compared to Group- N. This indicates that nebulization with Dexmedetomidine in a dose of 2 mcg/kg is effective and safe in attenuating the laryngoscopy & tracheal intubation sympathetic response.

Keywords: Dexmedetomidine Nebulization; Laryngoscopy & Intubation; Sympathetic response.

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Introduction

Dexmedetomidine is a highly selective α_2 adrenoreceptor agonist. It has remarkable pharmacological properties including sedation, anxiolysis, and analgesia with the unique characteristic to cause no respiratory depression. In addition to this, it has sympatholytic and

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antinociceptive effects which allow hemodynamic stability during stressful conditions e.g. Laryngoscopy, tracheal intubation and surgical stimulation [1]. Bradycardia and hypotension are the most predictable, frequent and manageable side effects. Dexmedetomidine seems to be quite safer drug to be used.

Efficacy of intravenous Dexmedetomidine in various doses for attenuation of sympathetic response of laryngoscopy and tracheal intubation has already been established by various studies in past. There is paucity of available data showing the effect and efficacy of nebulisation by Dexmedetomidine in obtunding stress responses during laryngoscopy and intubation.

Aims and Objectives

- To assess the safety and efficacy of Dexmedetomidine, when administered via nebulization for attenuation of stress response to laryngoscopy and intubation in adult patients.

Materials and Methods

The present study was conducted on 70 patients of ASA physical status I and II, aged between 18-50 years of either sex, scheduled for elective surgeries under general anaesthesia. Approval of the institutional ethics committee was obtained. After obtaining informed written consent from all patients,

Exclusion criteria

- Patients of ASA physical status III and above
- Patients with predicted difficult airway as well as in whom laryngoscopy time may exceed 15 seconds
- Patients allergic to study drug Dexmedetomidine
- Patients addicted to narcotics; on long term therapy of beta blockers, anxiolytics, anticonvulsants, and antipsychotics were excluded from this study.

Using a computer-generated random numbers table, all patients were randomly allocated into two groups, Group- N and Group- D, with 35 patients in each group. Baseline hemodynamic parameters were recorded before nebulization like heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP) and oxygen saturation (SpO_2) in the patient waiting area of operation theatre. Group-N patients were nebulized with Normal saline (5 ml) and Group- D patients were nebulized with Dexmedetomidine solution (2 $\mu g.kg^{-1}$), 30 minutes before the induction & laryngoscopy. Study drugs were prepared in 5 ml of 0.9% normal saline. To achieve blinding, solutions were prepared in identical syringes by an independent investigator, who was not involved in the observation or the administration of anaesthesia.

All patients were nebulized for 10 to 15 minutes in sitting position in pre-operative area by nebulizer machine. Sedation was assessed at 2, 5 and 10 minutes using Modified Observers Assessment of Alertness/Sedation scale, just after completion of nebulization (Table 6).

Later patient was shifted to operation theatre. After attaching multipara monitor, baseline HR, SBP, DBP, MAP and SpO_2 were recorded. All patients were induced with Inj. Fentanyl 2 $\mu g\ kg^{-1}$ and Inj. Propofol 2 mg kg^{-1} and paralysed with Inj. Vecuronium 0.1 mg kg^{-1}. All patients were ventilated by bag mask ventilation with 100% oxygen for 3 minutes. After confirming adequate neuromuscular blockade HR, SBP, DBP and MAP were recorded again. Then laryngoscopy was done, keeping laryngoscopy timing less than 15 seconds, patient was intubated. Time taken for laryngoscopy and intubation was monitored. If it exceeded more than 15 seconds in any case, patient was excluded from the study.

Heart rate and blood pressure were recorded after intubation at 1minute interval for 5 minutes. During this time, no other stimulus was allowed to the patient. Comparison was made between haemodynamic parameters obtained at pre-laryngoscopy and post-laryngoscopy time period. Maintenance of general anaesthesia was done with O_2 and N_2O [Ratio of 50:50%], Isoflurane and Inj. Vecuronium 0.02 mg/kg. After completion of surgery, patients were reversed, extubated and shifted to post-anaesthesia recovery room.

In case of hypotension episode, it was to be managed by incremental boluses of intravenous Mephentermine 3 mg (SBP fall >20% from the baseline) and bolus intravenous atropine 0.6 mg to reverse any incidence of bradycardia (HR < 50 beats). Statistical analyses of collected data were carried out by software SPSS latest version. Results on categorical measurements are presented in number (%) and results on continuous measurements are presented as mean ± SD. Significance was assessed at 5% level of significance.

Results

Both groups were comparable in their demographic parameters [Table 1]. The baseline HR, SBP, DBP and MAP were comparable in both the study groups. Sympathetic response to intubation i.e. increases in HR, SBP, DBP and MAP was recorded at 2 minutes post-intubation time period point in both the groups. In Group-D, vital parameters were back to near the baseline values by 3minutes. In Group- N [where patients were nebulized with normal saline] haemodynamic variables never reached the baseline by 5 minutes post intubation time period point. Patients in Group- N had statistically higher values of hemodynamic parameters like HR, SBP, DBP and MAP after intubation at all time intervals in comparison to patients of Group- D. [Table 2, 3, 4, 5]. The attenuation of haemodynamic response was better in Group- D when compared with Group- N. The hemodynamic variables reaching the baseline value at 3 min after intubation in Group- D clearly indicates that nebulization with dexmedetomidine in a dose of 2 $\mu g.kg^{-1}$ was effective in obtunding the sympathetic response of intubation. There were no incidence of bradycardia and hypotension in any of the patients after nebulization of Dexmedetomidine in the dose of 2 $\mu g.kg^{-1}$. Patients in group- N were not sedated (sedation score was 6). The sedation scores were always more in Group- D, at all time intervals when compared to Group- N. Sedation score was never < 3 in Group- D and patients were easily arousable [Table 7]. SpO_2 never fell below 95% in any of the patient of either group.

Table 1: Demography of Patients

Parameters	Group- D	Group- N
Total no. of patients	35	35
Age (yrs) Mean ± SD	36.50 ± 4.33	32.50 ± 6.12
Weight (Kg) Mean ± SD	63.23 ± 1.46	59.78 ± 3.81
Male (%)	37.14% (13)	51.42% (18)
Female (%)	62.85% (22)	48.57% (17)
ASA I (%)	48.57% (17)	42.85% (15)
ASA II (%)	51.42% (18)	57.14% (20)

Table 2: Comparison of Heart Rate

Time period of Heart Rate	Group- D Heart Rate	Group- N Heart Rate	p value
Baseline (Before nebulization)	80.40 ± 05.67	81.50 ± 05.30	0.4047
1 min	86.47 ± 13.46	94.17 ± 12.22	0.14
2 min	88.65 ± 13.45	98.11 ± 11.06	0.002
3 min	86.54 ± 13.51	98.40 ± 10.23	0.000
4 min	86.45 + 13.46	93.25 ± 10.11	0.020
5 min	84.48 ± 13.50	91.22 ± 9.89	0.020

Table 3: Comparison of Systolic Blood Pressure

Time period of SBP	Group- D SBP	Group- N SBP	p value
Baseline (Before nebulization)	114.28 ± 13.08	120.00 ± 13.17	0.73
1 min	124.60 ± 13.87	133.74 ± 11.24	0.003
2 min	126.80 ± 13.91	137.08 ± 10.68	0.001
3 min	124.60 ± 13.87	137.40 ± 09.81	0.000
4 min	124.60 ± 13.87	132.25 ± 09.70	0.009
5 min	122.57 ± 13.87	130.22 ± 09.44	0.009

Table 4: Comparison of Diastolic Blood Pressure

Time period of DBP	Group- D DBP	Group- N DBP	p value
Baseline (Before nebulization)	75.42+13.00	80.28+12.80	0.120
1 min	86.88 + 14.00	93.17 + 11.82	0.046
2min	89.08 + 14.01	97.11 + 10.70	0.009
3 min	86.88 + 14.00	97.40 + 09.81	0.001
4 min	86.88 + 14.00	92.25 + 09.70	0.066
5 min	84.88 + 14.03	90.22 + 09.44	0.066

Table 5: Comparison of Mean Arterial Pressure

Time period of MAP	Group- D MAP	Group- N MAP	p value
Baseline (Before nebulization)	88.77 + 13.07	91.80 + 12.39	0.323
1 min	100.22 + 14.16	104.40 + 11.77	0.184
2 min	102.57 + 14.02	108.62 + 10.14	0.043
3 min	100.28 + 14.15	108.80 + 09.46	0.004
4 min	100.25 + 14.14	103.77 + 09.22	0.223
5 min	098.22 + 14.17	101.45 + 08.93	0.258

Table 6: Modified Observer's Assessment of Alertness/Sedation Scale

Score	Description of Score
0	Does not respond to noxious stimulus
1	Does not respond to mild prodding or shaking
2	Responds only mild prodding or shaking
3	Responds only after name is called loudly or repeatedly
4	Lethargic response to name spoken in normal tone
5	Appear asleep but respond readily to name spoken in normal tone
6	Appear alert and awake, response readily to name spoken in normal tone

Table 7: Mean Modified Observer's Assessment of Alertness / Sedation Score

Mean Sedation score Alertness / Sedation Score	Group- D	Group- N
Baseline	6	6
At 2 min	5.77	6
At 5 min	4.51	6
At 10 min	3.45	6

Discussion

Laryngoscopy and tracheal intubation stimulates sympathetic system and manifest as wide range of stress responses such as tachycardia, hypertension, laryngospasm, bronchospasm, raised intracranial pressure and intraocular pressure due to activation of sympathetic system [1]. Reid and Brace had very well described the hemodynamic repercussions of laryngoscopy and intubation [2]. The hemodynamic response gets initiated within 5 seconds of direct laryngoscopy, peaks in 1-2 minutes and returns to baseline values by 5 minutes [3]. These changes are usually short-lived and well tolerated by healthy patients. In patients with co-morbidities like cardiovascular and cerebrovascular disease, it may lead to serious adverse events such as myocardial ischemia, ventricular dysrhythmias, cerebrovascular accidents and pulmonary edema. [4] Various drugs have been proved to be useful in attenuating the noxious response of laryngoscopy, such as Lignocaine, Opioids, Nitroglycerine, calcium channel blockers such as Diltiazem and β-blockers such Esmelol [5,6,7,8]. The α_2-receptor agonists like Clonidine and Dexmedetomidine are the latest addition in this list. The α_2-receptor agonists mediate their action through α_2 A receptors located in locus caeruleus. Sedation and hypnosis are produced by inhibition of noradrenaline release due to presynaptic activation of α_2 A receptors in the locus caeruleus. Bradycardia and hypotension are caused by decreased sympathetic activity due to post-synaptic activation of α_2 receptors in central nervous system [9]. Dexmedetomidine is eight times more potent α_2 receptor agonist than Clonidine. The elimination half-time of Dexmedetomidine is 2 hours. Thus, action of Dexmedetomidine is short-lived [10,11].

Various studies have been done and published to study the efficacy of Dexmedetomidine in different doses, through various routes such as intravenous, intra-thecal, epidural, intra-nasal etc. Numerous studies have shown that Dexmedetomidine can be successfully used intra-nasally in paediatric patients for sedation and haemodynamic stability during intraoperative as well as postoperative period with smoother recovery. Sheta SA *et al.* has compared intra-nasal Dexmedetomidine versus Midazolam for premedication in children and found that intra-nasal Dexmedetomidine (1 $\mu g.kg^{-1}$) is an effective and safe alternative for premedication in children [12]. Zanaty OM *et al.* had done comparative evaluation of nebulized Dexmedetomidine, nebulized Ketamine, and their combination as premedication for outpatient paediatric dental surgery and concluded that nebulized Dexmedetomidine produced satisfactory sedation and smoother induction of general anaesthesia [13]. In a randomized trial, Gyanesh and colleagues compared intra-nasal Dexmedetomidine (1 $\mu g.kg^{-1}$), Ketamine (5 $mg.kg^{-1}$), and placebo (saline) in 150 children between 1 to 10 years undergoing MRI for intravenous cannula placement and documented that children of both nebulized Dexmedetomidine and Ketamine group were calm and co-operative while intravenous cannula placement [14]. Jia and colleagues studied the premedicant effects of various combinations of intra-nasal Dexmedetomidine combined with oral Ketamine in children and concluded that administration of 2 $\mu g.kg^{-1}$ intranasal Dexmedetomidine and 3 mg.kg-^{1} oral Ketamine was the optimal combination to facilitate separation from parents and intravenous cannula placement or facemask acceptance [15].

The main disadvantage of the intra-nasal route of administration of drug is transient nasal irritation and sometimes coughs. To overcome this disadvantage, administering the drug via nebulization as atomized spray was a better idea. This resulted in maximum surface area coverage with a thin layer of drug, less drug loss to the oropharynx, better patient acceptability, and improved clinical effectiveness [16]. Studies had shown that nebulized Dexmedetomidine administration may allow rapid drug absorption through nasal, respiratory, and buccal mucosa, which allow bioavailability of 65% through nasal mucosa and 82% through buccal mucosa [17].

Numerous studies have been done to prove the efficacy of intravenous Dexmedetomidine in different doses for attenuation of stress response of laryngoscopy for intubation. Sulaiman S *et al.* has suggested in their study that administration of Dexmedetomidine 15minutes before laryngoscopy and intubation, in the dose of 0.5 $\mu g.kg^{-1}$, in patients with coronary artery disease posted for elective off pump coronary artery bypass surgery was effective in obtunding the laryngoscopic response [18]. Menda F *et al.* has also concluded that in attenuating hemodynamic response of endotracheal intubation in patients undergoing fast-track CABG, Dexmedetomidine in the dose of 1 $\mu g.kg^{-1}$, as an adjunct to anesthetic induction is very effective [19]. Sebastian B *et al.* has suggested that Dexmedetomidine in a dose of 0.75 $\mu g.kg^{-1}$ intravenous is the optimal dose to obtund sympathetic response evoked by laryngoscopy and endotracheal intubation [20]. High sedation scores and episodes of apnea were documented in different

studies by various authors' after intravenous bolus administration of Dexmedetomidine in the dose of 1-2 $\mu g.kg^{-1}$ [21]. In our study, we have administered Dexmedetomidine in high dose i.e. 2 $\mu g.kg^{-1}$ but through nebulization rather than intravenous bolus. To eliminate confounding factor and to decrease noxious response to laryngoscopy, we have limited laryngoscopy time to 15 seconds in the study.

Conclusion

- Dexmedetomidine nebulization in dose of 2 $\mu g.kg^{-1}$, 30 minutes prior the laryngoscopy and intubation is effective in neutralizing sympathetic response of laryngoscopy and tracheal intubation.
- Dexmedetomidine nebulization in dose of 2 $\mu g.kg^{-1}$ is devoid of adverse effects like bradycardia and hypotension.

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