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COMPARISON OF TWO DIFFERENT DOSES OF DEXMEDETOMIDINE IN ATTENUATING CARDIOVASCULAR RESPONSES DURING TRACHEAL INTUBATION

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ABSTRACT

Background: Direct laryngoscopy and endotracheal intubation are the most frequently performed procedure. The noxious stimuli generated by the process of intubation leads to a period of extreme hemodynamic stress which is accompanied by intense sympathetic activity. This response mechanism to laryngoscopy and orotracheal intubation is somatovisceral reflexes.

Materials and Methods: In present study, 70 patients of ASA I, II of age 18 to 45 years were randomly divided in to two groups of 35 each. Group A received loading dose of 1 μg/kg body weight of dexmedetomidine in 10 ml saline over 10 min intravenously before induction. Group B received a loading dose of 0.5 μg/kg body weight of dexmedetomidine in 10 ml saline over 10 min intravenously before induction. Both the groups were administered standard general anaesthesia and requirement of Propofol was noted as an induction agent. Heart rate, blood pressure (systolic, diastolic and mean arterial pressure) were compared at baseline, 2 min, 5 min, 10 minutes (SD2, SD5, SD10) after study drugs administration, before induction (BI), after induction (AI), 1 minute (T1), 2 minutes (T2), 5 minutes (T5) and 10 minutes (T10) after laryngoscopy and intubation in both groups.

Results: Maximum number of male in both groups, Group A has 50% and Group B has 71.4%. The mean age in Group A and B were 40.43±5.54 and 39.54±6.59 respectively with a P value of 0.537.

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

Conclusions: Injection Dexmedetomidine 1µg/kg provides effective and complete attenuation of pressure response to laryngoscopy and endotracheal intubation as premedication with decreased requirement of inj. Propofol for induction without any side effects.

Keywords: Dexmedetomidine, Endotracheal intubation, Hemodynamic, Laryngoscopy, Premedication

INTRODUCTION

Laryngoscopy and endotracheal intubation is a commonly used measure for the maintenance of a secure airway during general anesthesia and it has specific indications. [1] The noxious stimuli generated by the process of intubation leading to a period of extreme hemodynamic stress which is accompanied by intense sympathetic activity. [2] Direct laryngoscopy and endotracheal intubation are the most frequently performed procedures, but their clinical benefits are not without a few undesirable effects due to afferent vagal stimulation and an efferent sympathoadrenal response. [3] These response mechanisms to laryngoscopy and orotracheal intubation is somatovisceral reflexes. [4]

Proprioceptors at the base of the tongue are stimulated during laryngoscopy leads to impulse dependent increases of systemic blood pressure, heart rate, and plasma catecholamine concentrations. Subsequent orotracheal intubation and passage of tube recruits additional receptor that elicit augmented hemodynamic and epinephrine responses as well as some vagus mediated inhibition of the heart. [5] The magnitude of response is directly proportional to the force and duration of laryngoscopy. [6] The response is initiated within 5 s of laryngoscopy, peaks in 1–2 min and returns to normal levels by 5 min. This is called vascular contraction reflex. [7] These changes are usually short lived and well tolerated by normal patients. However, in patients with cardiovascular disease, it can incite harmful effects such as myocardial ischemia, ventricular dysrhythmias, ventricular failure, and pulmonary edema. It can also lead to cerebrovascular accidents in susceptible patients. [8] The circulatory responses evolved by endotracheal intubation is not adequately suppressed by intravenous anesthetic induction agents. [9]

Alpha-2 agonists such as dexmedetomidine and clonidine reduce operational stimulus during surgery which is caused by sympathetic outflow and decreases cardiovascular behavior. [10] These drugs decrease sympathetic activity, which are beneficial for the cases. [11] Its hemodynamic effects are predictable and dose dependent. Dexmedetomidine, at clinically effective dosages, does not depress respiration, and therefore does not interfere with extubation. This pharmacological profile renders it suitable for premedication for general anesthesia in intravenous doses varying from 0.25 to 1 µg/kg for the attenuation of intubation responses, but the optimal dose not yet established. [12] Our study is to assess the effect of different doses of dexmedetomidine on hemodynamic response during laryngoscopy and tracheal intubation in surgeries at the Department of Anaesthesiology.

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

Aims: The aim of the study is to assess the optimal dose of dexmedetomidine for the purpose of attenuation of hemodynamic response during laryngoscopy and tracheal intubation.

MATERIAL AND METHODS

A prospective, comparative and randomized study was carried out in the Department of Anaesthesiology at Tertiary Care Teaching Hospital over a period of 1 year. A written informed valid anesthesia consent was obtained and explaining regarding drug and procedure in details to patients of ASA I, II of elective surgeries under general anesthesia were selected. They were divided in to two groups.

a. Group A received loading dose of 1 μg/kg body weight of dexmedetomidine in 10 ml saline over 10 min intravenously before induction
b. Group B received a loading dose of 0.5 μg/kg body weight of dexmedetomidine in 10 ml saline over 10 min intravenously before induction

Inclusion criteria were patients with mallampatti grade I, age group 18-60 Years and elective surgeries. Exclusion criteria were patients with difficult airway, obesity, emergency, and history of allergy to any drugs, pregnancy and systemic diseases (i.e. HT/DM/Renal/CNS/cardiac/RS disease). If laryngoscopy and intubation period exceeds more than 15 seconds, patients were excluded from study.

Detailed preanesthesia checkup, airway assessment and all necessary investigations (Blood, urine, ECG and Radiology) were carried out a day before surgery. Patients were kept nil by mouth for 10 hours before surgery. They were kept in calm, comfortable and peaceful preoperative room. Heart rate, Blood pressure (SBP, DBP and MAP), SpO2, respiratory rate was noted. I.V. line secured with 18 G cannula and inj. DNS was started. At operative room, HR (ECG), SBP, DBP and MAP recorded via multipara monitor Drager Vista 120, referred as baseline.

Patients were premedicted with Injection Ondansetron 4 mg iv. After 10 minutes, Study drug was administered according to groups and heart rate, blood pressure (SBP, DBP, MAP) observed at 2 min, 5 min and 10 minutes interval after study drug administration, referred as SD2, SD5 and SD10 respectively. Before induction (BI) parameters noted. Patients were preoxygenated for 3 minutes. Induction was done with injection Propofol in 10 mg/ml incremental dose till loss of eye reflexes. Endotracheal intubation was facilitated with inj. Suxamethonium 1.5mg/kg. Heart rate, systolic and diastolic blood pressure and mean arterial pressure recorded and referred as after induction(AI) value. Here required dose of inj. Propofol for induction was noted. Laryngoscopy performed with appropriate size of MacIanotosh blade, lasting not more than 15 seconds and intubation was performed with endotracheal tube.

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

Hemodynamic parameters in terms of Heart rate, systolic and diastolic blood pressure, mean arterial pressure observed and recorded at 1 min, 2 min, 5 min and 10 minutes interval after laryngoscopy and intubation, referred as T1, T2, T5 and T10. Anesthesia was maintained on 50% O2, 50% N2O, 1% Savoflurane and injection Vecuronium bromide 0.008 mg/kg immediate after intubation.

No any surgical or other procedure allowed till 10 minutes of intubation. We had decided to end study after 10 minutes of intubation with administration of inj. Fentanyl 2 µg/kg as analgesic. We also observed and assessed any complication or side effects like hypotension (blood pressure 25% of baseline), bradycardia (>60 beats/ minute), arrhythmias, bronchospasm or any other in relation to drug or procedure.

Statistical analysis

It is performed using "unpaired student t-test". p value was calculated using software. p value < 0.01 indicates highly significant difference. p 0.05 means no significant difference between two groups.

Result

In table 1, maximum number of male in both groups, Group A has 50% and Group B has 71.4%.

Table-1: Gender distribution of patients

Gender	Group A		Group B	
	No	**%**	**No**	**%**
Male	35	50	50	71.4
Female	35	50	20	28.6
Total	**70**	**100.0**	**70**	**100.0**

Table-2: Age distribution of patients

Age in years	Group A		Group B	
	No	**%**	**No**	**%**
<20	7	10	8	11.4
21-30	12	17.1	15	21.4
31-40	21	30	18	25.7
41-50	20	28.6	20	28.6
51-60	10	14.3	9	12.9
Total	**70**	**100.0**	**70**	**100.0**
Mean ± SD	40.43±5.54		39.54±6.59	

*data are expressed as Mean± standard deviation, p=0.436.

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

In table 2, the mean age in Group A and B were 40.43±5.54 and 39.54±6.59 respectively with a P value of 0.436.

Table-3: Comparison of types of surgical procedure in study groups

Surgery	**Group A**		**Group B**	
	No	**%**	**No**	**%**
Thoracic spine procedures	7	10	10	14.3
Cervical spine procedures	28	40	25	35.7
Lumbar spine procedures	35	50	35	50
Total	**70**	**100.0**	**70**	**100.0**

The types of surgery included lumbar spine surgeries (50% and 50% in Group A and B respectively), cervical spine surgeries (40% and 35.7% in Groups A and B respectively), thoracic spine surgeries (10%, 14.3% in groups A, B respectively) and were comparable between the groups. The average duration of surgery was 153.53±14.53 and 164.53±14.74 minutes in Groups A and B respectively which was comparable, with a P value of 0.462 in table 3.

Table 4: Comparison of changes in mean Heart Rate (HR) between Group A and Group B

Time	**Group A Mean ± SD**	**Group B Mean ± SD**	**P- Value**
Base	85.74 ± 7.54	85.44 ± 7.44	0.534
5 min with ongoing drug infusion	67.53 ± 5.34	77.25 ± 5.23	<0.0001
at completion of drug infusion	61.55 ± 4.23	73.88 ± 5.32	<0.0001
during induction	70.75 ± 5.16	68.85 ± 4.43	0.357
during intubation	77.54 ± 5.81	74.44 ± 5.98	0.063
1 min after intubation	70.54 ± 5.73	70.44 ± 5.29	0.073
5 min after intubation	71.41 ± 5.17	64.19 ± 5.75	<0.0001
10 min after intubation	67.71 ± 5.53	54.36 ± 5.33	<0.0001

Mean HR in Group A was 85.74 ± 7.54 per min and in group B it was 85.44 ± 7.44 per min at baseline level, which was comparable ($p>0.05$). At 5 minutes and 10 minutes of drug infusion, both Group A and Group B had fall in mean HR, but Group B had statistically significant fall in HR as compared to Group A ($p<0.05$). During induction, during intubation and at 1 minute after intubation, fall from baseline HR value was noted and this fall remained to be statistically insignificant between both group. ($p>0.05$). Maximum fall in mean HR was observed at 10

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

minutes after intubation in Group A and it was observed in Group B at 10 minutes of drug infusion in table 3.

Table 5: Comparison of changes in mean systolic blood pressure (SBP) between Group A and Group B

Time	Group A Mean ± SD	Group B Mean ± SD	P- Value
Base	133.75 ± 11.4	132.83 ± 11.4	0.536
5 min with ongoing drug infusion	123.44 ± 9.3	102.93 ± 9.5	<0.0001
at completion of drug infusion	121.65 ± 9.2	97.65 ± 7.8	<0.0001
during induction	119.55 ± 7.7	99.65 ± 5.8	<0.0001
during intubation	107.45 ± 7.7	107.77 ±5.4	0.041
1 min after intubation	106.63 ± 7.3	106.63 ± 6.2	0.641
5 min after intubation	97.23 ± 6.9	97.21 ± 5.4	0.364
10 min after intubation	97.77 ± 7.9	94.2 ± 5.2	<0.0001

Baseline SBP between two groups was comparable and found insignificant ($p>0.05$). There was fall in SBP from baseline value in group A while drug infusion was going on, while Group B showed transient rise from baseline value in SBP at 1 minutes of drug infusion which was statistically insignificant difference. The maximum fall in SBP in both groups was observed at 10 minutes following intubation, in group A and group B respectively, and this difference was also statistically highly significant ($p<0.0001$). Neither of the group showed deviation in SBP beyond 30% of the baseline value.

Table 6: Comparison of changes in mean Diastolic blood pressure (DBP) between Group A and Group B

Time	Group A Mean ± SD	Group B Mean ± SD	P- Value
Base	87.63 ± 10.7	87.63 ± 10.5	0.328
5 min with ongoing drug infusion	72.66 ± 8.2	87.66 ± 9.2	<0.0001
at completion of drug infusion	67.87 ± 8.2	79.65 ± 8.4	<0.0001
during induction	63.43 ± 8.2	78.65 ± 8.9	<0.0001
during intubation	74.82 ± 9.7	77.94 ± 8.3	0.0025
1 min after intubation	72.75 ± 8.5	76.98 ± 8.8	<0.0001
5 min after intubation	67.98 ± 9.9	73.84 ± 6.5	<0.0001
10 min after intubation	67.84 ± 8.6	61.73 ± 5.7	<0.0001

In table 6, the difference in mean DBP between two groups was statistically insignificant ($p>0.05$). Statistically significant decrease from baseline in DBP was observed in Group A at 5 and 10 minutes of drug infusion as compared to increase from baseline which was observed in Group B. ($p < 0.05$).

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

DISCUSSION

The results of the present study show that the preinduction administration of a single dose of dexmedetomidine of 0.5 mg/kg IV resulted in significant attenuation of cardiovascular responses to laryngoscopy and TI. In contrast to the previous studies where dexmedetomidine in a dose range of mg/kg was used, we decided to use 0.5 mg/kg because, in a preliminary study using a dose of 1 mg/kg, we observed significant bradycardia and hypotension requiring pharmacological intervention in the majority of our patients. A search of the available literature revealed few studies evaluating the role of lower doses of dexmedetomidine (0.5e0.6 mg/kg) in attenuation of pressor responses. [13]

Dexmedetomidine has been shown to distinctly portray nonlinear concentration-dependent pharmacokinetics leading to a biphasic blood pressure response. [14] At a higher concentration following a bolus administration, it stimulates peripheral a2 receptors of vascular smooth muscles, causing a transient increase in blood pressure and systemic vascular resistance. Afterward, as the concentration decays, the central sympatholytic effect (acting on the brainstem, medullary nuclei, and hypothalamus) predominates by activation of postjunctional vascular a2 receptors, causing a decrease in blood pressure and cardiac output. [15] It also causes bradycardia due to central sympatholysis with a resultant unopposed vagal tone and possibly due to presynaptic-mediated diminution of noradrenaline release. [16] In our study, dexmedetomidine was administered as a single low-dose infusion (0.5 mg/kg) over a period of 10 minutes. We avoided bolus administration of the study drug and preferred slow infusion, to circumvent the initial undesirable vasoconstrictor effects. We observed that by administering the drug as a continuous infusion over a definite and prolong period of time, this initial hemodynamic response can be abolished.

In the present study, in the dexmedetomidine group, the HR was significantly lower than the baseline values at all time intervals of the study (pre- and postinduction, and up to 15 minutes postintubation), compared to the placebo group. Remarkably, the maximum percentage increases in the HR from the preintubation values seen at 1 minute and 3 minutes were, respectively, 19.6% and 8.14% less in the dexmedetomidine group, as compared to the placebo group (12.96% and 11.23% in the dexmedetomidine group vs. 32.57% and 19.37% in the placebo group, respectively). This significant attenuation of rise in the HR in response to TI persisted until 3 minutes postintubation; thereafter, the results were comparable in both intra- and intergroup comparison.

In the dexmedetomidine group, SBP, DBP, and MBP were significantly lower than the baseline values at all time intervals of the study (pre- and postinduction, and up to 15 minutes postintubation), whereas there was a significant rise in SBP, MBP, and DBP 1 minute postintubation in the placebo group. The maximum percentage increases in SBP, DBP, and MBP at 1 minute postintubation were significantly lesser in the dexmedetomidine group than in the

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placebo group, thereby showing that dexmedetomidine significantly attenuated the pressor response that was observed until 5 minutes postintubation. Pressor response to TI is attributed to the rise in plasma catecholamine, with the concentration being maximum at 1 minute and persisting for 3 minutes, and we observed significant attenuation of this response with a lower dose of dexmedetomidine.

Various studies have used higher dosages of dexmedetomidine (1e2 mg/kg) and observed significant attenuation of pressor response to TI. [17] Many among the aforesaid studies consistently reported biphasic response of initial transient hypertension (vasoconstrictive effect of drug) followed later by severe hypotension and bradycardia (central sympatholytic effects) and/or respiratory depression (action on postsynaptic a2-adrenoceptors located in the locus coeruleus). [18]

Kunisawa administered dexmedetomidine as an initial dose (1.0 mg/kg for 10 minutes), followed by a continuous infusion (0.7 mg/kg/h) for 15 minutes prior to induction. Remarkably, they did not observe any significant hypotension or bradycardia, or difference in the frequencies of pharmacological interventions in any of the three study groups, which might be because of factors such as the stringent criterion for administration of a vasoactive agent (SBP 70 mmHg) or the lack of any premedication drugs.11 Bajwa observed a fall in oxygen saturation up to 94e95% in the dexmedetomidine group, after the completion of dexmedetomidine infusion (1 mg/kg in 20 minutes). Yildiz observed significant sedation (with a short period of apnea in 3 cases) and a fall in SpO2 values immediately after drug infusion (1 mg/kg in 5 minutes), although SpO2 values remained > 95% at all time intervals. Lawrence et al9 administered a single preinduction IV dose of dexmedetomidine of 2 mg/kg (given over 5 minutes), and observed that most of the patients, who also received atropine premedication, were deeply sedated (Ramsay score 4e5) and had a higher incidence of hypotension and bradycardia.

Very few investigators have studied the effect of smaller doses of dexmedetomidine (0.5e0.6 mg/kg IV) on sympathoadrenal responses after TI. [19] Results of the present study are in agreement with these studies that reported that after TI, the maximum increases in SBP, DBP, and HR were significantly lesser with lower doses of dexmedetomidine. [20] In addition, Jaakola also reported a significant reduction in plasma noradrenaline concentration when compared to the placebo group. Sulaiman also observed similar results while evaluating the effects of a single low dose of dexmedetomidine (0.5 mg/kg, slow IV infusion for 10 minutes, 15 minutes prior to TI) in patients with coronary artery disease, undergoing off-pump coronary artery bypass grafting

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

CONCLUSION

Dexmedetomidine used as an infusion in the loading dose of 0.5 μg/kg is therapeutically as effective as when used in the dose of 1.0 μg/kg in providing good intubating conditions and blunting the hemodynamic response to intubation for better anaesthetic results. A smaller dose is not only more cost-effective, but it also avoids adverse effects including hypotension and bradycardia, which are common with the greater dose of 1 μg/kg dexmedetomidine infusion.

REFERENCES

1. Prays RC, Green LT, Meloche R, Foex P. Studies of anaesthesia in relation to hypertension II. Haemodynamic consequences of induction and endotracheal intubation. Br J Anaesth. 1971;43(6): 531-47.
2. Fox EJ, Sklar GS, Hill CH, Villanue Var, King BD. Complications related to the pressure response to endotracheal intubation. Anaesthesiology. 1977; 47(6):524-25.
3. Bruder N, Ortega D, Granthil C. Consequences and prevention methods of hemodynamic changes during laryngoscopy and intratracheal intubation. Ann Fr Anesth Reanim. 1992;11(1);57-71.
4. Steeds C, Harris L, Greifenstein F, Elder J, Dripps RD. Reflex circulatory responses to direct laryngoscopy and intubation under general anaesthesia. Anaesthesiology. 1951;12(5):556-66.
5. Michael JS, Chang FL, Ho ST. Anaesthetic premedication: New horizons of an old practice. Acta Anesthesiologica Taiwainica. 2014;52(3):134-142.
6. Khan FA, Ullah H. Pharmacological agents for preventing morbidity associated with the haemodynamic response to tracheal intubation. Cochrane Database Syst Rev. 2013;7:CD004087.
7. Ebert JP, Pearson D, Gelman S, Harris C, Bradley EL. Circulatory response to laryngoscopy. The comparative effects of placebo, Fentanyl and Esmolol. Canadian J anaesthesia. 1989;36(3 pt. 1):301-6.
8. Gulabani M, Gurha P, Dass P, Kulshreshtha N. Comparative analysis of efficacy of lignocaine 1.5 mg/kg and two different doses of Dexmedetomidine (0.5 μg/kg and 1 μg/kg) in attenuating the hemodynamic pressure response to laryngoscopy and intubation. Anaesth essays Res. 2015;9(1):5-14.
9. Hassal HG, El-Sharkway TY, Renck H, Mansour G, Fouda A. Hemodynamic and catecholamine responses to laryngoscopy with vs. without endotracheal intubation. Acta Anaesthesiol Scand 1991;35:442-7.
10. Rose DK, Cohen MM. The airway: Problems and predictions in 18,500 patients. Can J Anaesth 1991;41:372-83.
11. Henderson J. Airway management in the adult. In: Miller RD, editor. Miller's Anesthesia. 7th ed. Philadelphia, PA: Churchill Livingstone; 2010. p. 1573-610.

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

12. Prys-Roberts C, Greene LT, Meloche R, Foex P. Studies of anaesthesia in relation to hypertension. II. Haemodynamic consequences of induction and endotracheal intubation. Br J Anaesth 1971;43:531-47.
13. Hasan A, Chhaya A, Upadhayaya RM. A comparative study of effect of two different doses of dexmedetomidine for attenuating the haemodynamic response of laryngoscopy and endotracheal intubation. Int J Biomed Res 2016;7:153-8.
14. Laudenbach V, Mantz J, Lagercrantz H, Desmonts JM, Evrard P, Gressens P. Effects of alpha (2)-adrenoceptor agonists on perinatal excitotoxic brain injury: Comparison of clonidine and dexmedetomidine. Anesthesiology 2002;96:134-41.
15. Kanazi G, Aouad M, Jabbour-Khoury S, Al Jazzar M, Alameddine M, Al-Yaman R, et al. Effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. Acta Anaesthesiol Scand 2006;50:222-7.
16. Gupta K, Bansal M, Gupta PK, Singh M, Agarwal S, Tiwari V. Dexmedetomidine premedication with three different dosages to attenuate the adverse hemodynamic responses of direct laryngoscopy and intubation: A comparative evaluation . Ain Shams J Anaesthesiol 2016;9:66-71.
17. Derbyshire DR, Chmielewski A, Fell D, Vater M, Achola K, Smith G. Plasma catecholamine responses to tracheal intubation. Br J Anaesth 1983;55:855-60.
18. Carollo DS, Nossaman BD, Ramadhyani U. Dexmedetomidine: a review of clinical application. Curr Opin Anesthesiol 2008;21:457e61.
19. .Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. Anesth Analg 2000;90:699e705.
20. Bhattacharjee DP, Nayek SK, Dawn S, Bandopadhyay G, Gupta K. Effects of dexmedetomidine on haemodynamics in patients undergoing laparoscopic cholecystectomyda comparative study. J Anaesthesiol Clin Pharmacol 2010;26: 45e8.