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Evaluation of Clinical Efficacy of Dexmedetomidine in Three Different Doses to Attenuate Hemodynamic Responses during Laryngoscopy and Intubation

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Abstract

Background: Laryngoscopy and tracheal intubation are noxious stimuli that produce marked sympathetic activity with exaggerated hemodynamic response manifesting as tachycardia, hypertension and dysrhythmias due to increase in concentration of plasma catecholamine. Use of α_2-adrenergic agonist like dexmedetomidine has been shown to blunt hemodynamic response to noxious stimulation and prevent hemodynamic variability.

Methods: 120 ASA I and II adult patients, scheduled for various elective surgical procedures under general anaesthesia were included in the study. The patients were randomly divided into 4 equal groups of 30 each; group A receiving 10 ml normal saline intravenous infusion serving as control and next three group (B, C, D) receiving dexmedetomidine infusion 0.25µg/kg, 0.50µg/kg and 0.75µg/kg diluted in 10 ml normal saline respectively, to see if dexmedetomidine could attenuate the rise in hemodynamic parameters resulting from laryngoscopy and endotracheal intubation.

Results: Both heart rate (HR) and blood pressure (SBP, DBP and MAP) rise significantly during laryngoscopy and intubation in control group (normal saline). Dexmedetomidine administered intravenously at the dose of 0.75µg/kg can attenuate the rise in heart rate and blood pressure following laryngoscopy and intubation more effectively ($p<0.05$) than 0.25µg/kg and 0.50µg/kg dose without any significant adverse effect like bradycardia, arrhythmias.

Conclusion: So dexmedetomidine 0.75µg/kg dose is the minimum effective dose to prevent stress response during laryngoscopy and intubation

Keywords: General anaesthesia, Hemodynamic response, Dexmedetomidine

Introduction

Laryngoscopy may be performed to facilitate tracheal intubation for general anesthesia or cardiopulmonary resuscitation or for procedures on the larynx and other parts of the upper tracheobronchial tree causing exaggerated hemodynamic response. Laryngoscopy and tracheal intubation are noxious stimuli that produce marked sympathetic activity with exaggerated hemodynamic response manifesting as tachycardia , hypertension, dysrhythmias due to increase in concentration of plasma catecholamine.[1,2,3] and these responses are thought to be initiated by lifting the base of tongue and epiglottis by the laryngoscope blade. Afferent impulses are carried through trigeminal, glossopharyngeal, vagus and sympathetic nerve from the airway. These impulses are relayed in cranial nerve nuclei, vasomotor and autonomic regulatory area.

The hemodynamic changes are generally transitory and without any sequel. However, in patients with pre-existing coronary artery disease, hypertension, cerebrovascular disease, presence of autonomic neuropathy in diabetic patients an increase in these circulatory parameters may have deleterious respiratory, neurological and cardiovascular effects and can precipitate myocardial ischemia[4], arrhythmias, infarction and even cerebral hemorrhage.

Various pharmacological interventions (both intravenous and topical), modification of instruments and use of other intubating devices (e.g. LMA) have been tried to obtund this hemodynamic response to laryngoscopy and intubation. Opioids are also widely used to control the neurovegetative response to intubation. Many studies have shown the effectiveness of fentanyl in blunting the pressure response to laryngoscopy and intubation.[5,6]

Use of α_2-adrenergic agonist like clonidine has been shown to blunt hemodynamic response to noxious stimulation and prevent hemodynamic variability.[7] Dexmedetomidine is an α_2-agonist having eight-times more affinity for α_2-adrenoceptors as compared to clonidine, which has shown only partial agonist activity and is known to decrease the perioperative catecholamine concentrations and promote hemodynamic and adrenergic stability.[8]

Dexmedetomidine in a dose of 0.5µg/kg and 1µg/kg are found to be effective in attenuation of stress response to laryngoscopy and endotracheal intubation.[9] However, some investigators found dexmedetomidine dose of 1µg/kg causes adverse effects of bradycardia and hypotension.[10] In the meantime, another previous study, indicated that dexmedetomidine 0.75µg/kg is the optimum dose for attenuation of hemodynamic response to laryngoscopy and intubation.[11] Hence, in order to find out the minimum effective dose of dexmedetomidine to attenuate the stress response of laryngoscopy and intubation, we conducted a randomized double blind study comparing the effectiveness of three different doses of dexmedetomidine 0.25µg/kg, 0.5µg/kg and 0.75µg/kg body weight in our study.

Aims And Objectives

The study was to determine the minimum effective dose of dexmedetomidine in attenuating cardiovascular responses during laryngoscopy and endotracheal intubation with three different doses (0.75µg/kg body weight, 0.50µg/kg body weight and 0.25µg/kg body weight dose)

Materials and Methods

The study was a randomized, double blinded and controlled one conducted in the Department of Anesthesiology, of a Tertiary care centre at Imphal, Manipur between September 2018 to August 2020. After obtaining approval from the Institutional Ethics Committee 120 patients above 18 years with ASA I & II admitted for surgery under general anesthesia were enrolled for the study after taking written inform consent. Patients with cardiovascular diseases, on beta blocker drug, Mallampatti class III and IV, allergy to the trial drug and patients undergoing procedures requiring head and neck manipulation were excluded from the study.

Patients were divided into four groups based on the computer generated randomization with 30 patients in each group viz-Group A received 10ml normal saline intravenous, Group B received intravenous Dexmedetomidine 0.25µg/kg diluted to 10ml with normal saline, Group C received intravenous Dexmedetomidine 0.5µg/kg diluted to 10ml with normal saline and Group D received intravenous Dexmedetomidine 0.75µg/kg diluted to 10ml with normal saline as infusion over 10 min.

Pre anesthetic evaluations consisting of detailed history, physical examination and basic investigation were performed in all patients. They were kept fasting overnight after 10pm, tablet ranitidine 150mg orally and tablet alprazolam 0.5mg orally were given as premedication at night before surgery. The double-blinding procedure was followed, in which both the person administering the drug and the patient were unaware as to which group he/she belonged to. One consultant anesthesiologist or colleague prepared the intravenous (IV) infusions, coded them and were handed over to the resident anesthetist who was unaware of the content of the syringe.

Patients were pre medicated with inj. glycopyrolate 0.2mg intramuscularly and inj.ondansetron4mg intravenously 30 min before induction. On arrival in the operation theatre, all patients were monitored

Volume 4, Issue 6; November-December 2021; Page No 1247-1253

with electrocardiography, pulse oximetry and non-invasive blood pressure. An intravenous line was secured and the patients were administered inj ringer lactate at a rate of 4-6ml/kg. Baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP) and oxygen saturation (SpO2) were measured after premedication. After 10 min, study drug infusion was given over 10 min. Hemodynamic parameters were measured after giving study drug and any incidence of bradycardia (HR <50 beats) were to be treated with IV atropine 0.6 mg. All the patients were pre-oxygenated for 3 min. General anesthesia technique was standardized for all the four groups. Patients were induced with intravenous propofol 2 mg/kg body weight and intubation facilitated by intravenous succinylcholine 2 mg/kg body weight. During induction hemodynamic parameters were measured. Following laryngoscopy and endotracheal intubation, the parameters like HR, SBP, DBP and MAP were recorded at 1, 3, 5 and 10 min after intubation. Anesthesia was maintained with oxygen and nitrous oxide with traces of sevoflurane. Muscle relaxation was maintained with loading dose of intravenous atracurium 0.5 mg/kg and maintenance dose of 0.1 mg/kg. After surgery, reversal was achieved with intravenous neostigmine 0.05 mg/kg and intravenousglycopyrolate0.01 mg/kg. After adequate recovery, patients were shifted to post-anesthesia care unit and monitored for1 hour and later shifted to ward. After completion of operation sedation was assessed at 1, 5, 10 minutes using Ramsay sedation score.

The sample size was calculated as 28 in each group based on difference in the systolic blood pressure between two doses of study drug at 3 minute post intubation which were 129.87±9.75mmHg and 124.67±8.41mmHg in a previous study done by Sebastian B et al.[12] Assuming a 5% drop out rate, the final sample size is rounded to 30 in each group. Data was represented as mean ± SD for interval and count (relative frequency) for categorical variables. Baseline data were compared among study groups by one-way analysis of variance (ANOVA), Student t test for interval and Chi-square test for categorical data. P<0.05 was deemed to be significant. Data was analyzed using SPSS statistics version 21 for windows and Microsoft word and Excel used to generate graphs and tables.

Results and Observations

The study protocols were completed in all the enrolled 120 patients. The demographic parameters such as age, weight, sex and ASA were comparable in all the three groups and did not affect the study protocol, as shown in table 1.

Table 1: showing the distribution and comparison of demographic profile in the four groups

Patient characteristics		***Group A (control) N=30***	***Group B (Dex0.25) N=30***	***Group C (Dex0.50) N=30***	***Group D (Dex0.75) N=30***	***Test statistics***	***P value***
Age(years)		40.10±10.92	41.43±11.20	39.27±12.22	38.70±10.05	F=0.342	0.795
Weight(kg)		61.97±9.88	61.03±8.73	60.80±6.80	63.30±5.712	F=0.612	0.609
Sex	*Male*	10(33.3%)	13(43.3%)	13(43.3%)	13(43.3%)	X^2=0.931	0.818
	Female	20(66.6%)	17((56.6%)	17(56.6%)	17(56.6%)		
ASA	*I*	23(76.6%)	21(70%)	23(76.6%)	22(73.3%)	X^2=0.478	0.924
	II	7(23.3%)	9(30%)	7(23.3%)	8(26.6%)		

P<0.05 is significant

The heart rate comparison in the four groups is shown in table 2. It rose significantly from its baseline value to a maximum at intubation and thereafter decreases to attain the baseline in the control group. However, in the

Volume 4, Issue 6; November-December 2021; Page No 1247-1253

Dexmedetomedine groups we did not record any significant rise at the intubation time point and the fall was more in the higher dose group.

Table2: Distribution and comparison of heart rate in the four groups

Heart rate	Group A (Control) (normal saline) N =30	Group B (Dex0.25) N =30	Group C (Dex0.50) N =30	Group D (Dex0.75) N =30	F value	P value
Baseline	82.97±9.16	81.27±7.51	83.87±7.66	84.33±8.83	0.793	0.500
Test drug	81.97±9.57	76.63±7.04	77.23±6.94	75.03±8.90	3.973	0.010*
Induction	76.77±8.12	72.83±6.77	72.83±6.19	69.13±8.23	5.352	0.002*
Intubation	104.40±9.72	82.88±6.82	83.53±7.17	76.63±7.53	70.561	0.000*
HR1	101.27±9.13	81.30±6.70	80.23±7.56	74.73±7.423	67.334	0.000*
HR3	99.57±9.59	79.13±6.95	78.30±7.05	72.70±7.77	66.497	0.000*
HR5	97.97±8.54	77.63±6.78	76.30±7.37	70.73±7.90	72.368	0.000*
HR10	95.27±8.12	75.93±6.76	75.23±7.09	69.00±7.42	71.247	0.000*

P<0.05 is significant

The blood pressure comparison in the four groups as represented by MAP is shown in table 3. It increased from its baseline value to a maximum at intubation and thereafter decreases to attain the baseline in the control group. In the other three Dexmeditomedine groups the rise at the intubation time point was minimal as compared with the baseline value and this was more pronounced in the higher dose group. Similarly, the SBP and DBP also followed the same trend as that of MAP.

Table 3: Distribution and comparison of MAP in the four groups

MAP (mmHg)	***Group A (control) (Normal saline) N =30***	***Group B (Dex0.25) N =30***	***Group C (Dex0.50) N =30***	***Group D (Dex0.75) N=30***	***F value***	***P value***
Baseline	105.23±6.25	99.63±6.68	103.67±7.67	101.57±6.72	4.615	0.004
Test drug	101.47±6.66	93.93±6.17	97.33±6.68	94.63±6.33	8.372	0.000*
Induction	96.33±6.27	89.53±6.60	92.07±5.85	88.93±6.11	8.799	0.000*
Intubation	116.13±6.21	100.13±7.02	102.13±7.22	94.73±5.92	57.007	0.000*
MAP1	111.10±5.11	96.87±6.11	98.53±6.16	92.53±5.93	55.873	0.000*

Volume 4, Issue 6; November-December 2021; Page No 1247-1253

MAP3	107.93±5.60	94.77±5.91	95.30±5.38	89.80±5.64	56.435	0.000*
MAP5	104.87±5.19	92.63±5.62	92.33±5.11	87.03±5.89	57.354	0.000*
MAP10	101.37±5.30	90.53±5.55	89.93±4.68	83.70±5.68	57.149	0.000*

P<0.05 is significant

The sedation score as assessed by Ramsay sedation score at different time points in the postoperative period were comparable and did not record significant sedation in all the groups even though better score were recorded in group D. Also, there were no significant side effects recorded in the study.

Discussion

Laryngoscopy and intubation is associated with cardiovascular responses like elevation of blood pressure, pulse rate, occasional dysrhythmias, cough reflexes, increased intracranial pressure and increased intraocular pressure. If no specific measures are taken to prevent hemodynamic response, the HR(heart rate) can increase from 26% to 66% depending on the method of induction and systolic blood pressure can increase from 36% to 45%.[13,14]Attenuation and obtundation of presser response during laryngoscopy and surgery has been one of the most researched topics in anesthesia, but with only a few positive established outcomes. Numerous drugs and their combinations have been tried in the past and studies have highlighted the use of these drugs in varying doses for suppression of stress response but not without the significant incidence of quite a few side-effects especially with high doses of opioids.[15,16]

Recently extensive studies are going on dexmedetomidine administration regarding the analgesic, sedation, anxiolytic, sympatholytic and blunting of exaggerated hemodynamic responses. Here in our prospective randomized study we attempted to do comparison among three different doses of dexmedetomidine (0.25µg/kg, 0.50µg/kg and 0.75µg/kg) for attenuating the hemodynamic response to laryngoscopy and tracheal intubation.

The heart rate in group A (control) fell little after induction and increased significantly during intubation and at 1, 3, 5, 10 minutes after intubation but it fell significantly after giving test drug and during induction in the group D, eventhough the fall were not significant in the other two doses. These changes could be due to α_2 agonist effect of dexmedetomidine which decrease central sympathetic outflow. Our finding is in agreement with the study of Ebert T et al.[17]

The systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial blood pressure (MAP) also showed similar trends as that of heart rate in our study. However, contemporary studies do not emphasize these parameters while studying stress response to laryngoscopy and intubation.

Yildiz M et al[15] studied the effects of dexmedetomidine and hemodynamic response to laryngoscopy and intubation. They concluded that preoperative administration of a single dose of dexmedetomidine resulted in progressive increase in sedation, blunted the hemodynamic response during laryngoscopy and reduced opioid and anesthetic requirements.

Jarineshin H et al[18] conducted similar study with three groups, the first set (A) got o.5µg/kg dexmedetomidine, the second set(B) got 1µg/kg dexmedetomidine and the third set(C) got an equal volume of saline as placebo, and found that HR, SBP, DBP and MAP were significantly lower in dexmedetomidine set (A, B) at all times after endotracheal intubation compared to group C. Our study also showed similar finding in dexmedetomidine groups compared to normal saline (placebo). Aso smilar study in support of our study was conducted by Sebastian B et al.[12]

Contrary to our study, some studies showed the dose related undesirable side effects of dexmedetomidine which should always be in our mind. Basar H et al[19] reported that the incidence of bradycardia after a single dose of 0.5 µg/kg of dexmedetomidine was about 5% , while a study of Sulaiman S et al[20] showed development of hypotension or bradycardia with a similar dosage of dexmedetomidine with an

Volume 4, Issue 6; November-December 2021; Page No 1247-1253

incidence of hypotension occurred by about 20% with the use of 1 µg/kg of dexmedetomidine in patients undergoing coronary artery bypass graft surgery.[20] Nevertheless, transient tachycardia, hypertension, and oxygen desaturation were observed after the use of 1 µg/kg of dexmedetomidine in the study of Bajwa SJ et al.[21]

There were a few limitations of this study. We did not measure the plasma concentration of catecholamine and could not demonstrate the effectiveness of this dosage of dexmedetomidine in decreasing the sympathetic nervous system activity. Use of noninvasive blood pressure monitoring (NIBP) monitoring if replaced by invasive blood pressure monitoring could have given more accurate BP readings.

Conclusion

Dexmedetomidine administered intravenously at the dose of 0.75µg/kg can attenuate the rise in heart rate and blood pressure following laryngoscopy and intubation more effectively than 0.25µg/kg and 0.50µg/kg dose without any significant adverse effect like bradycardia, arrhythmias. So dexmedetomidine 0.75µg/kg dose is the minimum effective dose to prevent stress response during laryngoscopy and intubation.

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Volume 4, Issue 6; November-December 2021; Page No 1247-1253

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Volume 4, Issue 6; November-December 2021; Page No 1247-1253