Section: Anaesthiology

Original Research Article

INTRAVENOUS DEXMEDETOMIDINE AND CLONIDINE FOR ATTENUATING THE PRESSOR RESPONSE TO LARYNGOSCOPY & ENDOTRACHEAL INTUBATION - AN OBSERVATIONAL STUDY

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Abstract

Background: Laryngoscopy and endotracheal intubation are potent stressful stimuli that lead to tachycardia and hypertension which may be detrimental in individuals with limited myocardial reserve and geriatric population. The aim of this present study is to compare the effects of intravenous Dexmedetomidine and Clonidine in attenuating the pressor response to laryngoscopy and intubation. **Materials and Methods:** A total of 124 patients of ASA grades I & II, aged between 18-65 years, scheduled for elective surgery under GA were divided into two group (n=62); Group D included patients who received Dexmedetomidine 1 µg/kg iv and Group C who received Clonidine 2 µg/kg iv, given prior to induction and infused slowly over 10 min. HR, SBP, DBP and MAP were recorded before (baseline) & after drug administration, after induction & at 1, 3, 5 & 10 minutes after intubation. **Result:** Demographic profile & baseline hemodynamic parameters were comparable in both the groups. A significant fall in HR, SBP, DBP and MBP was observed in group D after study drug administration & induction compared to group C. The increases in HR, SBP, DBP and MAP during 1 and 3 minutes after intubation were highly significant in Group C compared to Group D ($p < 0.001$). 4 patients in group D & 2 patients in group C had bradycardia whereas 3 patients in each group had hypotension. **Conclusion:** Both Dexmedetomidine and Clonidine were effective in blunting the pressor response to laryngoscopy & intubation however Dexmedetomidine was superior to Clonidine in providing hemodynamic stability.

INTRODUCTION

Hemodynamic stress response to laryngoscopy and tracheal intubation occurs due to mechanical stimulation of proprioceptors in the pharynx and larynx resulting in tachycardia, hypertension, arrhythmias and increase in plasma catecholamine concentrations.[1,2] Subsequent endotracheal intubation recruits additional receptors that elicit augmented hemodynamic and epinephrine responses as well as some vagal inhibition of the heart.[3] This short-lived hyper adrenergic state may increase perioperative mortality and morbidity, particularly in individuals who have limited myocardial reserve due to coronary artery disease, cardiac dysrhythmia, cardiomyopathy, congestive heart failure, uncontrolled hypertension, cerebrovascular disease & in geriatric population.[4,5] Herein lays the rationale to continue the quest for an anaesthetic technique where the cardiovascular response can be attenuated. Both Clonidine and Dexmedetomidine are imidazoline compounds and act by same mechanism, but has a difference in the α2 selectivity. Dexmedetomidine being 8 times more α2selective than Clonidine, is therefore assumed to have a more potent hemodynamic stabilizing effect than Clonidine.[6]

This observational study was designed to observe and compare the effects of intravenous Dexmedetomidine and Clonidine given prior to induction, in attenuating the pressor response to laryngoscopy and endotracheal intubation in patients undergoing elective surgeries under general anaesthesia.

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MATERIALS AND METHODS

This prospective, observational study was conducted at Pt. J. N. M. Medical College & Dr B.R.A.M. Hospital Raipur after approval from institutional ethics committee. A total of 124 patients of ASA(American Society of Anaesthesiologists) grade I and II, aged 18-65 yrs, scheduled for elective surgeries under general anaesthesia and received either iv Clonidine or iv Dexmedetomidine for attenuating the pressor response to laryngoscopy & intubation were chosen and divided into two groups. Data collection was done using preformed pretested proforma. Group C (n = 62) included patients who received iv Clonidine 2 µg/kg and Group D (n = 62) included patients who received iv Dexmedetomidine 1µg/kg, before the induction of anaesthesia. Patient who refused to participate, having history of allergy, difficult airway, severe cardiopulmonary disease, systemic hypertension, morbid obesity, psychiatric disease, severe renal or hepatic derangements, pregnant and lactating mothers were excluded from the study. Patients in whom laryngoscopy time was > three minutes, or when the laryngoscopy was done by first and second year residents were also excluded.

All the patients underwent thorough pre-anaesthetic evaluation. After taking written & informed consent from the patients, they were shifted to the operation theatre and were connected to a multi-channel monitor (Schiller's) for monitoring of electrocardiogram, oxygen saturation and non-invasive blood pressure continuously.

All the patients were premedicated with intravenous Ranitidine 50 mg, Glycopyrrolate 0.2 mg, Dexmedetomidine 1 µg/kg or Clonidine 2µg/kg (diluted in 10 ml of NS & infused slowly over 10 min) before induction. After pre-oxygenation with 100% oxygen for 3 min, induction was done with Propofol 2 mg/kg iv and Succinylcholine 1.5 mg/kg iv to facilitate endotracheal intubation. Laryngoscopy was done with a Macintosh laryngoscope and intubation done with a cuffed endotracheal tube of appropriate size. Anaesthesia was maintained with N2O:O2 (60:40), Isoflurane(1%) & Atracurium 0.3 mg/kg iv bolus followed by 0.1 mg/kg incremental doses on return of respiration. At the end of surgery, residual neuromuscular blockage was reversed with Neostigmine 50 µg/kg iv and Glycopyrrolate 10 µg/kg iv. Extubation was done after proper oral suctioning and oxygenation.

HR (heart rate), SBP (systolic blood pressure), DBP (diastolic blood pressure) and MAP (mean arterial pressure) were recorded at T0- before administration of study drugs (Baseline),T1- after completion of drug administration,T2- after induction,T3- 1 minute after intubation, and T4 to T6- 3, 5, and 10 minutes after intubation.

Patients who developed significant hypotension (SBP < 90 mmHg or DBP < 60 mmHg or both) during induction were first treated with fluid loading (10mL/Kg) and then with Mephentermine 6 mg i.v, if BP became worse or did not improve. Bradycardia was defined as a HR of less than 50/minute and was corrected with Atropine 0.5mg iv, if associated with hemodynamic instability. Other adverse effects like arrhythmias if any were noted.

For the purpose of power analysis, we used the study of Mondal S et al (2015).[7] The Sample size was calculated by using the mean values from the above mentioned study and using the formula:

$n= (Z\alpha/2+Z\beta)2 * (p1(1-p1)+p2(1-p2)) / (p1-p2)2$

where $Z\alpha/2$ is the critical value of the Normal distribution at $\alpha/2$ (e.g. for a confidence level of 90%, α is 0.05 and the critical value is 1.65), $Z\beta$ is the critical value of the Normal distribution at β (e.g. for a power of 80%, β is 0.2 and the critical value is 0.84) and p1 and p2 are the expected sample proportions of the two groups. From the formula above we have calculated the sample size to be sixty-two samples in each group with a total of one twenty four patients.

Statistical Analysis: Statistical analysis was conducted with SPSS version 13.0 for Windows statistical package using unpaired student's t test & Chi-square test. Qualitative data (sex & ASA grade) were compared between groups with Chi-Square (χ 2) test whereas quantitative data (age, body weight, height, HR, SBP, DBP and MAP) were compared between groups with unpaired student's t test. A p value < 0.05 was considered as statistically significant and < 0.01 was considered as highly significant.

RESULTS

Demographic profiles of both groups were comparable & statistically insignificant. [Table 1]

The baseline preoperative HR, SBP, DBP and MAP in Group D & Group C were comparable & statistically not significant (p > 0.05). A significant fall in HR was observed in group D after study drug infusion (p = 0.0340) & after induction (p =0.0201) compared to group C. The increase in HR during laryngoscopy and intubation at 1 minute was highly significant in Group C compared to group D (p< 0.0001). A significant difference in HR at 3 & 5 minutes was also observed between the two groups (p = 0.0393 & 0.0489, respectively). After 10 minutes of intubation, HR was comparable between the groups (p = 0.0999). [Table 2]

A significant fall in SBP, DBP and MAP following drug administration was observed in both the groups (p < 0.05) with Group D showing a more reduction than Group C. Peak rise in SBP, DBP and MAP was seen at 1 minute after laryngoscopy & intubation (122.4 ± 9.05/81.83 ±7.48/95.80 ± 7.84 mmHg in Group D & 130.76 ± 8.04/86.36 ± 9.13/101.13 ± 8.44 mmHg in Group C) which was statistically highly significant (p < 0.0001). Difference in mean BP was statistically significant at 3 mins post

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intubation ($p < 0.0001$), following which the values returned below baseline and became statistically insignificant at 5 & 10 minutes after intubation ($p > 0.05$). [Table 3 and Graphs 1 & 2]

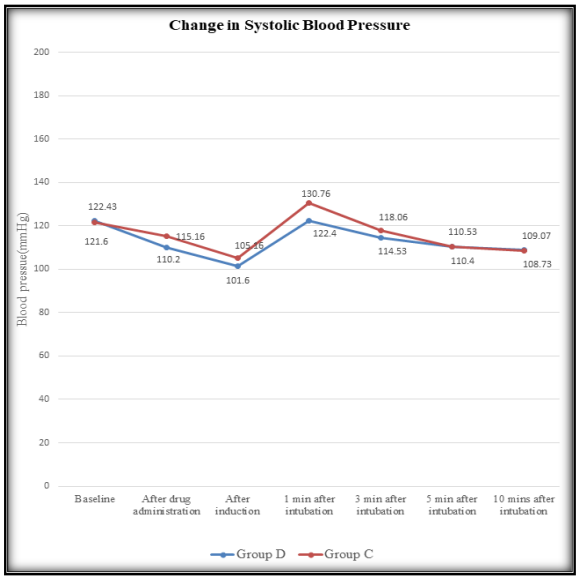

Figure 1: Change in Systolic Blood Pressure

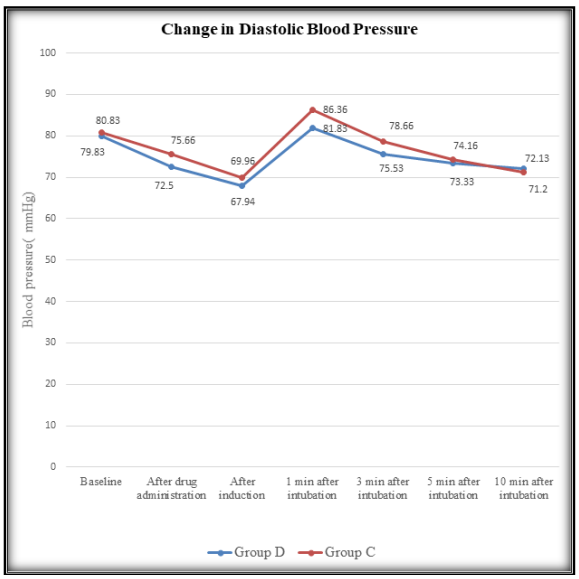

Figure 2: Change in Diastolic Blood Pressure

Table 1: Demographic Characteristics.

Variables	Group C (n =62)	Group D (n =62)	p value
Sex (M : F)	38 : 24	36: 26	0.7142
Age (yrs) (Mean ± SD)	36.09 ± 11.16	35.55 ± 11.48	0.7880
Weight (kgs) (Mean ± SD)	56.90 ± 9.94	56.39 ± 9.68	0.7771
Height (cms) (Mean ± SD)	160.3± 10.39	161.63 ± 9.39	0.7043
ASA grade (I : II)	46 : 16	45 : 17	0.8389

Table 2: Change in Heart Rate (beats/min)

Time interval	Group D (Mean±SD)	p Value	Group C (Mean±SD)	p Value	p Value (Group D vs C)
Baseline	83.86±8.78		83.13±9.16		0.59291
After drug administration	78.50±8.26	0.0008**	80.80±8.45	0.1502	0.0340*
After induction	75.56±7.90	<0.0001**	78.03±8.43	0.0019**	0.0201*
1 min after intubation	87.53±7.33	0.0631	93.63±7.01	<0.0001**	<0.0001**
3 min after intubation	81.93±6.50	0.1667	84.50±7.22	0.3648	0.0393*
5 min after intubation	77.93±6.62	<0.0001**	80.26±6.42	0.0618	0.0489*
10 min after intubation	75.73±6.78	<0.0001**	77.16±6.63	<0.0001**	0.0999

Table 3: Change in Mean Arterial pressure (mm Hg)

Time interval	Group D (Mean±SD)	p Value	Group C (Mean±SD)	p Value	p Value (Group D vs C)
Baseline	93.96±10.25		94.33±10.09		0.7768
After drug administration	85.70±9.33	< 0.0001**	89.06±9.51	0.0418	0.0493*
After induction	79.90±8.60	< 0.0001**	82.30±9.06	< 0.0001**	0.0364*
1 min after intubation	95.80±7.84	0.2716	101.13±8.44	<0.0001**	<0.0001**
3 min after intubation	88.56±7.54	0.0251	91.73±9.17	0.3006	0.0342*
5 min after intubation	85.50±7.44	< 0.0001**	86.30±9.13	< 0.0001**	0.4629
10 min after intubation	84.60±7.86	< 0.0001**	83.36±8.91	<0.0001**	0.2541

DISCUSSION

Laryngoscopy and endotracheal intubation are associated with rise in heart rate, blood pressure,[1,2] and occasional disturbance in cardiac rhythm which is detrimental in high risk patients especially in those with cardiovascular disease, increased intracranial pressure and anomalies of the cerebral blood vessels.[4,5] So, effective attenuation of hemodynamic response to laryngoscopy and tracheal intubation is of great importance in prevention of perioperative morbidity and mortality. Here we aimed to compare the two most popular α2-adrenergic agonists, Clonidine and Dexmedetomidine in blunting the hemodynamic response following laryngoscopy and endotracheal intubation. Dexmedetomidine is eight times more α2 selective than Clonidine with a α2:α1 activity ratio

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of 1620:1 compared to 220:1 of Clonidine. Therefore it is assumed that the high α2 selectivity of Dexmedetomidine may be responsible for better hemodynamic stability than Clonidine.[6]

Kakkar A et al,[8] (2015) compared 0.5 μg/kg with 1 μg/kg of Dexmedetomidine and found intubation response with 0.5 μg/kg but not with 1 μg/kg, so we decided to use 1 μg/kg as a single bolus dose for premedication and Mondal S et al,[7] (2015) found 2 μg/kg of Clonidine to be equally effective as Dexmedetomidine 1 μg/kg in attenuating the pressor response to intubation with minimum side effects, so we used 2 μg/kg Clonidine in our study.

The confounding factors in our study were age, sex, systemic comorbidites like hypertension, diabetes, cardiovascular, renal & hepatic insufficiencies as well as attempts and time taken for laryngoscopy & intubation were also taken into consideration. Demographic parameters were comparable between both the groups. Patients on antihypertensive drugs were also excluded as they might exhibit a decrease in pressor response to laryngoscopy and intubation. α2-agonists are extensively metabolized in liver and excreted in urine. Therefore, patients with altered liver functions and renal functions were not included in this study. The safety of α2-agonists in pregnancy is not well established till now. So, we excluded the women of reproductive age group with a history of amenorrhea and a positive urine test for pregnancy. To include a larger number of sample size pts aged from 18 to 65 years were selected for this study. Difficult intubation takes longer time and is invariably associated with marked hemodynamic change even in well premedicated patients. So, patients with higher Mallampatti class (III and IV) were excluded from this study.

In our study, there was a significant fall in hemodynamic parameters like HR and BP (SBP, DBP & MAP) following drug administration in both the groups ($p < 0.05$), with Group D showing a more reduction in HR & BP than Group C. This fall in hemodynamic parameters resulted from peripheral and central mechanism of α2 adrenoreceptor agonists with reduction in sympathetic tone mediated by norepinephrine release and inhibition of neurotransmission in sympathetic nerves[2,9]]The decrease in BP following induction was most likely due to vasodilatation and depression of medullary vasomotor centre due to Propofol. Peak rise in HR & BP was seen at 1 minute after laryngoscopy & intubation was statistically highly significant in group D compared to group C ($p < 0.01$). These values returned below baseline values from 3 minutes onwards and became statistically insignificant at 5 & 10 minutes after intubation ($p > 0.05$). The peak rise in hemodynamic parameters observed at 1 minute after intubation was probably due to the fact that plasma catecholamine concentration is maximum at 1 minute after laryngoscopy[3,10] and this responses normalize after 3 to 5 minutes after laryngoscopy. The results of Hazra R et al (2014),[11] Mondal S et al (2014),[7] Sharma NG A et al (2014),[12] Agarwal S et al (2016),[13] Arora S et al,[14] (2014) &V A et al,[15] (2015) were comparable to our study. Compared to our study, Kumar S et al,[16] (2014) and Anjum N et al,[17] (2015) noted no statistical difference in HR & MAP between the two groups at the time of intubation ($p < 0.05$). This could be due to use of iv Fentanyl & iv Vecuronium by Kumar S et al,[16] (2014) & use of higher dose of Clonidine (3 μg/kg) by Anjum N et al (2015),[2] along with use of continuous infusion of both the study drugs which provided hemodynamic stability throughout the surgery. Kakkar et al,[8] (2015) also observed that rise in blood pressure seen after intubation with all the groups, were comparable & statistically not significant ($p > 0.05$) which doesn't correlate to our study. This may be due to use of iv Fentanyl & iv Vecuronium, which may have affected the outcome of their studies.

The incidence of bradycardia was 6% in group D & 3% in group C which was corrected with iv Atropine. Hypotension was seen in 6% in Group D & 8% in Group C and was managed with iv fluids & iv Mephentermine. Both these adverse effects were comparable & statistically insignificant between both the groups. No other significant side effects were observed in our study.[18-20]

The limitations in our study were that we had no way to determine equipotent doses of Dexmedetomidine & Clonidine, all laryngoscopies were not done by same anaesthesiologists & use of invasive monitoring would have been technically better.

CONCLUSION

From the observations and analysis of the our study, we concluded that both Clonidine and Dexmedetomidine administered intravenously just before induction of anaesthesia effectively attenuated the hemodynamic response due to laryngoscopy and endotracheal intubation by limiting the extent of rises in heart rate and blood pressure without any serious side effects. However Dexmedetomidine was found to provide better hemodynamic stability than Clonidine.

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