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Dexmedetomidine May Attenuate Cardiovascular Stress During Endotracheal Intubation

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ABSTRACT

Background: Endotracheal intubation drives major sympathetic stimulation in the perioperative period and is responsible for haemodynamic disturbances. Transient rise of heart rate and blood pressure during this time may be detrimental in many patients who are already compromised due to their cardiovascular co-morbidities. Various drugs and methods are in practice to blunt or completely attenuate this reflex sympathetic stimulation. The sedative and analgesic effects of Dexmedetomidine are proven in many studies and it is also found to obtund sympathetic stimulation to major noxious stimuli.

Method: A study was carried out to evaluate the effectiveness of Dexmedetomidine in the attenuation of stress response to intubation. All the patients were premedicated with Fentanyl and Midazolam. The study group received Dexmedetomidine 1mcg/Kg in 100ml saline over 15 min and the control group patients received placebo. The patients were induced and given muscle relaxant after 5 minutes of starting the drug and intubated after another 3 minutes of bag and mask ventilation.

Results: It was found that Dexmedetomidine 1 mcg/Kg during intubation significantly blunted the heart rate, systolic blood pressure, mean arterial pressure and diastolic blood pressure in comparison to placebo. Also the study group showed favorable values of Rate pressure product and Pressure-rate quotient during the intubation and decreased the requirement of Thiopentone for induction.

Conclusion: It was concluded that Dexmedetomidine can be added to the drug regime during induction of anaesthesia to blunt the reflex sympathetic response to endotracheal intubation and thus to attenuate the cardiovascular stress.

KEYWORDS Dexmedetomidine, Endotracheal intubation, Hemodynamic response

Introduction

Endotracheal intubation is one of the major painful stimuli in the perioperative period. During the procedure there may be transient but sudden increase in heart rate (HR), blood pressure (BP) and sometimes sudden onset of arrhythmias[1]. This reflex response is usually tolerated in many healthy individuals. But in patients, who are already compromised due to cardiovascular diseases, such response may be detrimental. Various groups of drugs e.g. opioids, local anaesthetics, beta-blockers, vasodilators are in use to obtund the haemodynamic response. Clonidine is an alpha-2 adrenergic agonist, known to attenuate reflex responses to painful stimuli[2]. Dexmedetomidine is a new drug[3] in this group with more selective action[4] on the receptors. It is found that the drug has sedative, analgesic properties[5] effectively blunts the sympathetic tone[6], attenuates haemodynamic responses to noxious stimuli[7]. Therefore, we carried out a study to know whether Dexmedetomidine can be administered as an anaesthetic adjunct during intubation in an attempt to blunt the haemodynamic responses.

Materials and Methods

The study is a single centered double blind randomized placebo controlled trial conducted within one year time, after the clearance from the institutional ethical committee. The study included the ASA 1 and 2 patients undergoing surgery under general anaesthesia where airway is secured with an endotracheal tube. Patients were excluded from the study if they were found to have preoperative medication with clonidine or alpha methyl-dopa, severe systemic disorders (e.g. diabetes mellitus with complication, kidney or liver insufficiency, severe respiratory disorder, uncontrolled hypertension, diseases associated with peripheral/ autonomic neuropathy), conditions where Thiopentone & Vecuronium are contraindicated, patients with advanced heart block and/or severe ventricular dysfunction, age less than 18yrs and more than 60 years, body mass index (BMI) less than 18Kg/m^2 and more than 30 kg/m^2, intubation duration lasting longer than 20 seconds or more than one attempt of laryngoscopy, presence of prominent incisors or other predictors of difficult intubation. We defined "duration of intubation" as the time taken by the anaesthesiologist from opening the mouth for laryngoscopy to inflate the cuff to secure the endotracheal tube. The aim of the study was to find out whether Dexmedetomidine can be used as an anaesthetic adjunct to attenuate haemodynamic changes following intubation. The primary objective was to compare the heart rate (HR), systolic blood pressure (SBP), mean arterial pressure (MAP), diastolic blood pressure (DBP), rate pressure product (RPP), and pressure- rate quotient (PRQ) at different time interval during intubation in patients premedicated with Dexmedetomidine and placebo; and the secondary objectives were to compare the dose requirement of Thiopentone during induction of anesthesia and to compare the complications (if any) in both the groups.

Patients were accepted after a proper pre-operative check and were randomized by sealed envelope method to 2 groups after obtaining written informed consent. One group received Dexmedetomidine (Gp D) and the other group received the placebo (Gp P). Blinding was achieved by involving two anaesthesiologists: one prepared the study drug/ placebo and the other administered the drug and observed the hemodynamic parameters. Inside the Operation Theater, a 16- gauge peripheral venous cannula was inserted. Monitors were attached to record the ECG, HR, SpO2 and non-invasive blood pressure. The patients were premedicated with Midazolam (0.05mg/kg) & Fentanyl (1 µg/kg) and were preloaded with 500 ml Lactat-

ed Ringer's solution. A baseline recording (T0) of HR, SBP, DBP and MAP was done. The Gp D received a total dose of 1 µg/kg Dexmedetomidine diluted in 100 ml NS over 15 minutes and the patients in Gp P received 100 ml NS in 15 minutes by a IV drip method of administration. After 5min of starting the drip, patients were induced with injection Thiopentone in sleeping dose. After confirming ventilation, injection Vecuronium 1mg/kg was administered. After 3min of mechanical ventilation with bag and mask, patient was intubated with gentle laryngoscopy. A set of 6 readings per patient was recorded. The procedure of intubation was carried out by a single experienced anaesthesiologist. We also noted the occurrence of apnoea before induction which was noted if there is a cessation of respiration for a period of more than 10 seconds.

Statistics

Statistical analysis was done by Primer of Biostatistics[8] and WINPEPI software[9]. Data was summarized with mean and standard deviation (SD). Parametric statistics ANOVA and t-test were applied to test for significant differences in the outcomes. The sample size was calculated to be 17 in each group to keep the alpha error 0.05 and the power of the study 80% based on minimum difference of means to be detected is 10 and the standard deviation within groups 10. P<0.05 was considered to be significant.

Results

One hundred thirty-six patients were recruited for the study. Seventeen patients were excluded for uncontrolled hypertension, 8 for neuropathy, 3 for chronic kidney disease, 22 for age >60yrs and 2 cases for prolonged duration of intubation. A total of 84 patients (Gp P -45 pts and Gp D -39 pt) from different types of surgeries were included in the study. There were no significant differences between the groups when compared in terms of age, sex or ASA category (table-1).

Table 1. Demographic profile

	Group P	Group D	p value
Age	43.73	43.92	1.19
Sex F M	 26 19	 17 22	0.281
ASA 1 2	 13 32	 17 22	0.240

Table2. Comparison of haemodynamic parameters in both the groups (Values in mean±SD)

		T0	T1	T2	T3	T4	T5
HR	Control	85.71±11.93	81.18±11.04	77.24±11.28	94.20±10.88	92.58±12.77	88.73±11.29
	Study	86.05±13.55	79.18±10.05	73.90±8.88	79.46±9.17	74.44±7.72	71.46±6.98
	P value	0.903	0.391	0.140	0.000	0.000	0.000
SBP	Control	126.91±15.08	118.60±14.19	113.49±13.17	142.49±21.11	138.36±19.17	132.87±19.90
	Study	133.05±13.11	119.77±15.23	111.87±16.36	125.15±16.99	118.05±15.91	110.26±14.23
	P value	0.051	0.717	0.617	0.000	0.000	0.000
MAP	Control	94.87±11.62	88.47±10.93	84.82±10.54	102.80±14.02	99.60±12.95	96.24±13.92
	Study	98.56±11.49	89.72±13.26	83.95±14.10	95.00±16.54	87.82±14.06	82.15±12.13
	P value	0.148	0.637	0.748	0.022	0.000	0.000
DBP	Control	79.73±10.16	74.64±9.70	71.58±9.74	84.89±11.99	81.58±11.18	78.47±11.29
	Study	82.85±10.07	75.59±11.80	71.56±12.38	80.23±16.05	74.85±12.44	69.31±11.34
	P value	0.162	0.983	0.993	0.132	0.011	0.000
RPP	Control	10870.09±1974.32	9617.20±1738.94	8748.76±1563.56	13408.89±2439.19	12825.18±2625.04	11812.13±2444.87
	Study	11400.31±1784.58	9472.28±1681.31	8251.38±1472.95	9975.56±1977.06	8804.87±1642.14	7879.95±1296.87
	P value	0.203	0.700	0.139	0.04500	0.000	0.000
PRQ	Control	1.13±0.20	1.11±0.20	1.12±0.22	1.11±0.20	1.09±0.20	1.10±0.19
	Study	1.18±0.24	1.15±0.23	1.15±0.24	1.20±0.20	1.19±0.21	1.16±0.20
	P value	0.301	0.396	0.552	0.043	0.028	0.163

The comparison of haemodynamic parameters of both the groups was done from T0 to T5 (table 2). Statistically significant difference was found in the values of HR, SBP, MAP, DBP, RPP and PRQ values in the post-intubation period (after T2). Comparison of HR and blood pressure values in the individual group was compared before and after intubation (table 3 and 4) which reflected the exaggeration of cardiovascular response to intubation though attenuated in the Gr D. The attenuated response in Gr D is shown in Fig1-6.

Table 3- Comparison of HR, SBP, MAP, DBP in Gp P before(T2) and after(T3) intubation

Parameters Control gr	T2	T3	Rise by (%)	P value
HR	77.24	94.20	21	0.000
SBP	113.49	142.49	25	0.000
MAP	84.82	102.80	21	0.000
DBP	71.58	84.89	18	0.000

Table 4.- Comparison of HR, SBP, MAP, DBP in Gp D before (T2) and after (T3) intubation

Parameters study gr	T2	T3	Rise by (%)	P value
HR	73.9	79.46	7	0.008
SBP	111.87	125.15	11	0.000
MAP	83.95	95.00	13	0.002
DBP	71.56	80.23	12	0.009

We compared both the groups in view of complications (table 5) which was found statistically insignificant (p<0.05). Again when the groups were compared for the dose requirement of inducing agent (Fig 7), there was no significant difference (p=0.9).

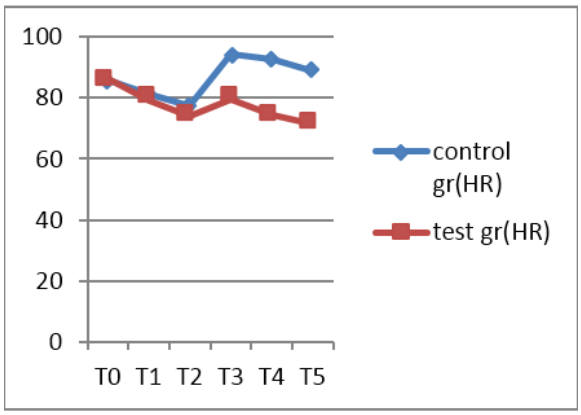

Fig 1: variation of HR over time in both the groups

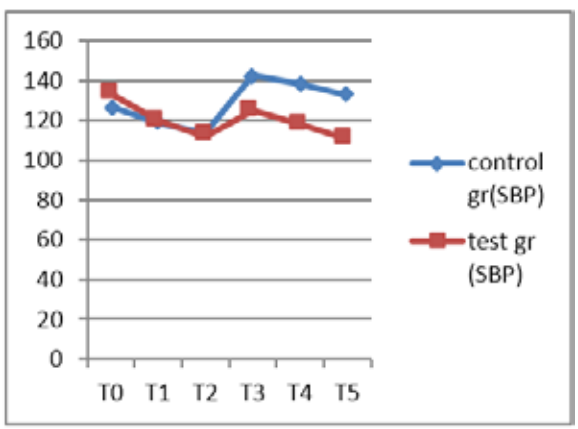

Fig 2: variation of SBP over time in both the groups

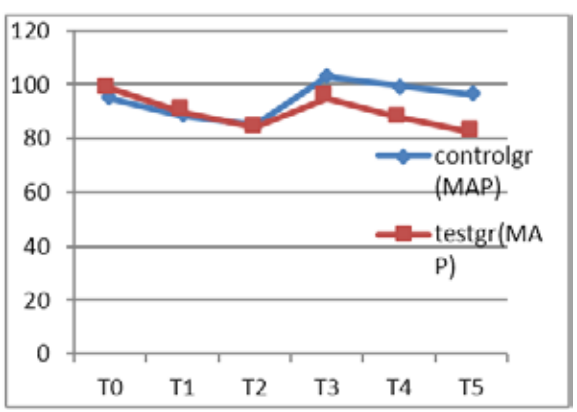

Fig 3: variation of MAP over time in both the groups

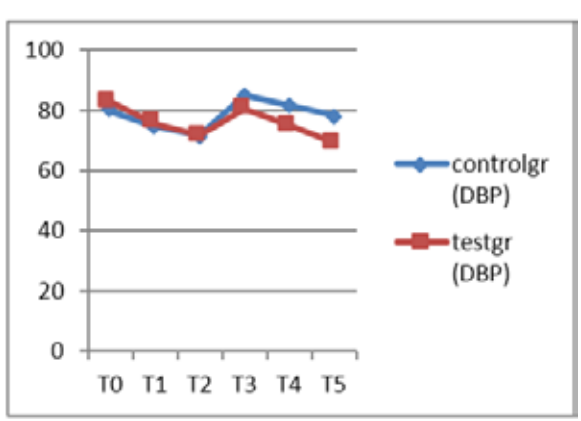

Fig 4: variation of DBP over time in both the groups

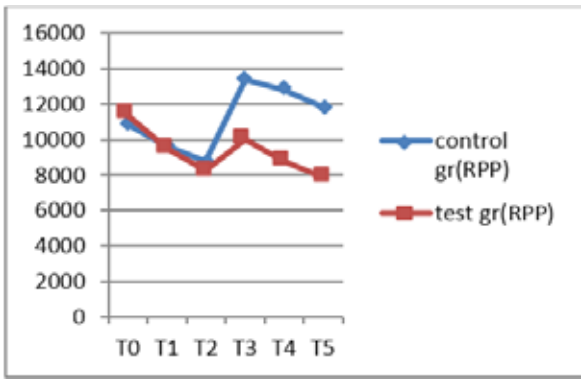

Fig 5: variation of RPP over time in both the groups

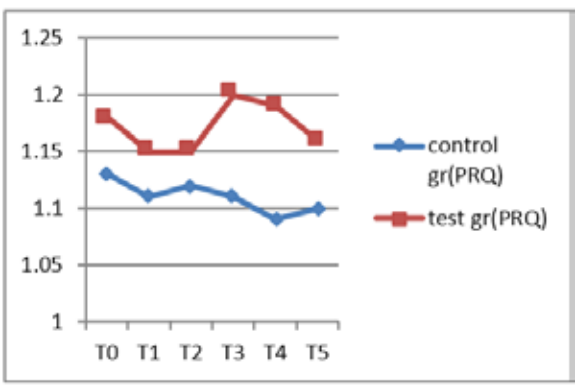

Fig 6: variation of PRQ over time in both the groups

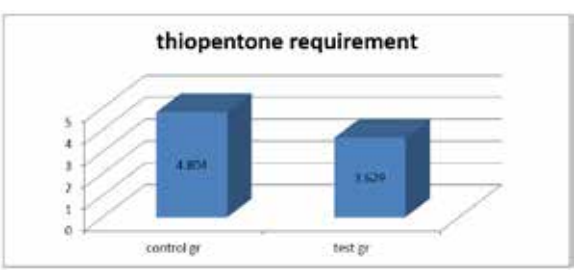

Fig 7: The average requirement of Thiopentone in both the groups.

Discussion

Direct laryngoscopy and passage of a tracheal tube are noxious stimuli that can provoke adverse responses in the cardiovascular, respiratory, and other physiologic systems due to diffuse sympathetic outflow[1]. The magnitude of the response is affected by many factors affecting the technique of laryngoscopy and tracheal intubation[10]. Premedication and induction drugs may attenuate the circulatory response[11]; many drugs and techniques have been tried in an effort to attenuate adverse hemodynamic responses to laryngoscopy and endotracheal intubation.

Intravenous administration of alpha2- adrenoceptor agonist leads to transient increase in arterial BP and systemic vascular resistance because of activation of post-junctional vascular alpha2 –adrenoceptors[12] In most of the studies[13] this post-junctional alpha2 effects are seen at 2-3 min after Dexmedetomidine administration. This is followed by a longer lasting decrease in heart rate and blood pressure because of a centrally mediated decrease in sympathetic tone. Aantaa et al[14] showed that Dexmedetomidine 1 mcg/kg decreased HR by 18%, but they observed no changes in HR with doses of 0.5mcg/kg. In our study, the recording started 5min after starting the drug and in Gr D, there was a fall of HR, SBP, MAP, and DBP by 7.98% (p=0.013), 9.98% (p<0.001), 8.96% (p=0.002) and 8.76% (p=0.005) respectively was noted dur-

ing this time (T1). But similar changes in the parameters were also seen in the Gp P and the intergroup difference is not statistically significant (table2) till intubation.

The subsequent trend of HR and BP in the study reflects the reflex response to intubation. Lawrence and Lange[15] didn't observe any change in SBP after laryngoscopy and endotracheal intubation with Dexmedetomidine 2mcg/kg, but DBP increased by 1%. We found, a fall of HR, SBP, MAP and DBP by 7% (p=0.014), 5% (p=0.024), 3% (p=0.273), 3% (p=0.391) respectively just after intubation (T3) in the Gp D when the values were compared to the baseline (T0) values. But these values showed a significant difference (p<0.05) when compared with corresponding values of Gp P (table 2).

The cardiovascular response to intubation, starts within 5 seconds, peaks in 1-2 minutes and gradually returns to normal within 5minutes[16]. Rate pressure product (RPP) & Pressure rate quotient (PRQ) are two other parameters found to reflect cardiovascular stress in a particular moment. RPP is the product of HR & SBP and value of RPP is directly proportional to myocardial tissue oxygen consumption[17]. MK Urban et al[18] recommend maximum permitted value of RPP to be 12000 beats/min.mmHg and Urban et al[19] elicits RPP>12,000 beats/min.mmHg is associated with significant changes in myocardial tissue perfusion. Though the RPP values in both the groups were comparable before intubation but the values in the post-intubation period were significantly (p<0.05) low in Gp D (Table 2). Also earlier studies[20] denote RPP cannot be a marker for cardiovascular stress in elderly, as RPP is highest in 30-40 yrs age group which gradually decreases over the age when actually the cardiovascular stress is high. So Buffington[20] advocated pressure rate quotient (PRQ) to link with the cardiovascular stress. PRQ[21] was derived which is the ratio of MAP to HR and <1PRQ value sets the CVS system at risk. In our study all values in both the groups are >1 and there is no significant difference in the PRQ values in both the groups (except at time interval T3 & T4). Still the PRQ values of Gp D was always more than that in Gp P which shows less cardiovascular stress in Gp D.

Anaesthetic agent sparing effects of Dexmedetomidine may be due to its effects on CNS [22]. Thiopentone requirement (Fig 7) was lessened by 24% in comparison to the control group. This is in coherent with earlier reports [23], which quote that with Dexmedetomidine 1mcg/kg the Thiopentone requirement is decreased by 55% and with 0.5mcg/kg it is decreased by 37%.

Apnoea was found to be the only complications in this study (table 5). These cases developed apnoea before administration of Thiopentone thus suggests the sedative effects of the premedication with or without Dexmedetomidine. Alpha 2 adrenoceptors don't have an active role in respiratory center [24]. But studies [24, 25] have noticed apnoea due to infusion of Dexmedetomidine 2mcg/Kg. The cases were judged clinically and managed with bag and mask ventilation. Literature [24] also suggests various complications like bradycardia, hypotension due to loading dose more than 0.4mcg/Kg. But these effects are less when loading dose is administered over 20minutes. In our study there was no incidence of such complications.

Table 5. Complications

	Control group (n=45)	Study group (n=39)	P value
Apnoea	4(8.88%)	9(23%)	0.214

Conclusion

Dexmedetomidine 1 mcg/kg does not block the cardiovascular response to intubation completely though it significantly attenuates the effects. Values of RPP and PRQ certainly suggest obtundation of cardiovascular stress in patients who received Dexmedetomidine. But the sedative effects of the premedication can't be ignored and the patients should be monitored to avoid complications.

Conflicts of Interest

There is no conflict of interest.

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