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Attenuation of hemodynamic response during laryngoscopy & Endo tracheal intubation comparison between Thiopentone alone and with Dexmedetomidine: A Randomized Clinical Trial.

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Conflicts of Interest: Nil.

Abstract

Background and Aim

Laryngoscopy and endotracheal intubation are traditional method of securing the airway for administration of anaesthesia, but violates patient's protective airway reflexes and invariably cause haemodynamic changes associated with increased heart rate, increased blood pressure and infrequent disturbance in cardiac rhythm. Such changes arise in response to sympathoadrenal reflex causing release of catecholamine. Aim of our study is to evaluate the efficacy of Dexmedetomidine in the dose of 0.6ug/kg as a single bolus dose, before induction of anesthesia, in attenuating hemodynamic response to laryngoscopy & endotracheal intubation**.**

Method

In this randomized, double-blind, placebo-controlled, prospective study an attempt has been made to compare the efficacy of preoperative dexmedetomidine bolus infusions in attenuating the haemodynamic response following laryngoscopy and intubation. One hundred patients in the age group between 18and 50 years, of either sex, ASA- I and II, undergoing various elective abdominal surgeries under general anaesthesia were randomly allocated into two equal groups (n=50). Group-D received infusion of dexmedetomidine o.6 µg/ kg in normal saline. Group-N (control) received only normal saline infusion. The infusions were given 10 minutes before induction of anaesthesia over 10 minutes. Haemodynamic parameters (HR, SBP, DBP and MAP) were recorded before study, drug infusion, after infusion, after induction, during laryngoscopy and intubation and at 1, 2, 3, 5 and 10 minutes after intubation.

Results

Dexmadetomidine group showed less rise in HR and BP during laryngoscopy and intubation than control group. All haemodynamic parameter changes were also significantly less in Group-D at 1, 2, 3 and 5 minutes after intubation. At 10 minutes after intubation, only DBP and MAP were similar in all groups but HR and SBP still remained significantly high in Group-N.

Conclusion

Dexmedetomidine can effectively attenuate the haemodynamic response by limiting the extent of rise in heart rate and blood pressure.

Keywords: Dexmedetomidine, Laryngoscopy, Endotracheal intubation, Haemodynamic parameter alterations.

Introduction

Laryngoscopy and endotracheal intubation are traditional methods of securing the airway for administration of anaesthesia. The influence of airway manipulation on heart rate and blood pressure is well recognized for more than 50 years and the magnitude of the changes

depend mostly on the depth of anaesthesia.[1] It is now well established that laryngoscopy and endotracheal intubation violate the patient's protective airway reflexes and invariably cause heamodynamic changes such as increased heart rate, increased blood pressure and occasional disturbance in cardiac rhythm.[2,3] These heamodynamic changes arise as a form of sympathoadrenal reflex due to release of nor epinephrine and epinephrine.[4]In normotensive subjects these haemodynamic changes are short lived[5] and probably of little significance. However, these haemodynamic alterations are hazardous to the patients with hypertension, myocardial insufficiency or cerebrovascular disease.[6] In patients with coronary artery disease it may lead to myocardial ischemia and dysrhythmia because increase in heart rate and blood pressure associated with laryngoscopy and endotracheal intubation may result in an increase in myocardial oxygen demand and also demand for increased coronary flow. In hypertensive patients these exaggerated haemodynamic responses may lead to left ventricular failure, pulmonary oedema and congestive cardiac failure. In patients with intracranial aneurysm or dissecting aneurysm of the aorta the increase in systemic blood pressure may cause rupture of vessels with life threatening consequences. So effective attenuation of the sympathoadrenal stress response is an important goal in anesthesiology. Various pharmacologic and non-pharmacologic methods have been tried to limit the presser response following the insertion of endotracheal tube[7] . The success rate is variable with different methods because each method has its own merits and demerits.

In several clinical trials drugs like opioids, β-blockers, lidocaine, nitrates, calcium channel blockers or magnesium have already been used orally or parenterally to reduce this stress response. Recently, there is a considerable interest in the use of α_2-adrenergic agonists to provide haemodynamic stability during laryngoscopy and endotracheal intubation. Dexmedetomedine is an imidazoline, subclass of α_2- adrenoreceptor agonists, which reduce blood pressure and heart rate in a dose-dependent fashion.[8] The drug is reported to cause centrally mediated reduction of sympathetic nervous system activity and decrease haemodynamic response to stressful events.[9]. It is assumed that high α_2 selectivity of dexmedetomidine may result in more potent haemodynamic stabilizing effects. Available literatures suggest that premedication with intravenous dexmedetomidine significantly blunt the sympathetic stress response associated with laryngoscopy and intubation decreases haemodynamic response to endotracheal intubation following an intravenous loading dose of 0.6-2 µg/ kg [10]. In this study an attempt has been made to assess, and compare the efficacy of preoperative dexmedetomidine infusions in attenuating the haemodynamic response following laryngoscopy and endotracheal intubation.

Method

This prospective, randomized, double-blinded, placebo-controlled study was conducted after approval of the Ethical-cum-Screening Committee of V.S.S Medical College and Hospital, Burla. The study was carried out in the General Surgery OT, Gynecology OT of V.S.S Medical College and Hospital during the period from Nov'2013 to Nov'2016. In the preanaesthetic check-up clinic a detailed history was taken from each patient. A thorough general survey was performed along with examinations of the major systems. The airway of each patient was assessed according to Mallampati

classification. Routine hematological preoperative investigations and screening for HIV, HBsAg obtained. One hundred patients in the age group between 18 and 50 years, of either sex, belonging to ASA physical status I and II, undergoing various elective abdominal surgeries under general anaesthesia were selected for this study. Patients with history of cardiovascular, respiratory, hepatic or renal diseases and those on antihypertensive drugs (e.g. α_2-agonists, methyldopa, β- blockers, calcium channel blockers, ACE inhibitors), benzodiazepines and tricyclic antidepressants were excluded from the study. Patients with history of drug abuse and having serious adverse reaction or allergy to trial drug were not included in the study. Anticipated difficult intubation (Mallampati class III and IV) and pregnancy were also considered for exclusion criteria.

On the day before surgery, all patients included in the study were re- examined and advised for 8 hours fasting state preoperatively. Written informed consent was taken from all patients after explaining to them about the nature of the study and the risks involved. Night before surgery, all patients were premedicated with tablet Alprazolam 0.5 mg. In the operating room- heart rate (HR), noninvasive systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP), continuous lead II electrocardiography (ECG) and oxygen saturation (SpO_2) were recorded in every patient with the aid of multiparameter monitor . The readings obtained acted as preoperative baseline values. The 100 patients were randomly allocated into two equal groups (n=50): Group-D (dexmedetomidine), and Group-N (normal saline or control). Randomization was achieved by closed envelopes chosen by patients prior to the procedure. **Group-D:** Received 10 ml infusion containing dexmedetomidine 0.6 µg /kg in normal saline. **Group-N:** Received 10 ml infusion of 0.9% sodium chloride. The infusions were given 10 minutes before induction and infused over a period of 10 minutes. After study drug infusion, all patients were prmedicated with 0.004mg/kg glycopyrrolate and 0.5mg/kg pentazocine given intravenously and preoxygenated for 3 minutes with 100% O_2 through Mapleson-A breathing system. Induction of anaesthesia was done by 2.5% thiopentone at 5 mg/ kg slow intravenously till the eyelash reflex disappeared. Succinylcholin 1.5mg/kg were given for intubation. Subsequently tracheal intubation with an appropriate size endotracheal tube was performed using a Macintosh laryngoscope in less than 15 seconds. Confirmation of endotracheal placement of tube was done by bilateral chest auscultation and end-tidal carbon dioxide ($EtCO_2$) monitoring. Anaesthesia was maintained with 66% nitrous oxide in oxygen followed by the addition of Vecuronium bromide as muscle relaxant . Controlled ventilation was carried out with Bain coaxial breathing system adjusting the ventilation to maintain an $EtCO_2$ level between 35-40 mmHg. Haemodynamic parameters (HR, SBP, DBP and MAP) were recorded in the following specific time intervals; before study drug infusion (baseline value), after study drug infusion, after induction of anaesthesia, during laryngoscopy and intubation and 1,2,3,5,10 minutes after intubation. No surgical stimulus was allowed during the study period and haemodynamic changes beyond the study period were not taken into account. At the end of surgery, the patients were adequately reversed with neostigmine 0.05mg/kg and glycopyrrolate 0.004mg / kg intravenously as required. After oxygenation for about 15 minutes postoperatively, patients were sent to the recovery room. The patients were monitored in the postoperative period for any complications and appropriately treated if required.

Hemodynamic responses are compared in both groups by

measuring, Heart rat, Systolic blood pressure, diastolic blood pressure, mean arterial pressure as per protocol. Post operative recovery time recorded; sedation score studied as per Ramsay sedation score guide line. Results of intended study between the two groups compared statistically.

Result

The results obtained in each group of patients were tabulated, compiled and statistically analyzed using Microsoft Excel™ 2007 for Mac (version 12.0) and Smith's Statistical Package (Mac OS X) (version 2.80) software. Qualitative data (sex, ASA grade, types of operative procedures and postoperative complications) were compared between groups with Chi-Square (χ^2) test. Quantitative data (age, body weight, height, HR, SBP, DBP and MAP) were compared between groups with Microsoft Excel™ 2007. A p value < 0.05 was considered as statistically significant and < 0.01 was considered as highly significant.

Demographic Variables

Table 1. Comparison of demographic variables between two study groups.

Demographic variables	Group D (n =50) (Mean ± SD)	Group N (n =50) (Mean ± SD)	*p* value
Sex (M : F)	23:27	24:26	0.8237
Age (years)	39.07 ± 8.39	39.13 ± 8.37	0.8487
Body weight (kg)	56.90 ± 9.94	55.83 ± 8.91	0.9029
Height (cm)	160.03 ± 10.39	159.63 ± 9.57	0.7043
ASA grade (I : II)	43:7	42:8	0.9355

No significant differences were observedbetween the groups [Table 1].

Table 2. Comparison of heart rates between and within the study groups at different points of time.

Time intervals	Group N (n =50) (Mean ± D)	Group D (n =50) (Mean±SD)	P value
Before study drug infusion (baseline) (T1)	83.27 ± 9.49	84.03 ± 9.14	0.9213
After study drug infusion (T2)	83.93 ± 8.79	79.17 ± 8.66	0.0953
After induction of anaesthesia (T3)	81.80 ± 8.57	76.10 ± 8.18	0.0320
During laryngoscopy and intubation (T4)	98.47 ± 7.77	83.63 ± 6.74	<0.0001
1 minute after intubation (T5)	107.67 ± 6.38	87.63 ± 7.55	<0.0001
2 minutes after intubation (T6)	103.13 ± 6.76	86.07 ± 7.32	<0.0001
3 minutes after intubation (T7)	94.70 ± 8.41	81.83 ± 6.72	<0.0001
5 minutes after intubation (T8)	86.63 ± 6.63	78.00 ± 6.95	<0.0001
10 minutes after intubation (T9)	81.50 ± 7.48	76.83 ± 7.03	0.0200

When the preoperative baseline HR was compared between both groups, no statistically significant difference was found (p value 0.9213). HR was also similar in all groups after study drug infusion (p value 0.0953). After induction of anaesthesia, a significant reduction in HR was noted in Group D (p value0.032). The increases in HR during laryngoscopy and intubation, at 1, 2, 3 and 5 minutes after intubation were highly significant in Group N compared to Group D (p value < 0.01). After 10 minutes of intubation, it was also significant in Group N (p value 0.02).

Systolic Blood Pressure

Table 3: Comparison of systolic blood pressures between and within the study groups at different points of time

Time interval	Group N (n- 50) (Mean ± SD)	Group D (n =50) (Mean ± SD)	P value
Before study drug infusion (baseline) (T1)	120.63 ± 12.37	122.47 ± 12.22	0.8433
After study drug infusion (T2)	118.57 ± 11.12	109.70 ± 11.97	0.0104
After induction of anaesthesia (T3)	112.83 ± 11.37	101.33 ± 10.96	<0.0001
During laryngoscopy and intubation (T4)	137.60 ± 8.05	118.77 ± 8.15	<0.0001
1 minute after intubation (T5)	148.00 ± 7.60	123.50 ± 9.10	<0.0001
2 minutes after intubation (T6)	142.47 ± 7.52	122.53 ± 8.02	<0.0001
3 minutes after intubation (T7)	130.23 ± 7.97	113.73 ± 8.51	<0.0001
5 minutes after intubation (T8)	119.97 ± 7.87	110.30 ± 8.66	<0.0001
10 minutes after intubation (T9)	113.47 ± 8.44	109.07 ± 8.85	0.0363

When the preoperative baseline SBP was compared between two groups, no statistically significant difference was found. After study drug infusion, a

significant reduction in SBP was noted in Group D (*p* value0.0104). After induction of anaesthesia, this reduction in SBP became highly significant in Group D (*p* value < 0.01). The increases in SBP during laryngoscopy and intubation, at 1, 2, 3 and 5 minutes after intubation were highly significant in Group N compared to Group C and Group D (*p* value <0.01). After 10 minutes of intubation, it was also significant in Group N (*p* value 0.0363).

Diastolic Blood Pressure

Table 4: Comparison of diastolic blood pressures between and within the study groups at different points of time.

Time interval	Group N (n =50) (Mean ± SD)	Group D (n =50) (Mean ± SD)	p value
Before study drug infusion (baseline) (T1)	79.27 ± 9.67	79.73 ± 9.47	0.8082
After study drug infusion (T2)	78.00 ± 9.17	72.10 ± 8.25	0.0374
After induction of anaesthesia (T3)	73.53 ± 9.46	67.67 ± 7.69	0.0307
During laryngoscopy and intubation (T4)	87.83 ± 6.65	78.37 ± 7.42	<0.0001
1 minute after intubation (T5)	95.87 ± 7.21	81.83 ± 7.55	<0.0001
2 minutes after intubation (T6)	92.33 ± 6.79	80.47 ± 7.15	<0.0001
3 minutes after intubation (T7)	83.47 ± 7.21	75.93 ± 7.58	0.0019
5 minutes after intubation (T8)	78.83 ± 6.52	73.13 ± 7.41	0.0129
10 minutes after intubation (T9)	73.23 ± 7.27	72.37 ± 7.88	0.6217

When the preoperative baseline DBP was compared between three groups, no statistically significant difference was found (*p* value 0.8082). Significant reductions in DBP were noted in Group D after study drug infusion (*p* value 0.0374) and after induction of anaesthesia (*p* value 0.0307). The increases in DBP during laryngoscopy and intubation, at 1, 2, and 3 minutes after intubation were highly significant in Group N compared to Group C and Group D (*p* value < 0.01). After 5 minutes of intubation, it was also significant in Group N (*p* value 0.0129). DBP became similar in all groups after 10 minutes of intubation (*p* value 0.6217) .

Mean Arterial Pressure

Table 5. Comparison of mean arterial pressures between and within the study groups at different points of time.

Time interval	Group N (n =50) (Mean ± SD)	Group D (n =50) (Mean ± SD)	p value
Before study drug infusion (baseline) (T1)	93.07 ± 10.57	93.90 ± 10.33	0.8923
After study drug infusion (T2)	91.43 ± 9.66	84.70 ± 9.41	0.0246
After induction of anaesthesia (T3)	86.67 ± 10.09	78.90 ± 8.68	0.0069
During laryngoscopy and intubation (T4)	104.47 ± 6.88	91.83 ± 7.49	<0.0001
1 minute after intubation (T5)	113.20 ± 7.18	95.80 ± 7.91	<0.0001
2 minutes after intubation (T6)	109.07 ± 6.81	94.50 ± 7.33	<0.0001
3 minutes after intubation (T7)	99.00 ± 7.33	88.57 ± 7.61	<0.0001
5 minutes after intubation (T8)	92.50 ± 6.80	85.50 ± 7.51	0.0014
10 minutes after intubation (T9)	86.63 ± 7.58	84.60 ± 7.93	0.2971

When the preoperative baseline MAP was compared between three groups, no statistically significant difference was found (*p* value 0.8923). After study drug infusion, a significant reduction in MAP was noted in Group D (*p* value 0.0246). After induction of anaesthesia, this reduction in MAP became highly significant in Group D (*p* value < 0.0069). The increases in MAP during laryngoscopy and intubation, at 1, 2, 3 and 5 minutes after intubation were highly significant in Group N compared to Group C and Group D (*p* value < 0.01). MAP became similar in all groups after 10 minutes of intubation (*p* value 0.2971).

The HR in the postoperative period less than 60 bpm was considered as bradycardia. Two patients in Group D had HR below 60 bpm in the early postoperative period. Postoperative SBP less than 90 mmHg, or DBP less than 60 mmHg, or both were considered as hypotension. Non shows hypotension. Hypoxaemia was adjudged by any drop in SpO_2 below 90% and it was seen in six patients (two in each group) in the early postoperative period. Two patients in each group complained of shivering in the recovery room. Postoperative nausea was complained by two patients in Group D and six patients in Group N. When these complications were compared

between three groups with Chi- Square (χ^2) test, no statistically significant difference was found.

Discussion

Laryngoscopy and endotracheal intubation are associated with rise in heart rate, blood pressure and occasional disturbance in cardiac rhythm.[2,3] Although in normotensive subjects these responses of blood pressure and heart rate are transient,[5] they may prove to be detrimental in high risk patients especially in those with cardiovascular disease, increased intracranial pressure and anomalies of the cerebral blood vessels.[6] So, effective attenuation of haemodynamic response to laryngoscopy and tracheal intubation is of great importance in prevention of perioperative morbidity and mortality.

This randomized, double-blind, placebo-controlled study was undertaken to compare the usefulness most popular α_2-adrenergic agonists dexmedetomidine in attenuation of the haemodynamic response following laryngoscopy and endotracheal intubation. The factors influencing the cardiovascular changes associated with laryngoscopy and intubation are age, drugs, type and duration of procedures, depth of anaesthesia, hypoxia and hypercarbia etc. Variations in heart rate to stressful events decrease with increasing age. Marked fluctuations in haemodynamic response have been also reported in geriatric patients. Therefore, patients with an optimal age range of 18 to 50 years were selected for this study. Difficult intubation takes longer time and is invariably associated with marked haemodynamic change even in well premedicated patients. So, patients with higher Mallampati class (III and IV) were excluded from this study. Patients on antihypertensive drugs were also excluded as they might exhibit a decrease in pressure response to laryngoscopy and intubation. α_2 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.

Ideally, dexmedetomidine should be used as continuous infusion after a loading dose to achieve a sustained clinical effect as it has a short distribution half-life of 6 minutes. Here we used only loading dose0.6mic/kg of dexmedetomidine to blind our study easily. This is a short clinical study and main focus was on the first few minutes following laryngoscopy and intubation. This is another reason for using singl dose of dexmedetomidine.

After study drug infusion a significant fall in HR (p value < 0.05) and highly significant fall in NIBP (SBP, DBP and MAP) (p value < 0.01) were noted in Group D. This is most probably due to the difference between the onsets of action of two study drugs. Dexmedetomidine has rapid onset of action (15 minutes) after its administration .There was also a decrease in thiopental dose up to19% for induction loss of eye reflex as an indicator. BP decreased further in both groups after induction of anaesthesia. These decrements were highly significant in Group D (p value < 0.01) and significant in Group N (p value < 0.05). This is most likely due to vasodilatation and depression of medullary vasomotor centre caused by thiopental. Reflex tachycardia associated with thiopental induction, is not seen in this study. The baseline HR and post induction HR were similar in Group N (p value > 0.05). HR decreased significantly from the baseline value Group D (p value < 0.01) after induction of anaesthesia due to the negative chronotropic effect of the α_2-agonists.

The most significant factor influencing cardiovascular responses is the duration of laryngoscopy. The force applied during laryngoscopy has only minor effect. In this study the durations of laryngoscopy and intubation were limited to less than 15 seconds. During laryngoscopy adequate depth of anaesthesia was maintained avoiding hypoxia and hypercarbia. Haemodynamic parameters in Group D remained around the baseline value in first 2 to 3 minutes after intubation followed by a gradual fall in the next few minutes. Thereafter, no alteration in HR and BP was seen in Group D. Similar findings were documented by Kaya C *et al* (2006) in their study with intramuscular dexmedetomidine.

Ramsay sedation score before induction shows that out of 50 patients 5 are having score 3 and rest are having score 2 in dexmedetomidine group. In control group all patients showed sedation score of 2. In extubation Ramsay sedition score all 50 patients are having a score of 2, in dexmedetomidine group versus 47 patients had a score of 2 while 3 had a score of 1 in control group. Four in group N and 2 in group D patients showed certain dysrhythmia during laryngoscopy and intubation on continuous ECG monitoring. These included mostly sinus tachycardia and ventricular premature contractions. However, none of these dysrhythmias reached alarming levels during the study to require treatment and converted to normal sinus rhythms spontaneously.

Regarding complications, two patients in Group D had bradycardia in the early postoperative period. Intravenous atropine was prescribed them to normalize the HR. Hypoxaemia was seen in six patients (three in each group) in the early postoperative period, which was corrected by the administration of oxygen by face mask alone. None of them had to be intubated or required artificial ventilation postoperatively. Two patients in each group complained of shivering in the recovery room, which was resolved with warm blanket covering and oxygen supplementation. Postoperative nausea was complained, two patients in Group D and six patients in Group N. These patients were treated with intravenous ondansetron. Serum catecholamine is the most important markers to assess the sympathoadrenal stress response to any stimulus. But, in this study we could not measure its level in every patient due to scarcity of the resources. This is the major limitation of our study.

Conclusion

From these observations and analysis of the present study, it can be inferred that dexmedetomidine administered intravenously just before laryngoscopy and endotracheal intubation effectively attenuate the haemodynamic response by limiting the extent of rise in heart rate and blood pressure. Dexmedetomidine has been found to provide better haemodynamic stability and the α_2-agonist is devoid of any serious adverse effect and found safe in this study.

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