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Dexmedetomidine, the ideal drug for attenuating the pressor response

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Key points

Adult and pediatric patients with cardiovascular and cerebrovascular disease are at risk of tachycardia and hypertension following laryngoscopy and tracheal intubation with deleterious effects in the form of myocardial ischemia, pulmonary edema and cerebral hemorrhage. Many methods have been tried to obtund the pressor response, but none proved to be ideal. Administration of dexmedetomidine at a dose of 0.6 µg/kg IV, given 10 minutes before induction has served the purpose.

Abstract

Laryngoscopy and endotracheal intubation is often associated with hypertension and tachycardia because of the sympathoadrenal stimulation which is usually transient and lasts for 5-10 minutes. In patients with cardiovascular and cerebrovascular disease, this sudden rise in Heart Rate (HR) and blood pressure can produce deleterious effects in the form of myocardial ischemia, pulmonary edema and cerebral hemorrhage. Many methods have been tried to obtund the haemodynamic response in adult and pediatric patients, but none proved to be ideal. Dexmedetomidine has been particularly effective in blunting the haemodynamic response to laryngoscopy and tracheal intubation.

Aims

To study the efficacy of 0.6 µg/kg dexmedetomidine IV, given 10 minutes (min) before induction to obtund the pressor response of laryngoscopy and tracheal intubation.

Methods

100 normotensive patients aged 14-55 years old were assigned randomly into two groups. 10 min before induction these two groups received, group C (n=50): received 10 ml normal saline (NS) IV over 10 min, group D (n=50): received dexmedetomidine 0.6µg/kg body weight diluted to 10 ml NS IV over 10 min. After induction of anaesthesia, HR, SBP, DBP and MAP were recorded at various time intervals like before induction, after induction and 1, 3, 5 and 10 min after laryngoscopy and intubation.

Results

It was noted that in group C, following laryngoscopy and intubation, the mean rise in HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) were found to be 36.24 bpm, 30.02 mmHg, 22.34 mmHg and 26.42 mmHg respectively, one minute after intubation. In group D, the mean of HR, SBP, DBP and MAP were decreased

by 2.86 bpm, 15.86 mmHg, 9.54 mmHg and 1.98 mmHg respectively compared to basal values which was statistically highly significant (p=0.000). In addition dexmedetomidine reduces the requirement of thiopentone and vecuronium bromide and produces arousable sedation after extubation with minimal incidence of bradycardia and hypotension.

Conclusions

Dexmedetomidine (0.6µg/kg) IV, given 10 min before induction was seen to effectively attenuate the pressor response to laryngoscopy and tracheal intubation without any side effect.

Keywords: laryngoscopy; tracheal intubation; pressor response; dexmedetomidine.

Introduction

Laryngoscopy and tracheal intubation in adults are commonly accompanied by increase in arterial blood pressure and heart rate.[1]

The magnitude of haemodynamic changes observed may be dependent on various factors such as depth of anaesthesia, whether any measures are taken prior to airway manipulation, the anaesthetic agent used, the duration of laryngoscopy and intubation.

To date, the exact mechanism of haemodynamic responses to laryngoscopy and intubation has not been clarified. The principle mechanism in hypertension and tachycardia is the sympathetic response[2, 3] which may be the result of increase in catecholamine activity.[4]

The increase in the pulse rate and blood pressure are usually transitory, variable and unpredictable. Transitory hypertension and tachycardia are probably of no consequence in healthy individuals but either or both may be hazardous to those with hypertension, myocardial insufficiency or cerebrovascular diseases.[4] This laryngoscopic reaction in such individuals may predispose to development of pulmonary edema, myocardial insufficiency and cerebrovascular accident.[5,6]

Pressor response is exaggerated in hypertensive patients even though rendered normotensive pre-operatively by antihypertensive medication.[7]

Pressor response may result in intra-operative myocardial infarction,[8] acute left ventricular failure,[8] dysrrhythmias[9] and intracranial bleed[8] in individuals with end organ decompensation. Intravenous anaesthetic induction agents do not adequately or predictably suppress the circulatory responses evolved by endotracheal intubation.[10]

So prior to initiating laryngoscopy, additional pharmacological measures like use of volatile anaesthetics, topical and intravenous lidocaine, opioids, vasodilators – Sodium nitroprusside, Nitroglycerine, Calcium channel blockers and β-blockers have been tried by various authors.

Besides minimizing the cardiovascular response, anaesthesia induction for patients at risk must also satisfy the following requirements i.e. it must be applicable regardless of patients group, prevent impairment of cerebral blood flow and avoid awareness of the patient.

It should neither be time consuming nor affect the duration or modality of the ensuing anaesthesia and also should not have any effect on the recovery. None of these drugs mentioned above have been found to be effective in attenuating the pressor response to intubation. Hence there is a need of find out the drug which can attenuate pressor response. α_2 agonists is being used for attenuating the pressor response[11] and among α_2 agonists both clonidine and dexmedetomidine appear to fulfill all the above criteria.

Both clonidine and dexmedetomidine have actions on both α_1 and α_2 receptors but dexmedetomidine is highly specific and selective α_2 adrenoceptor agonist with α_2:α_1 binding selectivity ratio of 1620:1 compared to 220:1 for clonidine.[12]

The advantage of intravenous dexmedetomidine as premedicant in anaesthesia includes sedation, analgesia, anxiolysis and improved haemodynamic stability.

Because of these beneficial properties it has been found that the minimum alveolar concentration (MAC) of volatile anaesthetics also decreases significantly up to 90% and hence decreases the requirement of anaesthetic agents.[13, 14]

Aims and objectives

1. To evaluate the efficacy of intravenous dexmedetomidine in the dose of 0.6µg/kg body wt in attenuating the haemodynamic responses to laryngoscopy and endotracheal intubation.
2. To study the effects of dexmedetomidine on the induction dose requirement of thiopentone and dose requirement of vecuronium bromide in anaesthesia.
3. To study any adverse effects associated with dexmedetomidine administration such as increased sedation, prolonged recovery, hypotension and bradycardia.

Matherials and Methods

After obtaining ethical committee clearance as well as informed consent from all patients, 100 patients, scheduled for various elective surgical procedures belonging to ASA grade I and II of both the sex were included in the study. The patients were normotensive with age varying from 14 to 55 years. Patients with cardiac, coronary, renal, hepatic, cerebral, peripheral vascular diseases, hypertension, heart blocks, difficult airway and obese patients (BMI>30) and endocrinal diseases like hyperthyroidism, hypothyroidism, diabetes mellitus were excluded from the study.

The patients were randomly divided into two groups with 50 patients in each group. 10 min prior to induction, group C - Control group (n=50): received 10 ml of NS IV over 10 min using syringe pump, group D - Dexmedetomidine (n=50): received injection dexmedetomidine 0.6µg/kg body wt diluted to 10 ml NS IV over 10 min using syringe pump.

Pre-anaesthetic evaluation was done for all the patients and routine investigations like complete blood count (CBC), Urine examination (RE and ME), electrocardiogram (ECG) of all the patients were done.

On arrival of the patient in the pre-operating room, an 18-gauge intravenous cannula was inserted and an infusion of ringer lactate was started. The patients were connected to multiparameter monitor with HR, non-invasive measurements of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), end tidal carbon dioxide (EtCO2) and continuous ECG monitoring and oxygen saturation. After recording the baseline reading, 10 min before induction, patients in group D received dexmedetomidine 0.6µg/kg body wt diluted in 10 ml NS IV over 10 min using syringe pump and patients in group C received 10 ml NS IV using syringe pump. The study drug was prepared by the anaesthesiologist who was blinded with the study. A solution of 5 µg/ml of dexmedetomidine was prepared. Depending on the body wt, volume of the diluted drug in saline or NS was infused through a syringe pump.

All the patients were premedicated with Inj ranitidine 50 mg IV, Inj metaclopramide 10mg IV, Inj Midazolam 0.02mg/kg IV and injection Pentazocine 0.3mg/kg IV after test drug administration. Patients were preoxygenated for 3 min with face mask. Anaesthesia was induced with thiopentone 5 mg/ kg, as a 2.5% solution till loss of eye lash reflex occurred and dose of thiopentone required for loss of eye lash reflex recorded. Endotracheal intubation was done with 1.5mg/kg IV succinylcholine. Laryngoscopy was performed using Macintosh blade lasting for not more than 15 seconds and intubation with portex endotracheal tube (ETT), after confirmation of bilateral equal air entry, ETT was fixed. If time for laryngoscopy and intubation exceeded for 15 seconds, such patients are excluded from the study. Anaesthesia was maintained using 60% nitrous oxide and 40% of oxygen. After the patients recovered from the effect of succinylcholine further neuromuscular blockade was maintained with vecuronium 0.05 mg/ kg body weight. No surgical stimulus was applied during 10 min of study period and vecuronium was the only additional drug given during

this 10 min period. At the end of the procedure total dose of vecuronium required for the surgery was recorded and patients were reversed with neostigmine 0.05 mg/kg body weight and glycopyrollate 0.04 mg/ kg body weight. Sedation scoring at the end of the surgery was done using Ramsay sedation score. Vital parameters like HR, SBP, DBP and MBP were recorded before induction, after induction and 1, 3, 5 and 10 min after laryngoscopy and intubation.

Hypotension was defined as SBP ≤ 20% of baseline value. Tachycardia was defined as HR > 25% of baseline value. Bradycardia was defined as HR < 20% of base and dysrrhythmia was defined as any rhythm other than sinus.

Incidences of all these parameters were recorded in both the groups. The side effects of the study drug like hypotension, bradycardia and sedation were noted.

Statistical Methods

The sample size was determined by power analysis performed by a pilot study. A sample size of

50 patients per group was required to detect a 20% change in heart rate, blood pressure and pulmonary artery pressure between baseline and intubation time, with a power of 80% at the 5% significance level. Data are expressed as the mean±standard deviation. Independent *t*-test was used to compare the study group and the control group. Paired *t*-test was used to compare the variable before and after the intervention. Chi-square test was used to analyze the categorical data and for testing the association between the variables. Nonparametric tests (Wilcoxon signed rank tests [two tailed]) were used whenever the mean value was less than two times the standard deviation. A *P* value of less than 0.05 was considered statistically significant. The package SPSS 17.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

The groups were well-matched for their demographic data (Figure 1).

The basal heart rate were comparable in both groups (p=1.000). Statistical evaluation between the groups showed a significant fall in HR in group D at 2, 5 and 8 min of drug administration and before and after induction. The mean HR increase observed at 1, 3, 5 and 10 min after intubation in group C was statistically highly significant compared to mean HR in group D (p=0.000).

Figure 1*. Showing the age distribution. Mean age in years±SD, Group C 35.4±8.8, Group D 35.52± 8.76, p-value 0.835 (NS).*

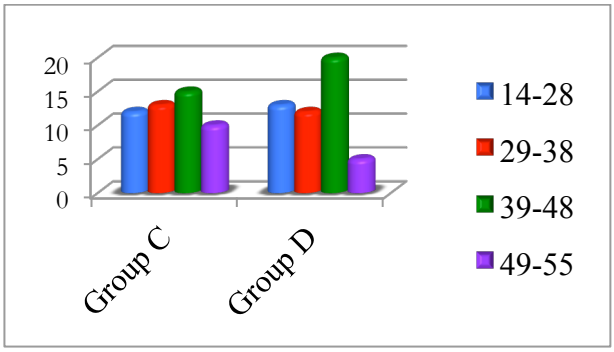
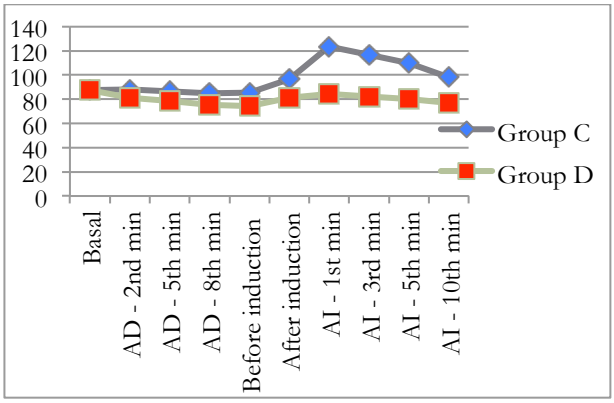


Figure 2. *Showing the comparison of mean heart rate (bpm) changes between Control group and Dexmedetomidine group. AI-After intubation*



The mean SBP were comparable in both groups (p=0.734). After 2 min of drug administration the change in SBP was not significant (0.456). The mean SBP values at 5 and 8 minutes of drug administration, before and after induction were significantly low (p=0.000) compared to group C. The increase in SBP in group C at 1, 3, 5 and 10 minutes after intubation was

statistically highly significant (p=0.000) compared to group D. The mean basal DBP are comparable in both groups (p=0.223). The mean DBP at 2nd min after drug administration was statistically not significant (p=0.674).

Figure 3. *Showing comparison of systolic blood pressure (SBP in mmHg) changes between Control group and Dexmedetomidine group*

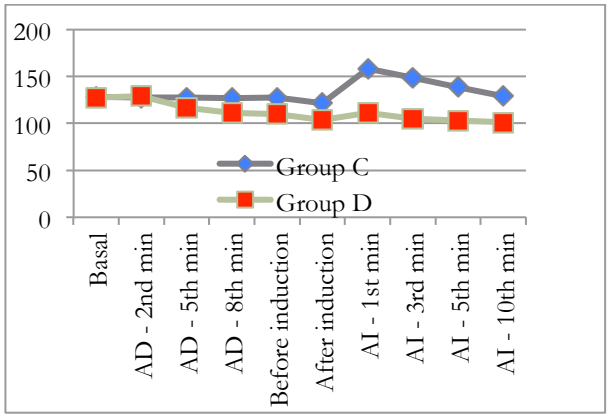
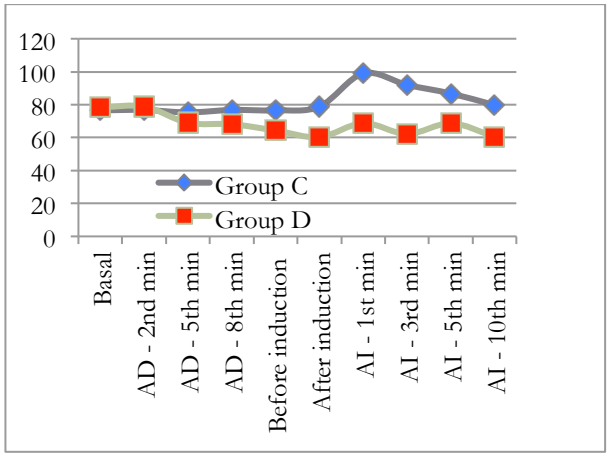
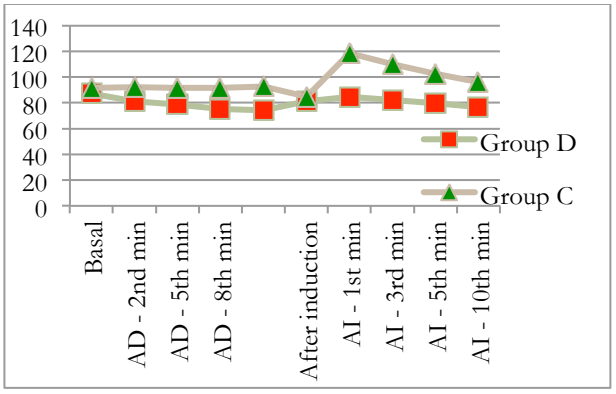


Figure 4. *Showing comparison of diastolic blood pressure (DBP in mmHg) changes between Control and Dexmedetomidine group. AI-After intubation*



The mean DBP values at 5 and 8 minutes of drug administration, before and after induction were significantly low (p=0.000) in group D compared to group C. The increase in DBP in group C at 1, 3, 5 and 10 minutes after intubation was statistically highly significant (p=0.000) compared to group D.

Figure 5. *Showing comparison of mean blood pressure (MBP in mmHg) changes between Control and Dexmedetomidine group. AI-After intubation*



The mean basal MBP are comparable in both groups (p=1.000). After 2 min of drug administration the change in MBP was statistically not significant (p=0.812).

There was a significant difference in MBP values at 5th min, 8th min after drug administration and before and after induction which was statistically highly significant (p=0.000). The increase in MBP in group C was statistically highly significant at 1 min and 3, 5 and 10 minutes after intubation (p=0.000) compared to group C.

Table 1. *Showing the dose of thiopentone required for induction in Control and Dexmedetomidine group.*
(p<0.01)- Highly significant (HS); (p<0.05)- Significant (S); (p>0.05) -Not significant (NS)

	Mean Dose of thiopentone required for induction (mg)
Group C	278±34.49
Group D	170.5±30.17
p-value	0.000 (HS)

Table 2. *Showing the total dose of vecuronium bromide required for muscle relaxation in Control and Dexmedetomidine group.*
(p<0.01)- Highly significant (HS); (p<0.05)- Significant (S); (p>0.05) -Not significant (NS)

	Dose of Vecuronium bromide required for muscle relaxation (mg)
Group C	4.70±1.36
Group D	3.74±1.22
p-value	0.000 (HS)

Table 3. *Showing the sedation score between Control and Dexmedetomidine group.*
(p<0.01)- Highly significant (HS); (p<0.05)- Significant (S); (p>0.05) -Not significant (NS)

	Sedation score
Group C	2.62±0.49
Group D	2.52±0.43
p-value	0.087 (NS)

Table 4. *Showing the side effects between Control and Dexmedetomidine group.*
(p<0.01)- Highly significant (HS); (p<0.05)- Significant (S); (p>0.05) -Not significant (NS)

	Nil	Bradycardia	Hypotension	Bradycardia and hypotension
Group C	50	0	0	0
Group D	42	5 (1 paediatric)	3	1
p-value	0.034 (S)			

HR values were statistically significantly lower in the dexmedetomidine group at all time intervals when compared with the control group (Figure 2). There was a statistical significance in the systolic arterial pressure (Figure 4), mean arterial pressure (Figure 3) and diastolic arterial pressure (Figure 5) between groups after drug at the 1st, 3rd, 5th and 8th min post intubation. The dexmedetomidine group had a better control of heart rate and blood pressure than the control group.

Statistical evaluation between the groups showed a statistically highly significant reduction in dose of thiopentone sodium required for induction (p=0.000) (Table 1), reduction in dose of vecuronium bromide for muscle relaxation (p=0.000) (Table 2). Sedation score between the two groups was not significant (Table 3). 5 patients (1 paediatric) had bradycardia, 3 had hypotension and one patient had both bradycardia and hypotension in dexmedetomidine group which did not need any treatment, while none with control (Table 4).

Discussion

Laryngoscopy and endotracheal intubation are considered as the most critical events during general anesthesia. They provoke a transient, but marked, sympathetic and sympathoadrenal response. But in patients with cardiovascular compromise like hypertension, ischemic heart disease, and cerebrovascular disease and in patients with intracranial aneurysms, even these transient changes in haemodynamics can result in potentially harmful effects like left ventricular failure,[8] pulmonary edema, myocardial ischemia,[8] ventricular dysrhythmias[9] and cerebral haemorrhage. α_2 adrenergic drugs, such as clonidine or dexmedetomidine, attenuate these potentially harmful cardiovascular reactions during induction of anesthesia. In our study, we compared dexmedetomidine, a newer α_2 agonist, with additional properties such as sedation, anxiolysis and sympatholysis for attenuating the hemodynamic response to laryngoscopy and tracheal intubation.

Dexmedetomidine offers a unique pharmacological profile with sedation, sympatholysis, analgesia, cardiovascular stability and with great advantage to avoid respiratory depression in adult and paediatric patients. In particular, dexmedetomidine can provide a dose dependent cooperative sedation that allows ready

interaction with the patient. All these above-said aspects of its pharmacological profile render it suitable as an anesthetic adjuvant and also as intensive care unit sedation.

Dexmedetomidine increases the hemodynamic stability by altering the stress induced sympathoadrenal responses to intubation during surgery and during emergence from anesthesia.[14] Jaakola et al.,[15] in their study concluded that dexmedetomidine attenuates the increase in heart rate and blood pressure during intubation. The dose used for this study was similar to the dose used by us.

Scheinin et al.,[16] studied the effect of dexmedetomidine on tracheal intubation, required dose of induction agent and preoperative analgesic requirements. They concluded that the required dose of thiopentone was significantly lower in the dexmedetomidine group and the drug attenuated the hemodynamic responses to intubation. The concentration of noradrenaline in mixed venous plasma was lesser in the dexmedetomidine group.

Lawrence et al.,[17] found that a single dose of 2 μg/kg of dexmedetomidine before induction of anesthesia attenuated the hemodynamic response to intubation as well as that to extubation. Bradycardia was observed at the 1st and 5th min after administration. This might have been due to bolus administration.

Sulaiman, et al.[21] studied the effects of dexmedetomidine on attenuation of stress response to endotracheal intubation in patients undergoing elective off pump coronary artery bypass grafting (CABG), they concluded that pretreatment with dexmedetomidine at a dose of 0.5 μg/kg as 10 min infusion prior to induction of anesthesia attenuate the hemodynamic response to laryngoscopy and intubation. Dexmedetomidine can be considered before induction of general anesthesia in patients undergoing myocardial revascularization, even if the patients are receiving beta blockers.

It is a well-known fact that depression of sympathetic response against laryngoscopy and intubation is an important advantage, especially in high risk patients. The hypotension and bradycardia caused by dexmedetomidine, theoretically, could limit its usage in previously beta blocked ischemia heart patients. Few studies used dexmedetomidine as an anesthetic adjuvant in CABG patients receiving beta blockers, and reported that the intraoperative incidence of bradycardia requiring treatment was not more common in the dexmedetomidine group than in the control group.[17,18] A biphasic cardiovascular response has been described after the administration of dexmedetomidine.[19] A bolus of 1 μg/kg results in a transient increase in arterial blood pressure and reflex decrease in heart rate in young healthy patients. Initial response is due to α_2 receptor stimulation of vascular smooth muscle. This response can be markedly decreased by slow infusion over 10 min. In our study, this effect was not noticed due to the slow infusion of the drug over 10 min.

Studies suggest that perioperative use of dexmedetomidine may result in a decreased risk of adverse cardiac events, including myocardial ischemia.[20] α adrenoreceptors stimulation can beneficially modulate coronary blood flow during myocardial ischemia by preventing transmural redistribution of blood flow away from the ischemic endocardium, by specific epicardial vasoconstrictive effects, leading to improvement in endocardial perfusion (the reverse steal effect) and by decreasing heart rate. This property along with hemodynamic stability and attenuation of intubation response makes dexmedetomidine an ideal anesthetic adjuvant, particularly for patients undergoing coronary bypass grafting. Dexmedetomidine has been also administered in infant following open heart surgery[22] with a decrease in heart rate during the immediate postoperative time together with an effective and safe sedation.

The limitations regarding this study are that we did not measure the plasma norepinephrine levels and extubation response was not studied.

Conclusions

Dexmedetomidine at a dose of 0.6µg/kg in 10 ml NS, given 10 min before induction significantly obtunds the haemodynamic response to laryngoscopy and tracheal intubation in adult and paediatric patients. It also decreases the requirement of induction dose of thiopentone and also the requirement of the total dose of vecuronium bromide for muscle relaxation without significant side effects.

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