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Attenuation of hemodynamic pressor response to endotracheal intubation by dexmedetomidine in elective cardiac surgery: A randomized controlled trial

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Abstract

Selective alpha$_2$ adrenergic agonist dexmedetomidine is well known to inhibit catecholamine release. The present study has been conducted to determine the effects of intravenously administered dexmedetomidine in attenuating hemodynamic pressor responses to endotracheal intubation during elective cardiac surgery. 90 patients of American Society of Anesthesiologists (ASA) physical status II and III, aged between 18 to 45 years of both the sex, were randomized into 2 groups receiving dexmedetomidine 0.5 µg/kg and normal saline respectively, administered over a period of 10 minutes before induction. Following intubation, significant (p<0.05) rise in heart rate and arterial pressure was observed in control group while dexmedetomidine group showed better control of hemodynamic pressor responses. In our double-blinded randomized controlled trial, administration of dexmedetomidine before commencement of anesthetic induction effectively attenuated hemodynamic pressor response to laryngoscopy and intubation. Further, larger trials are needed to confirm our findings.

Keywords: Dexmedetomidine, elective cardiac surgery, endotracheal intubation, hemodynamic pressor response.

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Introduction

Laryngoscopy and endotracheal intubation is an integral part of balanced general anesthesia and resuscitative measures in intensive care units. During endotracheal intubation, the blade of direct laryngoscope presses against the base of tongue to lift up the epiglottis and expose the vocal cords. It is a noxious stimulus, which can provoke untoward response in the cardiovascular, respiratory and other physiological systems [1]. This response can be sympathetic or parasympathetic. Parasympathetic response is seen in pediatric population while in adults, sympathetic response predominates [2, 3]. Increase in catecholamine release leads to sympathetic stimulation causing hemodynamic pressor response [4].

Hypertension, tachycardia and arrhythmia caused by endotracheal intubation can be deleterious in patients with poor cardiovascular reserve. Such hemodynamic changes may alter the delicate balance between myocardial oxygen demand and supply precipitating myocardial ischemia in patients with coronary artery disease [5, 6]. Anesthetic induction agents alone are not enough to suppress these circulatory changes. Different pharmacological agents like volatile anesthetics, topical and intravenous lignocaine, beta-blockers, calcium channel blockers, opioids, sodium nitroprusside, and nitroglycerine are often used to supplement anesthetic induction. But till date, the search for an ideal agent is going on which is easier to administer, has wide therapeutic range, has no effects on anesthetic agents used, has no serious adverse effects and will prevent significant changes in vital parameters during intubation. Alpha$_2$ adrenergic agonists are especially useful in this aspect.

Clonidine has been successfully used in coronary artery bypass graft patients [7]. Dexmedetomidine is a highly selective, potent and specific alpha$_2$ agonist with a shorter duration of action [8]. It has advantages of sedation, analgesia, anxiolysis and improved hemodynamic stability [9]. In addition, it may offer benefits in the prophylaxis and adjuvant treatment of perioperative myocardial ischemia [10]. The present study was designed in a prospective, randomized, double-blind fashion to determine the efficacy of intravenous dexmedetomidine in the attenuation of hemodynamic pressor response during endotracheal intubation in elective cardiac surgery.

Materials and methods

After approval from institutional ethical and written informed consent of the patients, this study was conducted in Nilratan Sircar Medical College and Hospital, a tertiary care medical college hospital in eastern India. 90 patients of American Society of Anesthesiologists (ASA) physical status II and III, aged between 18 to 45 years of both the sex scheduled for elective cardiac surgery (ASD and VSD closure) were enrolled in this study. Power calculations suggested that a minimum of 41 subjects per group were required to detect 20 beats/minute difference in heart rate between groups (taking type I or α error of 5%, type II or β error of 15% and Standard Deviation = 30). To be on a safer side, 45 patients were included in each group (n=45).

Patients with valvular dysfunction, left ventricular ejection fraction (LVEF) < 40%, second and third degree heart block, hepatic or renal disease, allergy to drugs used were excluded from the study. Patients concomitantly taking clonidine, methyl dopa, beta blockers, calcium channel blockers, benzodiazepines, MAO (Mono Amine Oxidase) inhibitors; patients having difficult airway or intubation taking more than 15 seconds were also excluded from the study.

During pre-anesthetic check up, patients were examined and interviewed. On arrival in the pre-operating room, a 16 gauge peripheral venous cannula was inserted after proper application of local anesthetic (LA). All patients were premedicated with midazolam 0.05 mg/kg. On arrival in the operation theatre (OT), monitors were attached and baseline parameters like heart rate, NIBP (Non Invasive Blood Pressure), oxygen saturation, ECG (Electrocardiogram) were recorded. Radial artery cannulation for IBP (Invasive Blood Pressure) done under LA. Folley's catheterization done with lignocaine gel for urine output monitoring.

Immediately before induction, patients were randomly divided into two equal groups (n=45) using sealed envelopes chosen by the patients.

The groups were:-

i) Control group (group C) – received 50 ml of normal saline.

ii) Dexmedetomidine group (group D) – received dexmedetomidine 0.5 µg/kg in normal saline.

Total volume of the study drug was adjusted to 50 ml and administered over a period of 10 minutes before induction. The preparation, labeling and administration of the study drugs were done by an anesthesiologist who was not involved in this study (so this was a prospective, randomized, double-blinded study).

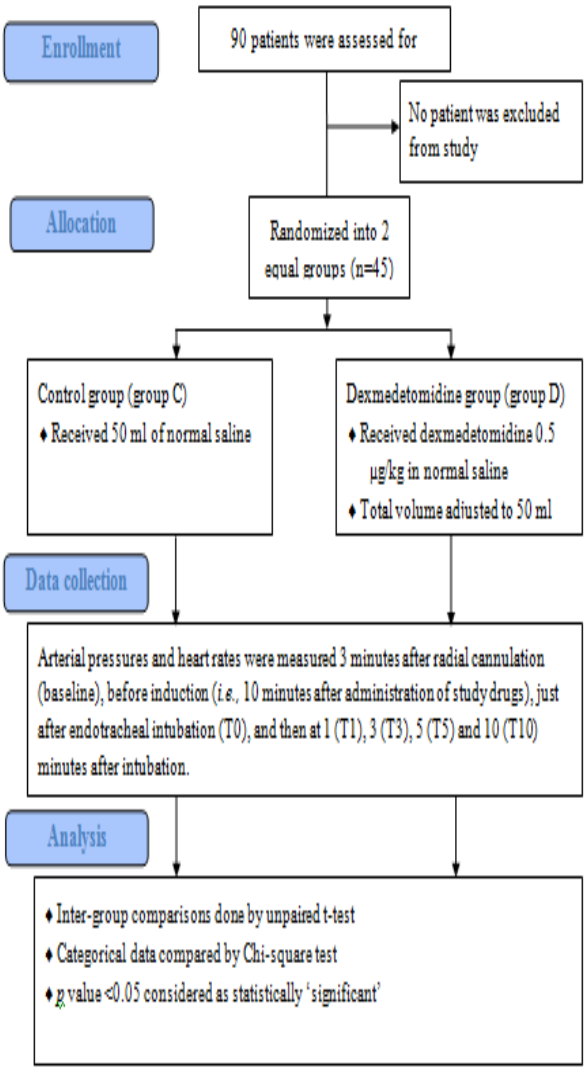
Baseline vital parameters were recorded after 3 minutes of resting period following insertion of the radial cannula. Over the next 10 minutes, study drugs were given through syringe pumps. Next 10 minutes were allowed for stabilization and then vital parameters were recorded. After pre-oxygenation for 3 minutes, anesthesia was induced in a standard anesthetic protocol using fentanyl 5 µg/kg and etomidate 0.2-0.4 mg/kg in titrating dose till loss of eyelash reflex. Tracheal intubation was facilitated by vecuronium bromide 0.1 mg/kg intravenously. After intubation, central venous catheter was inserted in the right internal jugular vein.

Anesthesia was maintained by nitrous oxide (N_2O): oxygen (O_2): sevoflurane (66:33:1) with controlled ventilation. Fentanyl and vecuronium were used in incremental doses every 20 minutes. Ventilation was adjusted to maintain normocarbia $ETCO_2$ (End Tidal Carbon Dioxide) was maintained between 25-40 mm Hg]. During surgery, Ringer's lactate solution was administered in maintenance dose as per Holiday Segar formula. At the end of operation, all patients were shifted to surgical ICU (Intensive Care Unit) and monitoring was done for next 24 hours.

Arterial pressures and heart rates were measured 3 minutes after radial cannulation (baseline), before induction (*i.e.*, 10 minutes after administration of study drugs), just after endotracheal intubation (T0), and then at 1 (T1), 3 (T3), 5 (T5) and 10 (T10) minutes after intubation. The anesthesiologist who measured the arterial pressures and heart rates was unaware of the study. Hypotension and hypertension were defined as SAP (systolic arterial pressure) ≤ 20% and ≥ 25% of baseline value, respectively. Similarly, bradycardia and tachycardia were defined as HR (heart rate) ≤ 20% and ≥ 25% of baseline value, respectively.

Statistical analysis: Data was expressed as mean and standard deviation. The homogeneity in 2 groups of mean and standard deviation (SD) were analyzed using SPSS version 20.0 software. Normality of the distribution in each group was checked by comparing a histogram of the sample data to a normal probability curve. Inter-group comparison was done by unpaired t-test. Categorical data was compared by Chi-square test. A *p* value of less than 0.05 was considered as statistically 'significant'.

Figure 1. Flow chart showing the progress in our study



Results

There were no significant differences between the two groups with regard to demographic data such as age, sex, weight, ASA grade and duration of surgery (Table 1). Preoperative baseline vital parameters were compared among the two groups of patients and no significant difference was found (Table 2). Hemodynamic variables recorded in two groups at specified timings as mentioned in methodology are shown in Figures 2-5. No patient was excluded from study.

Table 1: Demographic profile (Mean ± SD)

Demographic profile	Group C	Group D	*P* value
Age (years)	30.41±8.65	28.1±7.79	0.207
Sex (F : M)	22 : 23	22 : 23	1
Weight (Kg)	52.1±8.11	51.52±10.95	0.786
ASA Grade (I : II)	20 : 25	21 : 24	0.823
Duration of surgery (min)	**179.74± 10.72**	**177.71± 16.63**	**0.513**

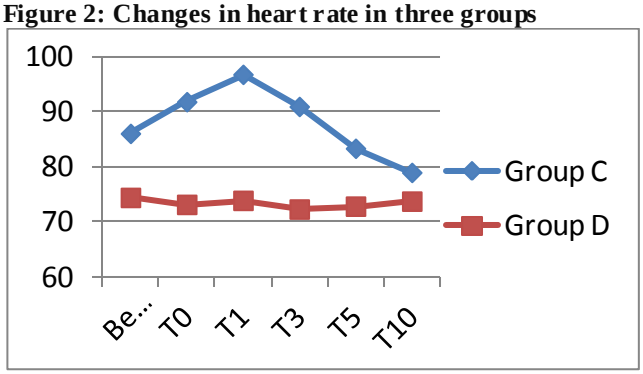
Table 2: Preoperative baseline vital parameters (Mean ± SD)

Baseline parameters	Group C	Group D	*P* value
HeartRate (bpm)	83.93±5.09	83.45±6.55	0.712
SAP (mm Hg)	130.33±8.96	132.83±9.6	0.226
MAP(mm Hg)	99.09±6.26	100.48±5.19	0.279
DAP (mm Hg)	83.95±4.28	84.54±5.86	0.604

SAP = Systolic arterial pressure; MAP = Mean arterial pressure; DAP = Diastolic arterial pressure

Heart rate was significantly (p <0.05) higher in control group in all the measurements. As per definition mentioned in methodology, 2 out of 45 patients (4.44%) in group D developed bradycardia which did not need any treatment; while in group C, 5 out of 45 patients (11.11%) developed tachycardia managed by injection esmolol in titrated dose. Systolic, mean and diastolic- all sort of arterial pressures were significantly (p <0.05) higher in control group in all the specified timings. Three out of 45 patients (6.67%) in group D developed hypotension managed by injection phenylephrine 20-100 µg as top-up dose. But in group C, 7 patients (15.56%) developed hypertension managed by injection esmolol in titrated dose.

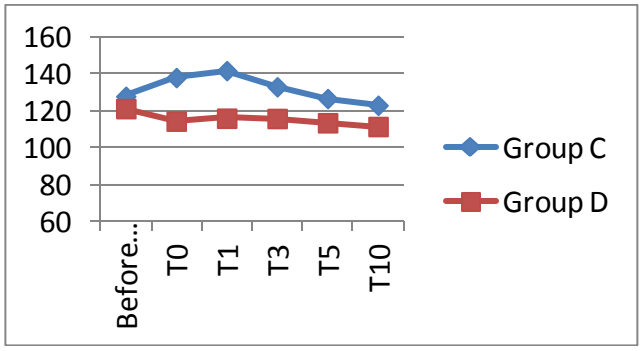
Figure 2: Changes in heart rate in three groups



T0, T1, T3, T5, T10 = immediately & 1, 3, 5, 10 minutes after intubation, respectively

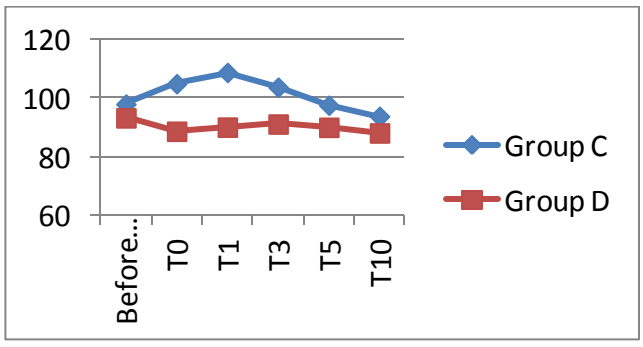
Systolic, mean and diastolic all sort of arterial pressures were significantly (p <0.05) higher in control group in all the specified timings. Three out of 45 patients (6.67%) in group D developed hypotension managed by injection phenylephrine 20-100 µg as top-up dose. But in group C, 7 patients (15.56%) developed hypertension managed by injection esmolol in titrated dose. Etomidate requirement for induction was significantly (p <0.05) lower in group D (12.14±1.87 vs 10±2.05).

Figure 3: Changes in systolic arterial pressure in three groups (Mean ± SD)



T0, T1, T3, T5, T10 = immediately & 1, 3, 5, 10 minutes after intubation, respectively

Figure 4: Changes in mean arterial pressure in three groups



T0, T1, T3, T5, T10 = immediately & 1, 3, 5, 10 minutes after intubation, respectively

Discussion

Both laryngoscopy and intubation separately result in sympathetic stimulation, but the catecholamine rise with intubation exceeds that with laryngoscopy alone [11]. Direct laryngoscopy involves stretching the oropharyngeal tissues in an attempt to straighten the angle between the mouth and glottis opening. This is a potential noxious stimulus causing pain and stress response [1]. These sympathetic stimulation leads to a transient but marked hemodynamic instability in the crucial period of anesthetic induction before cardiac surgery. Typically, the pressor response starts within 5 seconds, peaks at 60 seconds and normalizes within 10 minutes.

Heart rate is an important determinant of myocardial oxygen demand, and tachycardia in patients with ischemic heart disease is a risk factor for the development of perioperative myocardial ischemia and infarction [12]. Similarly, hypertension can lead to left ventricular failure, pulmonary edema, myocardial ischemia and ventricular dysrrhythmias [13]. Since tracheal intubation is unavoidable for major surgical procedures like cardiac surgery, the attempt to reduce the sympathetic stimulation is now directed towards minimizing the stretching of tissues in the oropharynx and laryngo-pharynx [14]. Till date, various anesthetic agents, adjuvants and analgesics have been used to blunt this stress response.

The α_2 receptors are involved in regulating the autonomic and cardiovascular systems. The α_{2A} receptors located on vessels can cause vasoconstriction while on the sympathetic terminals, they inhibit noradrenaline. The α_{2B} receptors located within the CNS (central nervous system) are responsible for sedation, reduction of sympathetic outflow and augmentation of cardiac vagal activity [15]. The use of α_2 agonists before induction has been associated with reduced anesthetic requirements and attenuated hemodynamic responses to intubation stress [7]. In addition, α_2 receptors within spinal cord modulate pain pathway, thereby providing some degree of analgesia.

Dexmedetomidine is a highly selective, potent and specific α_2-agonist (α_2: α_1 = 1620: 1) with a short duration of action (elimination half life of 2-3 hours). It attenuates the hemodynamic response to tracheal intubation, decreases plasma catecholamine concentration during anesthesia and decreases perioperative requirements of inhaled anesthetics [8]. Perioperative use of dexmedetomidine may result in a decreased risk of adverse cardiac events by

preventing redistribution of transmural blood flow away from the ischemic endocardium [10]. After intravenous administration of dexmedetomidine, a biphasic cardiovascular response is observed. An initial vasoconstrictor response may be seen following rapid bolus administration in young individuals [16].

Jalonen *et al* used dexmedetomidine as an adjuvant to anesthetic induction to attenuate the hemodynamic pressor response to endotracheal intubation in CABG (coronary artery bypass grafting) patients [17]. They used high dose pure opioid technique during cardiac anesthetic induction, while in our study, low dose fentanyl and etomidate induction was done with dexmedetomidine as an adjuvant.

Menda *et al* observed that dexmedetomidine 1 µg/kg can safely be used to attenuate hemodynamic pressor response to endotracheal intubation in patients undergoing myocardial revascularisation receiving beta blockers [18]. Jaakola *et al* successfully used dexmedetomidine 0.6 µg/kg as an anesthetic adjuvant for endotracheal intubation in CABG patients [19].

Sulaiman *et al* concluded that pretreatment with dexmedetomidine 0.5 µg/kg attenuate the hemodynamic pressor response to laryngoscopy and intubation [20]. Dexmedetomidine was given as infusion over 10 minutes. The same principle and dosage was used in our study. In this study, etomidate and fentanyl were used as induction agents. Etomidate has been used successfully as an induction agent in patients with pre-existing cardiovascular disease [21]. Weiss-Bloom *et al* has shown that etomidate 0.3 mg/kg with fentanyl 5-10 µg/kg provide hemodynamic stability [22].

$Alpha_2$ agonists have also been reported to increase the risk of hypotension and bradycardia, especially in young healthy volunteers on rapid bolus administration [10]. Bradycardia is a baroreceptor-mediated reflex action against initial transient peripheral postsynaptic adrenoreceptors mediated vasoconstriction, while hypotension is a manifestation of central action. Other side effects are minimal and may include transient arrhythmia, decreased respiratory rate, peripheral venous desaturation, vomiting, transient hyperglycemia etc. In this study, out of 45 patients in dexmedetomidine group, 2 patients developed bradycardia and another 3 patients developed hypotension.

There were several limitations of this study like small sample size, single-center design and selected study population. Further large scale multicentric study is required to confirm our findings.

Conclusion

In our double-blinded randomized controlled trial, administration of dexmedetomidine before commencement of anesthetic induction effectively attenuated hemodynamic pressor response to laryngoscopy and intubation. It also decreased the requirement of induction dose of etomidate.

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