Original Research Article

A Comparative Study of Two Different Doses of Dexmedetomidine on Attenuation of Stress Response to Endotracheal Intubation in Patients Undergoing Elective Surgeries Under General Anaesthesia

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Abstract

Introduction: Under general anaesthesia, laryngoscopy and endotracheal intubation elicit a strong sympathoadrenal response with potentially fatal implications in individuals with cardiovascular and cerebrovascular illnesses. To counteract this reaction, a variety of pharmacological treatments have been used.**Aim:** The present study was planned to compare the effects of two different doses of dexmedetomidine (bolus doses) on attenuation of stress response to Laryngoscopy and Endotracheal Intubation. **Materials & Methods:** A Randomized double-blinded prospective comparative study. Sixty patients of both sex (ASA grade I or II) undergoing GA were randomly divided into two groups equally as Group A (dexmedetomidine 1μg·kg− 1) and Group B (dexmedetomidine 0.5μg.kg− 1). Heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure were recorded at baseline, after completion of infusion (T1), 1 min (T2), 3min (T3), 5min (T4), & 10min (T5) following intubation.**Results:** The Student's independent t-test was employed for comparing continuous variables. Chi-square test or Fisher's exact test, whichever is appropriate, was applied for comparing categorical variables. Immediately after intubation, there was a lesser rise of SBP, DBP, and MAP in both the groups but there was a significant reduction in pressure values in group A at 1 minute after intubation compared to group B. **Conclusion:** Dexmedetomidine at a dose of 1μg·kg^{-1}administered over 10 minutes before induction of general anaesthesia more effectively attenuates the haemodynamic response to laryngoscopy and intubation than dexmedetomidine 0.5μg·kg^{-1}infusion over the same period, without any significant adverse effects.

Keywords: Dexmedetomidine, Laryngoscopy, Tracheal intubation, Stress response.

Introduction

Endotracheal intubation with laryngoscopy has become an integral part of anaesthetic management following its first description by Rowbotham and Magill in 1921[1]. Laryngoscopy causes a pressor response characterized by elevation of systolic and diastolic pressures within 5 seconds, with further increase in pressor response during negotiation of the tube into the trachea. The average rise in systolic blood pressure is about 25-50 mm/Hg[2-6], a plateau at or above this peak pressure is maintained for 1-2 minutes followed by a gradual return to prelaryngoscopic level within 5-10 minutes[7,8]. These adverse responses occur in normal sequences of induction and intubation and can further be aggravated by light plane of anaesthesia, hypoxia, hypercarbia, anxiety and reflex baroreceptors effects following administration of induction agents like thiopentone sodium[9]. Hypertensive patients are more prone to a significant increase in blood pressure whether they are treated or not. Such transient haemodynamic changes are not serious problems in a normal individual i.e.; American Society of Anaesthesiologists (ASA)[1] patient. But, in patients with compromised circulatory or cerebrovascular disorders, such changes may lead to life-threatening complications including myocardial ischemia, acute heart failure and cerebral haemorrhage[10,11].

Reid et al were the first to report the circulatory responses to laryngoscopy and intubation in anaesthetized persons[12]. Extensive research works have been done to prevent or to attenuate these responses. Some of which includes smooth gentle intubation with a shorter duration of laryngoscopy, blocking superior and recurrent laryngeal nerve, the deep plane of anaesthesia, opioids, topical lignocaine, antihypertensive like beta-blockers & calcium channel blockers, intravenous lignocaine[13-17]. Newer Alpha-2 agonists, clonidine and dexmedetomidine reduce plasma catecholamine levels and result in decreased sympathetic tone and sympatholytic effects; prevent hypertension and tachycardia.

Dexmedetomidine a selective Alpha-2 agonist decreases sympathetic tone, lowers systolic blood pressure, heart rate and thereby reduces rate pressure product (RPP). This reduction in RPP reduces myocardial oxygen requirement which is an advantage for patients with coronary artery diseases. In comparison with clonidine (220:1), dexmedetomidine has an α^2: α^1 adrenoreceptor agonist effect of approximately 1600: 1 (eight times higher than clonidine)[18]. This makes it primarily a sedative–anxiolytic. Further, a short half-life of dexmedetomidine makes it an ideal drug for intravenous titration. Both Hypertension and hypotension have been observed following the

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loading dose of dexmedetomidine[19,20]. Sometimes hypertension is seen due to the transient activation of peripheral alpha-2B receptors that cause vasoconstriction which overwhelms the competing vasodilator effect of central alpha-2A receptors. However, hypotension is the more common side effect and occurs when the vasodilator effects of the central alpha-2A receptors predominate[21]. This effect of dexmedetomidine may be beneficial in patients with risk of hypertension, with controlling of blood pressure and heart rate. This study has been designed to analyze and compare two different doses of dexmedetomidine administered to the patient undergoing surgery under GA with Endotracheal intubation.

Methodology

It is a prospective parallel randomized controlled double-blind study done in a tertiary care teaching hospital in Puducherry, a Union Territory in South India. On sixty patients of both sexes (American society of anesthesiologists Physical Status Classification System – ASA I and II), between the age range of 18-60 years scheduled for elective major surgeries requiring GA with endotracheal intubation, following institutional ethical committee approval.

Patients with an anticipated difficult airway, BMI more than thirty, Patients on anti-hypertensive, hypnotics & antidepressants therapy and history of chronic diseases were excluded from the study.

Having followed a discussion with the statistician, the sample size was calculated using data from the pilot study. According to the findings, each group should comprise about 23 patients to have a study power of 0.80 for detecting clinically significant variations of 15% in heart rate and mean arterial blood pressure. Assuming a 5% dropout rate, the sample size was computed to be 30 patients per group, with a type 1 alpha error of 0.05, a type 2 error of beta=0.2, and a power of 0.8.

The total sample of 44 subjects achieves 90% power to detect differences among the means versus the alternative of equal means using an F test with a 0.05 significance level. Given an anticipated dropout rate of 10%, a total of 60 patients (n = 60) were incorporated in the study and were distributed randomly into two groups, Group A and B, each having an equal number of patients (n=30) using a sealed envelope technique. Participants were unaware of their group assignments.

All patients were explained about the anaesthesia technique & written informed consent was taken from every patient as per the protocol. Patients were kept nil per oral (NPO) for eight hours before surgery.

Group A patients received I V dexmedetomidine infusion at 1µg per kg over 10 min in 10 ml of normal saline 10 min before induction.

Similarly, Group B patients received IV dexmedetomidine at 0.5µg per kg over 10 min in 10 ml of normal saline 10 min before induction.

Basal systolic blood pressure (SBP), diastolic blood pressure (DBP), Mean arterial pressure (MAP), heart rate (HR), ECG & SpO2 were recorded (T0).

After 60 sec of completion of infusion SBP, DBP, MAP, Heart rate, SpO2 (T1) were recorded.

Conventional method of induction with intravenous Inj. Glycopyrrolate 5µg·kg^{-1}, Inj. Midazolam 0.05mg.kg^{-1}, Inj. fentanyl 2µg·kg^{-1}, Inj. propofol 2mg.kg^{-1}and muscle relaxant succinyl choline 2 mg.kg^{-1}were given and intubated with adequate size endotracheal tube.

Anaesthesia was maintained with N2O, O2, sevoflurane, controlled ventilation with appropriate fresh gas flow. SBP, DBP, MAP, Heart rate, SpO2 were recorded at 1 min (T2), 3min (T3), 5min (T4), & 10min (T5) following laryngoscopy & intubation.

Surgery was commenced after 10 min of laryngoscopy & intubation. No form of the stimulus was applied during the study period. Anaesthesia continued with N2O (50%), O2 (50%) sevoflurane, vecuronium bolus and top-up doses, analgesics & IV fluids were administered based on the requirements.

At the end of the surgery, when patients showed respiratory attempts, residual neuromuscular blockade was reversed with Inj.Neostigmine (0.04mg.kg^{-1}) and Inj.Glycopyrrolate (0.01mg.kg^{-1}). Following adequate recovery, extubation was done after thorough throat suction.

Data Analysis

The data were entered in Microsoft Excel and analyzed using statistical software epi info 3.4.3 and SPSS version 24.0. Quantitative variables were represented using Mean +/- SD. Categorical variables were represented using frequency and percentages. The study data were analyzed statistically by using the chi-square test, student's t-test, Mann Whitney U test. Data were expressed as mean +/-SD. P-value <0.05 was considered significant.

Results

The primary aim of this investigation was to study the efficacy of two different doses of dexmedetomidine in attenuating hemodynamic response to laryngoscopy and endotracheal intubation. Patients in the age group between 18 to 60 years with ASA I & II were included. And they were randomized into two groups by sealed envelope technique (Group A and Group B). Group A patients received IV dexmedetomidine infusion at 1µg per kg for over 10 min. Similarly, Group B patients received IV dexmedetomidine at 0.5µg per kg. Study parameters and outcomes of haemodynamic were recorded as per protocol and observations were noted. Demographic data (age, sex, BMI) were statistically analyzed. Such demographic data were statistically comparable and showed no significant difference between the groups. Demographic data did not influence the study. Basal SBP, DBP, MAP, Heart rate, SpO2 were recorded and also recorded after 60 seconds of study drug infusion. The haemodynamic response was also recorded at 1 min (T2), 3min (T3), 5min (T4), & 10min (T5) following laryngoscopy & intubation.

The basal readings of HR, SBP, DBP and MAP were comparable in both groups but statistically not significant.

Maximum intubation response was seen at 1 minute after intubation in both the groups and was statistically significant (p = < 0.05).

Group A had a statistically lesser value of SBP, DBP and MAP at 1 minute after intubation when compared to Group B. Apart from the finding mentioned there was no statistically significant difference between Group A and Group B in any of the parameters at time intervals, however, data's were comparable. The hemodynamic response was completely obtunded in Group A when compared with Group B. This indicates that dexmedetomidine in a dose of 1µg.kg^{-1}(group A) was superior to dexmedetomidine in a dose of 0.5µg.kg^{-1}(group B) in attenuating the intubation response [Tables 1-4]. Neither bradycardia nor hypotension was observed in any of the patients. There was no fall in SpO_2 below 90 % in any of the patients studied.

Two patients from group A had hypotension with bradycardia which was more than 20 % fall from the basal values and similarly, two patients from group B had hypotension without bradycardia and those patients were managed with Inj. Atropine 0.6 mg and Inj. Ephedrine 6 mg iv respectively. No further haemodynamic instability and other adverse effects were noted among the two groups.

Table 1: Distribution of study groups based on demographic data (n = 60)

Gender	Study group	
	Group A n (%)	Group B n (%)
Male	14(46.7)	11(36.7)
Female	16(53.3)	19(63.3)
Underweight	5(16.7)	2(6.7)
Underweight	5(16.7)	2(6.7)

Normal	18(60.0)	19(63.3)
Overweight	6(20.0)	6(20.0)
Obese	1(3.3)	3(10.0)
Age 18-30	17(56.7)	14(46.7)
Age 31-45	6(20.0)	12(40.0)
Age 46-60	5(16.7)	4(13.3)
Age > 60	2(6.7)	0(0.0)

Table 2: Distribution of study groups based on baseline HR (n=60)

Heart Rate (in beats/min)	Group A (n = 30)		Group B (n = 30)		The difference in mean (95% CI)	p-value*
	Median	IQR	Median	IQR		
At baseline	76	70-87.5	73	66-76.5	4.3(-1.6-10.3)	0.108
1 min after dexmedetomidine infusion	75	70.75-83.25	72	67.5-80	3.5(-2.6-9.6)	0.203
1 min after intubation	75.5	69.75- 84.0	71.5	66-78.5	1.9(-4.9-8.8)	0.267
3 min after intubation	79	72-85	72	67.5-82	2.73(-3.1-8.6)	0.127
5 min after intubation	77	73.75-81	72	68-81.75	2.2(-2.9-7.4)	0.184
10 min after intubation	78	72-83.25	75	70-82.5	1(-3.6-5.6)	0.378

*Mann Whitney U test was applied for comparison of means

Table 3: Distribution of study groups based on baseline SBP (n=60)

Diastolic BP (in mm of Hg)	Group A (n = 30)		Group B (n = 30)		The difference in mean (95% CI)	p-value*
	Mean	SD	Mean	SD		
At baseline	123.63	12.8	122.7	14.9	0.93(-6.3-8.1)	0.796
1 min after dexmedetomidine infusion	118.8	13.8	119.27	13.9	-0.47(-7.6-6.7)	0.897
1 min after intubation	100	90-111.25	110	99.5-112.75	-9.6(-19.8-0.6)	0.012
3 min after intubation	103.2	11.1	103	15.7	0.2(-6.8-7.2)	0.955
5 min after intubation	104.87	9.6	104.4	17.2	0.43(-6.7-7.6)	0.904
10 min after intubation	108	98.75-111.25	103	95.75-110	1.3(-4.7-7.2)	0.385

*Independent Sample, student t-test was applied for comparison of means

Table 4: Distribution of study groups based on baseline SBP (n=60)

Diastolic BP (in mm of Hg)	Group A (n = 30)		Group B (n = 30)		The difference in mean (95% CI)	p-value*
	Mean	SD	Mean	SD		
At base line	76.27	9.1	74.57	9.0	1.7(-2.9-6.4)	0.471
1 min after dexmedetomidine infusion	74.53	9.3	74.43	9.0	0.1(-4.6-4.8)	0.967
1 min after intubation	61.6	9.1	70.2	15.3	-8.6(-15.1- -2.1)	0.010
3 min after intubation	67	9.5	65.03	9.8	1.97(-3.0-6.9)	0.434
5 min after intubation	63.5	60-70.5	62.5	59-70	1.6(-3.0-6.3)	0.481
10 min after intubation	108	98.75-111.25	103	95.75-110	1.3(-4.7-7.2)	0.385

*Independent Sample, student t-test was applied for comparison of means

Table 5: Distribution of study groups based on baseline SBP (n=60)

Diastolic BP (in mm of Hg)	Group A (n = 30)		Group B (n = 30)		The difference in mean (95% CI)	p-value*
	Mean	SD	Mean	SD		
At baseline	91.97	9.4	89.4	10.0	2.6(-2.4-7.6)	0.311
1 min after dexmedetomidine infusion	89.1	10.4	89.27	9.3	-0.17(-5.2-4.9)	0.948
1 min after intubation	74.37	10.4	83.57	15.9	-9.2(-16.2-2.2)	0.010
3 min after intubation	79.03	9.4	77.2	10.3	1.83(-3.2-6.9)	0.473
5 min after intubation	78.7	7.4	77.5	11.6	1.2(-3.8-6.2)	0.644
10 min after intubation	78.73	7.2	79.27	8.5	-0.53(2.0-4.6)	0.794

Discussion

Laryngoscopy endotracheal intubation has been the mainstay in safeguarding the airway during GA. The standard technique of laryngoscopy and endotracheal intubation involves stimulation of the larynx, pharynx, epipharynx and trachea, which are extensively innervated by the autonomic nervous system, parasympathetic innervation via the vagus and glossopharyngeal nerves and sympathetic via superior cervical ganglion. Laryngoscopy and endotracheal intubation are noxious stimuli that may be capable of producing a huge spectrum of stress responses such as tachycardia, hypertension, laryngospasm, bronchospasm, raised intracranial pressure and raised intraocular pressure (Reflex sympathetic discharge). The haemodynamic reaction begins within seconds of direct laryngoscopy and continues to rise as the endotracheal tube is passed through. The response is initiated within 5 seconds of laryngoscopy, peaks in 1–2 min and returns to normal levels by 5 min.

Various pharmacological and non – pharmacological methods have been tried to attenuate the haemodynamic response to laryngoscopy and endotracheal intubation.

The pharmacologic measures local anaesthetics, opioids, vasodilators, beta-blockers and calcium channel blockers have been used in the past. However, none of the above approaches or agents has been proved to be ideal. Hence there is a gap in the field and needs further research for an ideal agent to attenuate the hemodynamic responses to tracheal intubation. Newer agents like Alpha-2 agonist are of interest now. In this group clonidine and dexmedetomidine have been assessed in various studies.

Dexmedetomidine is a highly selective Alpha-2 agonist that has been shown to have sedative, analgesic and anaesthetic sparing effects. It causes a dose-dependent decrease in arterial blood pressure and heart rate, associated with a decrease in serum norepinephrine concentration.

Laha et al[22] studied the effects of a pre-induction loading dose of dexmedetomidine 1μg·kg^{-1} on attenuation of the sympathoadrenal

response to laryngoscopy and intubation and requirement of anaesthetic agents. They concluded that administration of dexmedetomidine despite attenuating the mean HR, SBP, and DBP after intubation at 1, 2, 3 and 5 minutes and also significantly reduces the requirement of anaesthetic drugs[22].

Yildiz M et al evaluated the effect of a single pre-induction intravenous dose of dexmedetomidine 1μg·kg^{-1} on cardiovascular response resulting from laryngoscopy and endotracheal intubation. They found blood pressure and heart rate were significantly lower in the dexmedetomidine group. They concluded dexmedetomidine 1μg·kg^{-1} was effective in attenuating stress response to intubation and laryngoscopy[23].

In another study, Anish Sharma et al, compared clonidine with dexmedetomidine and found that dexmedetomidine was more effective in attenuating the tachycardia response[24]. And some patients among the clonidine group showed profound hypotension when compared to the dexmedetomidine group. Yildiz M et al evaluated the effect of a single pre-induction intravenous dose of dexmedetomidine 1μg·kg^{-1} on cardiovascular response resulting from laryngoscopy and endotracheal intubation. They found blood pressure and heart rate were significantly lower in the dexmedetomidine group. They concluded dexmedetomidine 1μg·kg^{-1} was effective in attenuating stress response to intubation and laryngoscopy[23].

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The present study findings with 1μg·kg^{-1} of dexmedetomidine in attenuation of pressor response are comparable with their findings.

Dexmedetomidine was well tolerated in both groups, and no serious side effects or adverse reactions occurred in the present study. No haemodynamic instability occurred in any patient in both groups. The HR, SBP, DBP and MAP was comparable in the two groups till dexmedetomidine infusion, after one minute of intubation there was a statistically significant fall in SBP, DBP and MAP but it was acceptable and no profound fall was seen throughout the study [figure 1-4]. The above findings suggest that pressor response to intubation following the laryngoscopy has been attenuated by dexmedetomidine premedication effectively.

Some of the studies using dexmedetomidine have reported side effects of sinus pause or bradycardia and recommended Glycopyrrolate[25] or atropine for the treatment. Anticholinergic prophylaxis before dexmedetomidine injection has been advised by Peden et al in individuals under the age of 40[26]. In the present study, though the heart rate was relatively lower in the dexmedetomidine group, none of them required therapeutic intervention with an anticholinergic drug. The hypotension and bradycardia caused by dexmedetomidine, theoretically, could limit its usage in bradycardic patients but no severe bradycardia or hypotension was observed in any of the patients in either group in this study except 4 patients (two from each group).

Conclusion

We concluded that bolus Injection of dexmedetomidine 1μg.kg^{-1} given intravenously over 10 min before induction followed consistent and reliable protection against the stress response during laryngoscopy and endotracheal intubation when compared to the dose of dexmedetomidine 0.5μg·kg^{-1}, without any significant adverse effects.

Limitations and Future Studies

Present study could not establish the potential benefit of dexmedetomidine in attenuating haemodynamic extubation response and its outcomes in the immediate postoperative period. So also cost-benefit constraint or cost sparing of anaesthetic agents was not possible in this study. Plasma catecholamine, cortisol, insulin levels were not measured because it was not feasible in our setup.

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