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CAN DEXMEDETOMIDINE BE A BETTER ALTERNATIVE TO ESMOLOL IN ATTENUATING THE IMMEDIATE STRESS RESPONSE TO DIRECT LARYNGOSCOPY AND TRACHEAL INTUBATION? – A PILOT STUDY

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ABSTRACT

Background & Objectives: Laryngoscopy and tracheal intubation trigger reflex sympathetic response often amounting to cardiovascular collapse in susceptible individuals. Perioperative physicians are in constant quest for measures to attenuate the same. Dexmedetomidine, a newer α_2 agonist having titrable effects on heart rate and blood pressure, can be a better alternative to the nonselective β blocker esmolol. **Methods:** Fifty patients receiving general anesthesia and endotracheal intubation were randomly divided into two groups (n= 25). Group D received 0.8 mcg/kg of dexmedetomidine and group E received 2.0 mg/kg of esmolol before intubation of trachea. All patients were uniformly premedicated, induced and intubated as per standard protocol. Hemodynamic parameters were recorded at various time intervals. Statistical analysis was carried out using IBM SPSS statistics 20.0 software. A p value of 0.05 or less was set for statistical significance. **Results:** The decline in heart rates were highly significantat the following time intervals, ie Ti, T0B, T0A and T1 ($p<0.05$) and insignificant during T3($p>0.05$). There was a transient rise in SBP (8% increase in group D and 6.7% increase in group E), DBP (2.9% rise in group D and 2.7% rise in group E) and MAP (5.2% increase in MAP in group D and 2.7% increase in group E) immediately following intubation. The difference between the groups was not statistically significant. **Conclusion:** Dexmedetomidine 0.8 mcg/kg was more effective in prevention of tachycardia compared to esmolol 2.0mg/kg.

KEYWORDS: Direct laryngoscopy and Tracheal intubation, Stress response, Dexmedetomidine, Esmolol.

INTRODUCTION

Both laryngoscopy and tracheal intubation are noxious stimuli that are associated with significant rise in heart rate and arterial blood pressure. These changes are maximal immediately after intubation and may have deleterious effects in patients with decreased cardiovascular and cerebrovascular reserve and may lead to life threatening complications.[1,2]

There are several factors which determine the magnitude of stress response. Exaggerated increase in Systolic blood pressure was observed following laryngoscopy and intubation in elderly and middle aged patients as compared to young.[3] The pressor response can also be influenced by time taken for intubation, number of attempts, applied physical force of laryngoscopy, external manipulations and type of laryngoscope.[1] Thus the skill and experience of the anaesthesiologist also influences the hemodynamic response.

Continuous researches are being undertaken from time to time, to blunt the hemodynamic response that accompanies direct laryngoscopy and tracheal intubation. The various methods used include, measures which minimize the mechanical stimulation of the airway, use of special types of laryngoscopes and topical or regional anaesthesia applied to airway. Various drugs like opioids, barbiturates, benzodiazepines, calcium channel blockers, β blockers, α_2 agonists, vasodilators and local anaesthetics are also used for this purpose.[4]

Dexmedetomidine is an imidazole group derivative and is a highly selective α_2 adrenergic receptor agonist that produces sedation, anxiolysis, hypnosis, and analgesia. Its primary action is as an agonist on $\alpha_2$receptors in the locus coeruleus leading to decreased systemic norepinephrine levels. The distribution half.-life of Dexmedetomidine is 6 minutes with a context-sensitive half-life of 4 minutes after a 10-minute infusion.[5,6]

Esmolol is an ultra-short acting cardio-selective β adrenergic receptor blocker. Esmolol, when administered parenterally, exhibits rapid onset and a short duration of action due to its rapid clearance (9 minutes) by red blood cell esterase. The peak effects of a loading dose are seen within 6 to 10 minutes. These drugs are an important part of the armamentarium of the anaesthesiologists in the on-

going attempt to limit stress responses perioperatively and to protect the cardiovascular system.[7,8]

A basic need is often felt among anaesthesiologists for the availability of a drug that effectively suppresses all the hazardous responses to direct laryngoscopy and tracheal intubation with maximum safety margin. With emphasis on beneficial systemic effects as well as safety profile of dexmedetomidine and cardioselectivity along with ultrashort acting nature of esmolol, we designed a prospective observational study to compare the effects of dexmedetomidine and esmolol in attenuation of early stress response during direct laryngoscopy and tracheal intubation.

MATERIALS AND METHODS

After getting approval from Institutional research committee and ethics committee, 50 patients belonging to ASA physical status class I and II, of either sex and ages between 40-60 years who underwent elective non-cardiac surgery under general anesthesiawith endotracheal intubation were included in this study. Those patients who refused to consent, patients with anticipated difficult airway, those in whom intubation attempt took > 20seconds, patients on beta blockers, heart rate<70 per minute, heart block or systolic BP<100mm Hg were excluded. No additional expense was incurred to the patient.

An informed written consent was obtained from all the patients who satisfied the inclusion criteria. They were advised to fast overnight and tablets alprazolam 0.5mg and metoclopromide 10mg were given orally at bed time on the previous day of surgery.

In the operating room routine monitors such as pulse oximeter, electrocardiography (ECG) and non-invasive blood pressure (NIBP) were attached and monitored using a multipara monitor (mindray iMEC12). A balanced salt solution was infused after securing an intravenous (IV) line with an 18G venous cannula after infiltration of local anaesthetic. Baseline vital parameters of patients like heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were recorded preoperatively.

The study population was divided into two equal groups of 25 each (group D and group E) by a qualified anaesthetist who was not involved in the study. Patients in group D and E received dexmedetomidine 0.8µg/kg and esmolol 2mg/kg respectively, as slow intravenous infusion over a period of 10 minutes in such a way that the infusion was completed 3 minutes prior to intubation. All the patients were uniformly premedicated with IV ondansetron 0.08mg/kg, IV glycopyrrolate 0.004mg/kg and IV midazolam 0.02mg/kg and Morphine 0.1mg/kg, 5 minutes after initiation of study drug infusion.

Pre-oxygenation with 100% oxygen for 3 minutes was achieved by the time, the study drug infusion was completed. They were induced with thiopentone sodium (loss of eyelash reflex was taken as endpoint of induction) and vecuronium 0.1mg/kg was administered as a standard protocol.

Direct laryngoscopy was attempted after 3 minutes with Macintosh curved blade. The trachea was intubated with appropriate size cuffed endotracheal tube. Time taken for direct laryngoscopy and tracheal intubation were recorded. Those subjects in whom direct laryngoscopy and tracheal intubation took more than 20 seconds were noted and excluded from the study.

After confirmation of position and fixation of endotracheal tube, anaesthesia was maintained with 66% N2O in 33% oxygen and 0.8% isoflurane through closed circuit. Study parameters such as HR, SBP, DBP and MAP were recorded as follows using a multipara monitor (mindray iMEC12).

1. At baseline (TB) - values recorded before the start of study drug infusion
2. After study drug infusion (TA) – values recorded 5 minutes after the study drug infusion and after the administration of premedication
3. After induction (Ti) – values recorded after induction
4. Before intubation (T0B) – values recorded 3 minutes after induction and prior to intubation
5. Immediately after intubation (T0A) – values recorded immediately after intubation
6. 1 minute after intubation (T1) – values recorded 1 minute after intubation
7. 3 minutes after intubation (T3) – values recorded 3 minutes after intubation

Surgical stimulation was permitted only after the study period of 3minutes in order to prevent the hemodynamic alterations induced by the same.

The hemodynamic alterations which are significant (more than 20% above or below the baseline value) were attended timely and measures to maintain hemodynamic stability were taken. Those subjects were exempted from the study. Afterwards, anaesthesia proceeded as routine. Patients were extubated after complete recovery and were monitored during the postoperative period.

Statistical Analysis

In the present study, results are given as mean ± standard deviation and range of values for continuous data. Independent t test was used to compare the two groups. Categorical data are expressed as numbers and percentages and difference between the groups was compared by chi-square test. A p value of 0.05 or less was set for statistical significance. Software used was SPSS statistics 20.0 (Statistical Package for Social Science

RESULTS AND DISCUSSION

The minimum age in the study was 40 years and the maximum was 60 years. The groups were compared with student t test and the p value was 0.191, showing no statistical difference between the groups.

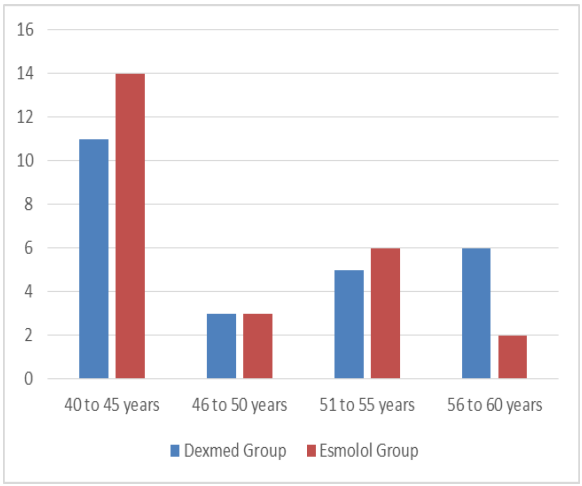

Figure 1: Age group distribution between the groups

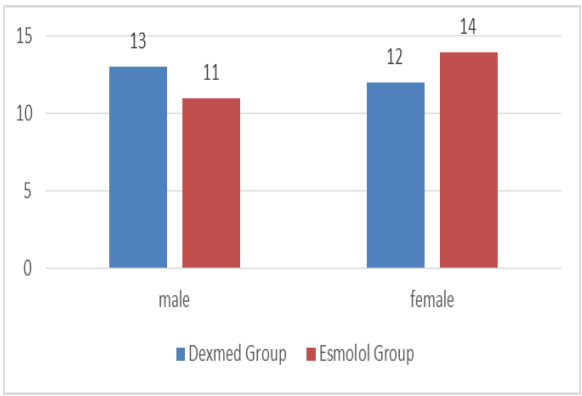

Figure 2: Distribution of sex between the groups

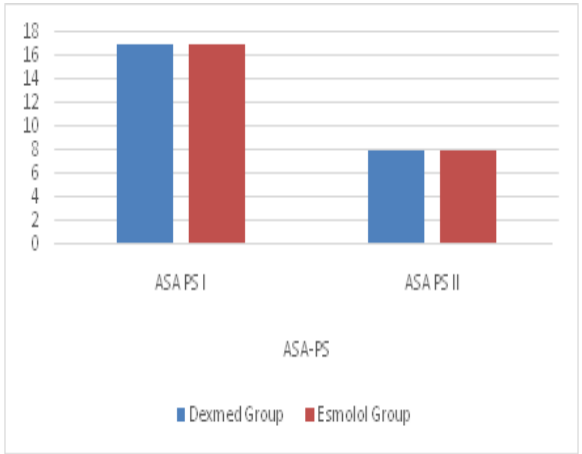

Figure 3: Comparison of ASA PS between the groups

The demographic profile of the patients in terms of age, male: female ratio and ASA PS status were comparable and there were no significant differences among the two groups (p>0.05).

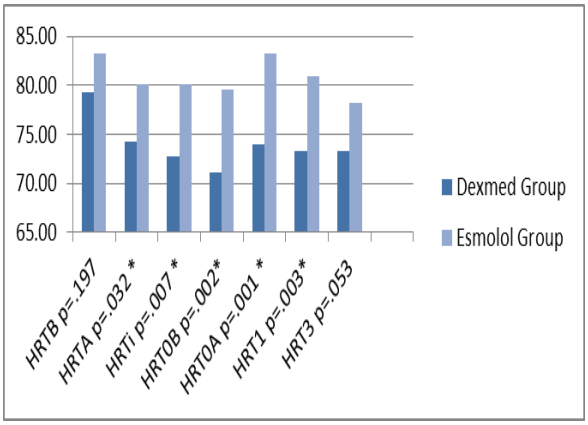

Figure 4: Comparison of heart rate between the groups

Baseline mean heart rates were comparable between the 2 groups (p value 0.197) Significant difference between the groups were noted at following time intervals –TA, Ti, T0B, T0A and T1.

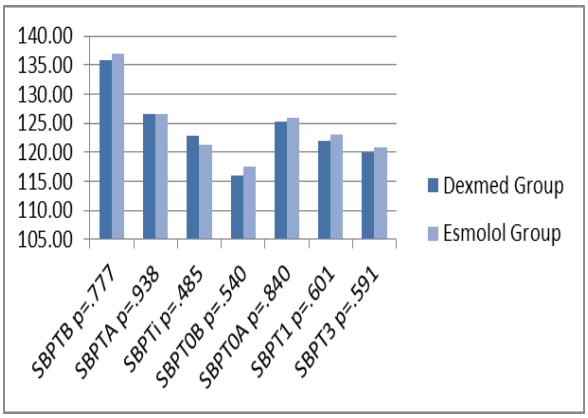

Figure 5: Comparison of SBP between the groups

The mean baseline systolic blood pressures were comparable in both the groups. (p value 0.777).

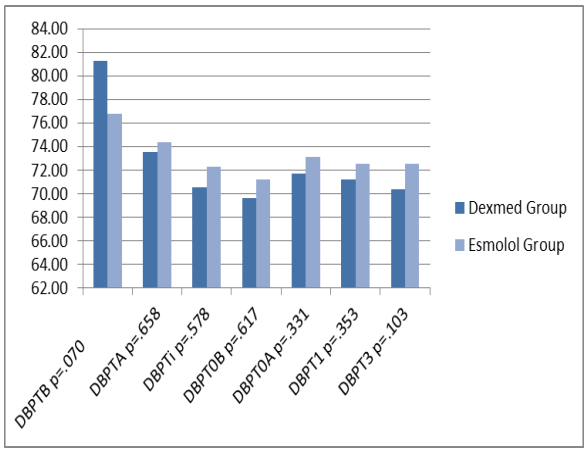

Figure 6: Comparison of DBP between the groups

The baseline diastolic BPs were comparable in both the groups (p value 0.070). Both the groups showed a reduction in diastolic BP following study drug infusion.

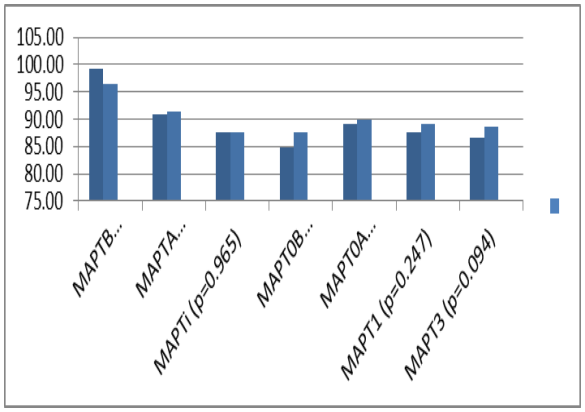

Figure 7: Comparison of MAP between the groups

Baseline values of MAP were comparable in both the groups (p value 0.224).

DISCUSSION

Tachycardia, hypertension and arrhythmia are the undesired effects of pressor response which may be hazardous in patients with cardiovascular or neurologic disorders. Various methods have been tried to obtund this response, both pharmacological and non-pharmacological, none of which proved to be ideal.

Dexmedetomidine is a novel α_2 agonist with very high α_2 selectivity, suppress the plasma catecholamine levels and decrease the pressor response. Esmolol, an ultrashort acting cardioselective β blocker is also used with this aim. Bajwa S et al used dexmedetomidine at a dose of 1µg/kg over 20 minutes given 3 minutes prior to induction decreased the magnitude of hemodynamic response to intubation, and extubation[9] We chose a lesser dose of 0.8µg/kg of dexmedetomidine to obtund the pressor response.

Atlee et al after evaluating the effects of 1 mg/kg of esmolol found that it did not prevent blood pressure change during intubation when they administered solely.[10] Figueredo et al performed a meta-analysis of different esmolol doses and observed that infusion was more effective than single dose administration to prevent cardiovascular stress response.[11]

We compared a dose of 0.8µg/kg dexmedetomidine with a dose of 2mg/kg esmolol in attenuation of stress response to direct laryngoscopy and intubation. We designed the study in such a way that both the study drug infusions are finished 3 minutes prior to intubation. This is supported by the study published by Singhal S.K. et al in 2010, on efficacy of esmolol administration at different time intervals in attenuating hemodynamic response to tracheal intubation. According to this study, administration of esmolol is safe and more effective when administered 3 minutes prior to intubation.[12]

Both the groups were comparable in terms of age, sex and ASA PS classification. The mean age of patients in group D was 49.4±7.39 and that of group E was 46.88±5.96 (p value 0.191). We selected optimal range of 40-60 years in order to eliminate the hemodynamic variability associated with extremes of age. Age is an important factor determining the degree of pressor response to direct laryngoscopy and intubation. In elderly increased sympathetic activity is present at rest, and there is exaggerated response to stimuli that increase sympathetic activity.

The hemodynamic parameters namely, HR, SBP, DBP, MAP and SPO_2 were compared at various time points between the groups.

Heart rate

Baseline heart rate was 79.24±10.94 in group D. There was a gradual fall in HR following study drug infusion with a maximum of 10.2% fall at T0B (just before intubation). The HR was increased by 4% at T0A (immediately after intubation). The rise in heart rate was gradually settled over the next 10 minutes. In group E the baseline heart rate was 83.28±10.92. Following study drug infusion a decreasing trend was noted accounting upto 4.5% fall in HR at T0B (just before intubation). There was a transient rise (4.8%) in HR at T0A (immediately after intubation). Baseline mean heart rates were comparable between the groups (p value 0.197). At all the time intervals following intubation, the mean heart rate was suppressed (maximum of 10.2%) in group D (dexmedetomidine) whereas the mean heart rate was suppressed but to a lesser extend (maximum of 7.7%) in group E (esmolol). The difference in decline of heart rates between the groups was highly significant (p value <0.05) at the following time intervals, ie Ti, T0B, T0A and T1 showing superior effect of dexmedetomidine in prevention of tachycardia following direct laryngoscopy and intubation. No elevation of mean heart rate above the baseline was noted at any point following study drug infusion in both the groups.

Similar observations were noted by Gogus N et al, in a study to compare the effects of dexmedetomidine (1µg/kg), fentanyl (2µg/kg) and esmolol (2mg/kg) on prevention of hemodynamic response to intubation. Ninety elective surgery patients who needed endotracheal intubation belonging to ASA PS I&II groups and aged between 21 and 65 years were included in that prospective, randomized, double-blind study. They arrived at a conclusion that dexmedetomidine was more effective than esmolol and fentanyl in the prevention of tachycardia.[13] The heart rate response to dexmedetomidine was also similar to the study conducted by Gulabani M et al who noticed that dexmedetomidine 1µg/kg adequately attenuated the tachycardia in response to laryngoscopy and endotracheal intubation.[14] The attenuation of tachycardia by esmolol is supported by findings of Gupta A et al who studied esmolol (1.5 mg/kg) as a bolus in attenuation of the heart rate response effectively, without any deleterious effects.[15]

Systolic blood pressure

The baseline SBP was 135.92±12.29 in group D. There was a gradual fall in SBP following study drug infusion. At T0B (just before intubation) the SBP was decreased by 14.5% from the baseline. An 8% increase in SBP was noted immediately after intubation, at T0A. Thereafter the SBP showed a declining trend to a value below the baseline. In group E, the baseline SBP was 136.84±10.48. The SBP was gradually decreased over time with a 14.17% fall at T0B (just before intubation). Immediately following intubation SBP showed a sudden hike of 6.7 %, which again got settled over the next few minutes. The mean baseline systolic blood pressures were comparable in both the groups (p value 0.777). The SBP was reduced following drug infusion in both the groups. There was a transient rise in SBP immediately after intubation accounting to 8% increase in group D and 6.7% increase in group E. Though esmolol group seemed to have a better profile in prevention of SBP, the difference was not statistically significant. (p value o.84).

Diastolic blood pressure

The baseline DBP was 81.28±10.48 in group D, which showed a falling trend following study drug infusion. The value just prior to intubation (T0B) was 14.3% below the baseline value. Following intubation (T0A), we noted a rise in DBP accounting to 2.9%. In group E, the baseline DBP was 76.76±7.04. There was a gradual reduction in DBP following study drug infusion. The fall was maximal at T0B (just before intubation) with a 7.2% decline from baseline. Following intubation there was a small rise in DBP (2.7%), again followed by gradual decline reaching 4.9% below the baseline value. The baseline diastolic blood pressures were comparable in both the groups (p value 0.070). Both the groups showed a reduction in diastolic BP following study drug infusion. Dexmedetomidine did not prevent the pressor response (2.9% rise in DBP) immediately following intubation. In esmolol group the pressor response was almost similar, with a 2.7% rise of DBP immediately following intubation. The difference was not statistically significant (p value 0.331).

Mean arterial pressure

The baseline MAP was 99.24±9.59 in group D. It was observed to have a decreasing trend following study drug infusion. The value just before intubation (T0B) was 14.5% below the baseline. The increase in MAP noted following intubation (T0A) was accounting to a hike of 5.2%. In group E, the baseline MAP was 96.4±6.39. There was a gradual reduction in MAP following study drug infusion. The decline was amounting to 9.3% from the baseline. Immediately following intubation (T0A) there was a rise of 2.7% and thereafter the MAP values were gradually declined reaching 10.3% below the baseline.

When MAP is considered, baseline values were comparable in both the groups (p value 0.224). Both the groups showed a transient rise in MAP following intubation, which was still below the baseline value. There was 5.2% increase in MAP in group D and 2.7% increase in MAP in group E, immediately following intubation. Though suppression of the rise in MAP was better with esmolol compared to dexmedetomidine, the difference was not statistically significant (p value 0.669). The blood pressure response was in contrast to the findings of Reddy S.V. et al who conducted a randomised double blind clinical study to compare the effects of dexmedetomidine versus Esmolol in attenuating the hemodynamic response during laryngoscopy and tracheal intubation. They found that, with esmolol there was a significant increase in SBP and a transient rise in DBP after intubation compared to the baseline values. They concluded that, of the two drugs administered, dexmedetomidine 1.0 µg/kg provides a consistent, reliable and effective attenuation of pressor responses when compared to esmolol 2.0 mg/kg.[16]

Study undertaken by Vucevic M et al to compare the hemodynamic effects of laryngoscopy and tracheal intubation during an infusion of esmolol and an infusion of placebo revealed similar findings to our study that esmolol prevented the rise in BP following laryngoscopyand intubation.[17] According to Prasad SR et al dexmedetomidine at a dose of 1µg/kg effectively suppressed the hypertensive response following laryngoscopy and endotracheal intubation, when given as an infusion over 10 minutes.[18]

Our study revealed that both the drugs were effective in attenuation of stress response to direct laryngoscopy and intubation. Dexmedetomidine was superior in preventing tachycardia, whereas effects of dexmedetomidine and esmolol were comparable in terms of reducing hypertensive response. In our study, side effects and complications like bradycardia and hypotension encountered were very few and could be easily treated.

The intrinsic response to stress of laryngoscopy and intubation have significant inter individual variability and would have affected the values recorded. This could be a possible drawback of the study. There can also be an inter individual variation in performing the laryngoscopy to trigger a response and so do its magnitude.

CONCLUSION

From our pilot study, we could draw the following conclusions,

1. Dexmedetomidine (0.8µg/kg) was more effective than esmolol (2mg/kg) In attenuation of heart rate response to direct laryngoscopy and tracheal intubation.
2. Dexmedetomidine (0.8µg/kg) and esmolol (2mg/kg) had comparable efficacy in prevention of hypertensive response to direct laryngoscopy and tracheal intubation.

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