Comparative Study to Evaluate Attenuation of Haemodynamic Changes during Laryngoscopy and Endotracheal Intubation Using Intravenous Esmolol and Intravenous Dexmedetomidine

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ABSTRACT

BACKGROUND

Dexmedetomidine a highly selective α2 - adrenoreceptor agonist and esmolol an ultra - short-acting β1 - cardioselective adrenergic receptor blocker appear to be quite suitable to control the detrimental effects of laryngeal and tracheal stimulation. The study was conducted to compare the efficacy of dexmedetomidine and esmolol for attenuation of hemodynamic responses to laryngoscopy and intubation

METHODS

200 patients of age 18–60 years, belonging to American Society of Anesthesiologists (ASA) physical state of I & II of either are posted for elective surgical procedure randomized into two groups of 100 each to receive dexmedetomidine (Group D): 1 µg / Kg in 20 mL normal saline over 10 mins, 7 min. prior to intubation and esmolol (Group E) : 1 mg / Kg over 1 min, 2 min prior to intubation. Changes in heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) any side effects associated with the drugs during the study, i.e., 15 min of intubation, were observed and statistically analysed.

RESULTS

A statistically significant difference ($p < 0.01$) between Groups D and E was observed in mean heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) during intubation, 1 min, 3 min, 5 min & 15 min after intubation.

CONCLUSIONS

Dexmedetomidine was better as compared to esmolol in attenuation of hemodynamic response to laryngoscopy and tracheal intubation.

KEYWORDS

Laryngoscopy, Haemodynamic Response, Intubation**,** Dexmedetomidine, Esmolol

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BACKGROUND

Laryngoscopy and endotracheal intubation is one of the most commonly performed procedures. Laryngoscopy and endotracheal intubation marked a new era in the history of anaesthesia and has led to provision of safer anaesthesia due to better control of airway and ventilation. Laryngoscopy and endotracheal intubation are noxious stimuli capable of producing a huge spectrum of stress responses such as tachycardia, hypertension, laryngospasm, bronchospasm, raised intracranial pressure and intraocular pressure. The mechanisms of the responses to laryngoscopy and orotracheal intubation are proposed to be by somato - visceral reflexes.[1,2,3]

A variety of anaesthetic techniques and drugs are available to control the hemodynamic response to laryngoscopy and intubation. The common strategies adapted are narcotics, vasodilators, Beta blockers, calcium channel blockers, lidocaine and other sympatholytics.[4,5,6,7]

Reid and Brace first described the haemodynamic response to laryngoscopy and endotracheal intubation. He found that the stimulation of the upper respiratory tract provoked an increase in the vagal activity.[8] Dexmedetomidine is a new intravenous drug gaining popularity in anaesthesia and critical care practice. This alpha-2 adrenergic receptor agonist offers a unique "cooperative sedation," anxiolysis and analgesia with no respiratory depression. Cerebral effects are generally consistent with a desirable neurophysiological profile, including neuroprotective characteristics.[9,10,11] Esmolol is an ultra - short acting selective beta-1 receptor antagonist that reduces heart rate and, to a lesser extent, blood pressure with proven efficacy to provide haemodynamic stability during laryngoscopy and tracheal intubation without severe side-effects.[12,13,14] In our study, we have compared the efficacy of IV Dexmedetomidine and IV Esmolol in attenuating the haemodynamic response during laryngoscopy and endotracheal intubation in patient undergoing elective procedure under general anaesthesia.

METHODS

This prospective, randomized, comparative study was conducted in the Department of Anaesthesiology, MAIMRE Agroha. After obtaining approval from Hospital Ethics Committee, 200 patients belonging to American Society of Anaesthesiologists (ASA) physical status I & II of either sex, aged between 18-60 years, weight between 50 - 60 Kg undergoing elective surgical procedure under general anaesthesia were included in this study with informed and written consent obtained from each patient.

Exclusion Criteria

1. Anticipated difficult airway.
2. Preoperative heart rate <50 beats per minute.
3. First or second or third degree heart block.
4. Known allergy to esmolol and dexmedetomidine.
5. Patient with coronary artery disease, left ventricular dysfunction.
6. Pregnant or nursing woman.
7. Patients on antihypertensive medication.
8. Patient refusal to participate in study.

Group Allocation and Study Design

Patients were randomly allocated to two groups comprising of 100 patients each. Group D received dexmedetomidine (n =100) loading dose of 1 mcg per Kg in 20 mL normal saline over 10 min; 7 min prior to induction. Group E received (n=100) esmolol loading dose of 1 mg per Kg infused over 1 min; 2 min prior to intubation.

Preparation of Patients

All patients were subjected to complete physical as well as systemic examination. Routine investigations were carried out in all patients. The purpose and protocol of the study was explained and a written informed consent was obtained from all the patients. On arrival in the operating room standard monitors were connected such as ECG, blood pressure monitoring, pulse oximetry probe. Venous cannulation with 18-gauge cannula was done and the ringers lactate infusion was started.

Anaesthesia Technique

Baseline heart rate and blood pressure were recorded. Patients in group D received loading dose of dexmedetomidine 1 mcg per Kg in 20 mL normal saline given over 10 min, 7 min prior to induction. Patients in group E received injection esmolol after induction in loading dose of 1 mg per Kg over 1 min, 2 min prior to intubation.

After preoxygenating for 3 minutes with oxygen flow rate 6 L min-1 on circle breathing system, all the patients were premedicated with injection midazolam 30 mcg per Kg and injection fentanyl 1.5 mcg per Kg, 5 minutes prior to induction. Intravenous induction was done with thiopentone 5 mg per Kg. I.V. Muscle relaxation was achieved with injection vecuronium bromide 0.12 mg per Kg I.V. followed by laryngoscopy and endotracheal intubation after 3 minutes. Cuff was inflated and correct placement of endotracheal tube was judged by adequate chest rise, bilateral chest auscultation and capnography using manual positive pressure ventilation. Tube was fixed and connected to anaesthesia breathing circuit. Anaesthesia was maintained with 0.8 - 1.0 % of isoflurane in oxygen (33 %) and nitrous oxide (66 %). Patient was mechanically ventilated with tidal volume 8 - 10 mL per Kg and respiratory rate 12 / minute.

Parameters Measured

Blood pressure (Systolic, Diastolic and Mean Blood Pressure) via NIBP and heart rate through continuous ECG monitoring was recorded at preinduction, post induction, just before intubation and 1,3,5 and 15 minutes after laryngoscopy and intubation in both groups.

Duration of laryngoscopy was recorded. Any event of hypotension (MAP<60 mm Hg), bradycardia (HR<50 / min) and arrhythmias was noted.

Statistical Analysis

Statistical analysis was done using SPSS for window version 16.0 software. For noncontinuous data Chi - square test was used. The mean and standard deviation (Mean ± SD) of the parameter studied during observation was calculated for the two groups and compared using student 't' test. p <0.05 was considered significant.

RESULTS

This study was done in the department of Anaesthesiology at Maharaja Agrasen Medical College, Agroha. It comprised of 200 patients of either sex, between 18-60 years of age and ASA Grade I-II. All patients were scheduled for elective surgery under general anaesthesia and required endotracheal intubation.

It was a prospective, randomized, comparative study. Patients with anticipated difficult intubation, respiratory, hepatic, renal artery disease, coronary artery disease, heart block, angina, patients on beta blockers, calcium channel blockers and any other drug causing haemodynamic instability were excluded from this study. Random allocation in two groups of 100 each was done. Group D (n=100) received intravenous dexmedetomidine 1 mcg / Kg 7 minutes prior to induction and Group E (n=100) received intravenous esmolol 1 mg / Kg, 2 minutes prior to intubation.

HR	Group D Mean ± SD	Group E Mean ± SD	P Value
Pre Induction	97.26 ± 7.61	98.78 ± 9.65	0.217
After Giving Study Drug	83.92 ± 6.67	86.2 ± 10.74	0.092
After Induction Of Anaesthesia	80.23 ± 6.50	84.17 ± 9.81	0.001
Just Before Intubation	79.13 ± 6.34	83.18 ± 9.72	0.001
T1 (1 Min)	83.95 ± 6.04	92.91 ± 8.22	<0.001
T3 (3 Min)	81.87 ± 6.24	91.97 ± 8.36	<0.001
T5 (5 Min)	79.25 ± 6.09	88.44 ± 7.56	<0.001
T15 (15 Min)	76.44 ± 8.73	83.11 ± 7.55	<0.001

Table 1. Comparison of Heart Rate between the Two Groups at Different Time Points

The table and shows the comparison of mean Heart Rate across various time points between the two groups under the study. Group D had a greater fall in heart rate as compared to Group E. The difference was statistically significant between the two groups (p value of 0.001). The mean heart rate at pre-induction and after giving study drugs were comparable between the two groups.

SBP (mmHg)	Group D Mean ± SD	Group E Mean ± SD	P Value
Pre Induction	127.56 ± 11.01	126.37 ± 9.92	0.423
After Giving Study Drug	127.3 ± 10.11	125.36 ± 8.79	0.149
After Induction Of Anaesthesia	120.96 ± 8.18	121.39 ± 7.23	0.694
Just Before Intubation	115.26 ± 8.19	119.35 ± 6.49	<0.001
T1 (1 Min)	121.2 ± 7.68	141.38 ± 7.36	<0.001
T3 (3 Min)	119.94 ± 6.17	138.63 ± 7.23	<0.001
T5 (5 Min)	117.6 ± 5.26	134.00 ± 7.10	<0.001
T15 (15 Min)	113.59 ± 7.93	128.87 ± 6.94	<0.001

Table 2. Comparison of SBP between the Two Groups at Different Time Points

The table shows the comparison of SBP across various time points between the two groups under the study. Group D had a greater fall in SBP as compared to Group E. The difference was statistically significant between the two groups (p value of 0.001). The SBP at pre-induction and after giving study drugs were comparable between the two groups.

DBP (mmHg)	Group D Mean ± SD	Group E Mean ± SD	P Value
Pre Induction	85.82 ± 8.39	84.27 ± 8.34	0.192
After Giving Study Drug	81.26 ± 7.78	82.81 ± 8.06	0.168
After Induction Of Anaesthesia	77.2 ± 7.88	78.73 ± 8.27	0.182
Just Before Intubation	73.33 ± 7.6	76.18 ± 7.39	0.008
T1 (1 Min)	77.92 ± 7.87	93.46 ± 5.29	<0.001
2T3 (3 Min)	76.44 ± 7.37	91.49 ± 5.65	<0.001
T5 (5 Min)	73.97 ± 7.07	88.58 ± 5.93	<0.001
T15 (15 Min)	70.43 ± 6.62	85.61 ± 6.01	<0.001

Table 3. Comparison of DBP among the Three Groups at Different Time Points

The table the comparison of mean diastolic blood pressure across various time points between the two groups under the study. Group D had a greater fall in mean diastolic blood pressure as compared to Group E. The difference was statistically significant between the two groups (p value of 0.001). The mean diastolic blood pressure at pre-induction and after giving study drugs were comparable between the two groups.

MAP	Group D Mean ± SD	Group E Mean ± SD	P Value
Pre Induction	99.73 ± 8.61	98.3 ± 8.25	0.232
After Giving Study Drug	96.61 ± 7.93	96.99 ± 7.65	0.726
After Induction Of Anaesthesia	91.79 ± 7.52	92.95 ± 7.24	0.266
Just Before Intubation	87.31 ± 7.35	90.57 ± 6.25	0.001
T1 (1 Min)	92.35 ± 7.36	109.43 ± 5.04	<0.001
T3 (3 Min)	90.94 ± 6.44	107.2 ± 5.46	<0.001
T5 (5 Min)	88.51 ± 5.96	103.72 ± 5.62	<0.001
T15 (15 Min)	84.82 ± 6.16	100.03 ± 5.79	<0.001

Table 4. Comparison of MAP between the Two Groups at Different Time Points

The table the comparison of mean arterial pressure across various time points between the two groups under the study. Group D had a greater fall in mean arterial pressure as compared to Group E. The difference was statistically significant between the two groups (p value of 0.001). The mean arterial pressure at pre-induction and after giving study drugs were comparable between the two groups.

Intraoperative Hypotension (MAP <60 mmHg)	Group D		Group E		P Value
	Frequency	%	Frequency	%	
No	96	96.0%	100	100.0%	
Yes	4	4.0%	0	0.0%	0.121
Total	**100**	**100%**	**100**	**100%**	

Table 5. Comparison of Intraoperative Hypotension between the Two Groups

The table the correlation pertaining to Intraoperative complications hypotension between the two study groups. It was observed that under the group D, 96% of the patients witnessed no Intraoperative complications hypotension while 4 % witnessed Intraoperative complications hypotension. Under the group E, 100 % of the patients witnessed no Intraoperative complications hypotension.

Further, it was observed that there was no significant correlation between the two study groups (p value of 0.121).

DISCUSSION

The present study is aimed at comparing the efficacy of intravenous dexmedetomidine and intravenous esmolol in attenuation of haemodynamic response to laryngoscopy and intubation. The haemodynamic changes brought about by laryngoscopy and intubation was described by Reid and Brace.[8] The haemodynamic response is initiated within seconds of direct laryngoscopy and further increases with passage of endotracheal tube. The response is initiated within 5 seconds of laryngoscopy, peaks in 1 - 2 min and returns to normal levels by 5 - 10 min. These changes are short lived and well tolerated by normal patients. The pressor response to laryngoscopy and endotracheal intubation in the form of tachycardia, hypertension and arrhythmias, though transient, may be potentially dangerous.[3] This response is due to reflex sympathetic discharge caused by epipharyngeal and laryngopharyngeal stimulation.

The analgesic, sedative, anxiolytic, sympatholytic and blunting of exaggerated hemodynamic responses by administration of dexmedetomidine are being extensively studied and are mainly mediated by the activation of α-2 receptors located in the postsynaptic terminals in the central nervous system (CNS), which causes decreased neuronal activity and augmentation of the vagal activity.[14,15,10,11] The role of α-2 agonists in regulating the autonomic and cardiovascular responses is well understood, whereby they inhibit release of catecholamines (norepinephrine) from the sympathetic nerve terminals by augmentation of a vasoconstrictive effect.[16,17]

Esmolol is water soluble, rapid onset, ultra – short - acting, selective beta-adrenergic receptor antagonist with proven efficacy to provide hemodynamic stability during severe side effects. It has been administered in various doses ranging from 0.5 - 2 mg / Kg. Esmolol hydrochloride is a β 1 – selective adrenergic receptor (cardioselective) blocking agent with no significant membrane stabilizing activity or intrinsic sympathomimetic at therapeutic dose.[12,1]

In our study, both groups were comparable regarding age, weight and sex distribution. Our reason for studying the patients up to 60 years of age was that elderly patients more often on drugs such as antidepressants, hypnotics and antihypertensives and also exhibit increased sensitivity to drugs. Dexmedetomidine is an alpha-2 adrenergic agonist with antinociceptive and sedative properties. The sedation effect of dexmedetomidine may be due to decreased tonic activity of locus coeruleus which modulates the stimuli arriving in the central nervous system and adrenergic receptor.[15] Gertler R et al in their study shown the role of dexmedetomidine as a novel sedative and analgesic agent.[11]

Heart Rate

Following intubation, there was increase in heart rate in both the groups but in dexmedetomidine group it remained below baseline till the time of observation in our study that is 15 minutes. But in esmolol group, increase in heart rate was maximum at 1 min which gets decreased to the baseline heart rate till 5 min of observation.

Srivastava VK et al in their study compared the efficacy of dexmedetomidine and esmolol in attenuation of sympathomimetic response to laryngoscopy and intubation in elective neurosurgical patients. In our study also dexmedetomidine was found to be more effective in keeping the heart rate below baseline after intubation. Various studies have used dexmedetomidine in doses ranging from 0.5 to 10 µg / Kg / h with not so much conclusive data but definitely associated with a significant incidence of bradycardia and hypotension in higher doses.[18,19]

Reddy SV et al in their study also concluded that of the two drugs administered, dexmedetomidine 1.0 µg/Kg provides a consistent, reliable and effective attenuation of pressure responses (specially heart rate) when compared to esmolol 2.0 mg / Kg.[20] Keniya VM et al study observed that bradycardia occurred in two patients in dexmedetomidine group intraoperatively.[21] In contrast to other studies, Bajwa SS et al demonstrated that increase in HR and MAP for 3-5 min was observed after the start of dexmedetomidine infusion and was probably due to the vasoconstriction effect of dexmedetomidine appearing earlier than the central sympathetic action.[22]

Miller et al.(1989) concluded that the cardiovascular response to tracheal intubation was effectively attenuated by administration of 100 mg bolus of esmolol in a Canadian multicentre trial.[23] Sharma et al (1996) concluded that in hypertensive patients, the cardiovascular response to tracheal intubation was suppressed by 100 mg esmolol.[24]

Oxorn et al. concluded that esmolol in bolus doses of 100 mg and 200 mg affects solely the chronotropic response in a significant manner.[25] Kindler et al. found that esmolol administration before laryngoscopy was sufficient to control HR after intubation but it did not affect SAP.[6] Yarkan Uysal et al (2012) reported that in hypertensive patients, esmolol was not effective in attenuating the blood pressure response but it attenuated the heart rate response to tracheal intubation.[26]

Blood Pressure

Baseline systolic blood pressure, diastolic blood pressure and mean arterial pressure were similar in both the groups. After giving the drug and following induction fall of SBP, DBP and MAP was seen in both the groups but more significant in dexmedetomidine group ($p<0.001$). Following intubation SBP,DBP and MAP increased from baseline values in esmolol group at T1, T3 and took time to return to baseline values. Mean increased from 98.3 ± 8.25 to 98.3 ± 8.25(T1) and returned to 100.03 ± 5.79 in 15 minutes in esmolol group. In dexmedetomidine group, SBP, DBP and MAP remained below baseline even at 1 min after intubation.

Hale Yarkan Uysal et al (2012) reported that in hypertensive patients, there are no significant differences in blood pressure between baseline value and after intubation value in dexmedetomidine group. But the mean percentage variation analysis showed an absence of increase in HR, SAP and DAP in dexmedetomidine group.[26] Scheinin et al. (1992) concluded that in healthy individuals dexmedetomidine 0.6 µg / Kg decreased, but not totally abolished, the cardiovascular response to laryngoscopy and tracheal

intubation.[27] Results of our study are better showing dexmedetomidine to be superior than esmolol because we have used dose of dexmedetomidine greater (1 mcg/Kg) than in their study (0.6 mcg / Kg). Menda et al (2010) also showed similar results.[28]

Jaakola et al. found that the maximal blood pressure and heart rate in the group injected with 0.6 µg/Kg of dexmedetomidine before anaesthesia, were significantly lower than those of the control group; furthermore, Lawrence and De Lange reported that the maximal blood pressure and heart rate in the group injected with 2 µg / Kg of dexmedetomidine were considerably lower than those of the control group.[29,30] Kindler et al. found that esmolol administration before laryngoscopy was sufficient to control HR after intubation but it did not affect SBP.[6] Similarly, Reddy et al in their study showed that esmolol was not as effective on attenuating the hypertensive response as it was on attenuating the chronotropic response to tracheal intubation. In fact, a significant increase in SBP and a transient raise in DBP was observed after intubation compared to the baseline values and when compared with dexmedetomidine the increase in SBP was greater and more significant in this study.[20] In our study also, esmolol has no significant effect in controlling the increase in blood pressure following laryngoscopy and intubation, thereby justifying our results through these references.

Unlike HR and SBP, in DBP difference was statistically significant at 1 min and 3 min. after intubation and the groups were comparable at 5 min and 15 min. Similar result was seen in Reddy SV et al study.[20] In contrast, Dr Sagar Gandhi in his study observed that DBP remain low in Dexmedetomidine group after intubation for period of 10 minutes.[31]

There are conflicting results in various studies which compare both these drugs. Alagol et al. found that esmolol was found to control hemodynamic better than dexmedetomidine, while others report superiority of dexmedetomidine over esmolol.[32]

In our study, loading dose of dexmedetomidine 1.0 µg/Kg prior to induction of anaesthesia suppressed the hemodynamic response to tracheal intubation in normotensive patients. This suppression in cardiovascular responses was found to be greater with dexmedetomidine infusion than with esmolol. In the present study the haemodynamic response to laryngoscopy and intubation was studied for a period of 15 min as this is the average period for which haemodynamic changes are believed to last. It was found that with this dose dexmedetomidine had better control over HR, SBP, DBP and MAP even after laryngoscopy and intubation. There was significant increase in heart rate and blood pressure from baseline after laryngoscopy and intubation in both groups, maximum rise in heart rate and blood pressure was noted at one minute after intubation but the rise in heart rate and blood pressure in dexmedetomidine group was significantly lower, less pronounced and shorter lasting as compared to esmolol group. On comparison between the two groups, the heart rate and blood pressure was better controlled with dexmedetomidine than esmolol after laryngoscopy and intubation over period of 15 minutes.

The limitations of our study were that we did not compared different doses of both the drugs and effects at different time intervals of administration. We did not assess sedation and anxiety scores and did not perform psychoanalytic tests in the post-operative period, extubation responses and plasma catecholamines levels.

CONCLUSIONS

Dexmedetomidine (1 mcg / Kg) loading dose 2 minutes prior to induction of anaesthesia attenuated the rise in heart rate and blood pressure following laryngoscopy and tracheal intubation, whereas, Esmolol (1.0 mg / Kg) bolus injection 2 minutes prior to induction of anaesthesia, failed to attenuate the cardiovascular response following laryngoscopy and tracheal intubation.

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