Original Research Article

Comparative evaluation of Intravenous Dexmedetomidine vs Esmolol for Attenuation of Hemodynamic Stress Response during Laryngoscopy and Endotracheal Intubation

Gagan Deep[1], Amanjot Singh[2], Akshay Kalia[3], Kewal Krishan Gupta[4]

[1]Assistant Professor, [2]Associate Professor, [3]Senior Resident, [4]Associate Professor, Department of Anesthesiology and Intensive Care, Guru Gobind Singh Medical College and Hospital., Faridkot, Punjab, India.

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Abstract

Background & Aims: Endotracheal intubation is essential for safe general anesthesia practice but it is associated with stress response due to sympathetic stimulation resulting in hypertension and tachycardia. So, to attenuate this stress response during laryngoscopy and endotracheal intubation, the efficacy of intravenous dexmedetomidine and esmolol were compared in this study.

Materials And Methods: The study was carried on total 210 ASA grade I or II patients of aged 18-60 years who were scheduled for elective laparoscopy surgery under general anesthesia. All the patients were randomly divided into the three groups of 70 each. In control group (group C)-intravenous (IV) 0.9% saline plain, dexmedetomidine group (group D)- 1 µg/kg dexmedetomidine and esmolol group (group E)- 1.5 mg/kg esmolol diluted with 0.9% saline in volume of 20 ml IV were infused over 10 minutes and after that induction of anaesthesia was done. Hemodynamic parameters were recorded atbaseline, before intubation, during intubation, and then every 1 minute upto 10 minutes.

Results: In group D, increase in heart rate and blood pressure after intubation at any time intervals was not statistically significant, whereas in group E, there was a statistically significant increase in blood pressure after intubation at 1, 2, and 3 minutes only and in heart rate up to 5 minutes.

Conclusion- Dexmedetomidine is better alternative to esmolol for attenuating the stress response to laryngoscopy and intubation during general anaesthesia.

Key words: Dexmedetomidine, endotracheal intubation, esmolol, stress response.

Introduction

Endotracheal intubation is the most valuable procedure for maintaining the airway before any surgery under general anaesthesia. However,

Corresponding Author: Kewal Krishan Gupta, Associate Professor, Department of Anesthesiology and Intensive Care, GGS Medical College & Hospital, Faridkot, Punjab, India.

E-mail: doc_krishan31@yahoo.co.in

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endotracheal intubation is noxious stimuli that produce transient but marked stress response showing as tachycardia, hypertension, raised intraocular and intracranial pressure even in anaesthetised patients. These changes are seen maximum immediately after intubation and last for 5 to 10 minutes. [1] Transient hypertension and tachycardia are probably of no consequence in healthy individuals, but either or both may be hazardous to those with hypertension, myocardial insufficiency, and cerebrovascular diseaseespecially in cardiac patients. [2]The mechanisms of the responses to laryngoscopy and orotracheal intubation are proposed to be by somatovisceral reflexes.To control the increase in these hemodynamic values, numerous pharmacological and physiological prophylactic interventions have been tried. Previously, intravenous (IV) lidocaine, inhaled anaesthetics, opioids, adrenergic blockers, calcium channel blockers or vasodilators have been commonly used to blunt the stress response with laryngoscopy and intubation [3-6] but with some side effects. Like inhaled anaesthetics and opioids use will cause sedation, respiratory depression, and delayed recovery. Thus, research regarding an ideal pharmacological intervention is continued.

Dexmedetomidine is a novel, highly selective α2 agonist with sympatholytic properties which produces sedation, anxiolysis, and analgesia with minimal respiratory depression.[7,8] Esmolol is an ultra-short acting (elimination half-life of 9 min) **β1 -adrenergic receptor blocke**r with minimal sedation and no analgesic properties.[9,10]The pharmacologic properties of dexmedetomidine and esmolol suggested that these drugs may be a good choice for attenuating hemodynamic stress response to tracheal intubation without interfering with the recovery process and causing significant respiratory depression. However, the question of whether dexmedetomidine for attenuating hemodynamic response to tracheal intubation is superior to esmolol remains unclear. So, this prospective, double-blinded study was planned to compare the effect of dexmedetomidine and esmolol in attenuation of stress response to endotracheal intubation during laparoscopic surgeries. Here, we hypothesized that use of intravenous (IV) dexmedetomidine would more effectively attenuate the stress response to endotracheal intubation than IV esmolol.

Material and Methods

This prospective, randomized, clinical study was conducted over a period of 14 months as per biomedical research guidelines and the principles of Declaration of Helsinki (2013). After approval from the Institutional Ethical Committee (ECR/836/Inst/PB/2016) dated 13/02/18 and the Clinical Trial Registry of India registration(CTRI/2018/06/020503). This study was done on 210 patients of ASA Grade I or II, of either sex and aged between 18-60 years who were scheduled for elective laparoscopy surgery like laparoscopy cholecystectomy, laparoscopy hysterectomy, laparoscopy cystectomy under general anesthesia.Patients with or more than ASA grade III, predicted difficult airway (Mallampati grade – III/IV, mouth opening < 3 fingers, Thyromental distance <6.5cm), on preoperative β-blocker therapy or allergic to study drugs, systemic illness such as hypertension, diabetes, hepatic or renal failure were excluded from the study. After obtaining written informed consent, all the 210 patients were randomly allocated to either of the three study groups (70 each) by using a sealed envelope randomization technique (non-probability) which were comprising of three drug codes i.e., C, D and E. The envelopes were randomly selected and opened before the start of the study by chosenanesthetist (not included in the study protocol), who preparedall the drugs as per code in identical 20ml syringes. A record of the patients along with codes of syringes were kept, which were revealed on completion of study. In case of drop outs from the study due to any reason (laryngoscopy time >20 s and need for more than one attempt of intubation), the code of that patient was given to another patient under the study so that the number of patients in the three study groups remained the same. GROUP C – received 20 ml of 0.9% normal saline.

GROUP D– received Dexmedetomidine **1µg/kg intravenous diluted with 0.9% normal saline to 20 ml**.

GROUP E– received Esmolol 1.5mg/kg intravenous diluted with 0.9% normal saline to 20ml.

The study drugs were infused over 10 mins prior to induction of anaesthesia. Tab Alprazolam 0.5mg and Tab Ranitidine 150mg orally at night before surgery were given to each patient and they were kept 6 hours nil per orally prior to surgery. After

securing IV line in preoperative area, premedication with Inj. Ondansetron 4mg IV and Inj. Pentazocine 30mg IV were given prior to surgery. After shifting to operation theatre, routine standard monitor including heart rate (HR), noninvasive blood pressure mean (MAP) and oxygen saturation ($SpO_{2)}$ were applied and baseline reading of HR, MAP and SpO_2 were recorded (T0). The study drugs were infused as per group allocated using syringe pump (Perfusor Compact S, B Braun, Germany) @ 120ml/hr and induction was done with Propofol 2 -2.5 mg/kg at the end of 10 minutes (T10) of starting the infusion. After confirming ventilation, patient was intubated under standard condition using inj. Suxamethonium, 1.5 mg/kg by the senior anaesthesiologist in all cases. Successful placement of ETT(endotracheal tube) and ventilation was confirmed by end tidal CO_2 ($EtCO_2$ 35-45mmHg). Anaesthesia was maintained with oxygen (40%),nitrous oxide (60%), isoflurane and inj vecuronium for neuromuscular blockade. The hemodynamic parameters like heart rate (HR), mean arterial pressure (MAP) and SpO2 were recorded at baseline T0, after study drug administration(T10), during intubation(Ti) and 1 (T1i),2 (T2i), 4(T4i), 6 (T6i), 8 (T8i), and 10 (T10i) min after orotracheal intubation by independent anaesthesiologist who was not aware of content of syringe and study protocol. Till then surgery was not allowed to start. Any episode of bradycardia (Heart rate <50 beats/min), hypotension (MAP <60 mmHg) and other adverse events were also noted and managed accordingly. At the end of the surgery, 100% oxygen, inj. Neostigmine 0.05mg/kg with inj. Glycopyrrolate 0.01mg/kg was given and patient extubated.

Before the study, to calculate the essential number of patients in each group based on change in MAP, a power analysis was performed. We conducted 5 pilot cases in each group (not included in the study), and found minimum significant difference of 10.2 mmHg in MAP with standard deviation (SD) of 6.4 from control group. So, 66 patients were required in each group with power of study 90% and alpha error of 0.05. Thus, we enrolled 70 patients in each group to cover any dropout due to any reason. Data were compiled and analysed after completion of study using Statistical Package of Social Sciences (SPSS) version 17.0 (Chicago, IL, USA). Data was represented as mean ± standard deviation. Student's t-test, Chi-square test or Fisher's exact test were used as appropriate. For intergroup comparison, two-way analysis of variance was used. $P< 0.05$ was considered significant.

Results

All the three groups were comparable for demographic characteristics including age, sex, height, weight, ASA status, Mallampati grading and duration of laryngoscopy (Table 1).

There was no difference in baseline hemodynamic parameters among the groups.After administration of study drugs i.e., at T10, the change in mean HR occurred and the inter group comparison of these changes was statistically highly significant (p value <0.001) between groups D & C and groups E & D but nonsignificant between groups E & C. At Ti (during laryngoscopy and intubation), the rise in mean HR from baseline value in group C was 17.5±6.07, in group E was 5±2.43 whereas in group D the mean HR remained lower than the baseline value by 5.99±1.45. Maximum increase in HR from the baseline value occurred at 1 minute after laryngoscopy and intubation (T1i) and this increase was 18.51±9.45 in group C and 5.06±3.5 in group E, whereas in group D, the HR remained below the baseline value by 1.37±1.3. The inter group comparison of these changes is statistically highly significant between groups D & C, D & E and E & C (Table 2).In inter group comparison, the difference of change in mean HR from the baseline value between group D & E and D &C was statistically significant at all the time intervals. The difference in change in mean HR from the baseline value in groups C&E was statistically significant at Ti, T1i and T2i and T4i whereas this difference in mean HR was nonsignificant for rest of the time intervals (Table 2). In group D, the heart rate remained lower than the baseline value at all the time intervals.

Baseline values of mean MAP were comparable between all the three groups but after administration of study drugs, there was significant decrease in mean MAP in group D only. During induction, the rise in MAP from baseline value in group E and C was 6.82±2.18 mm Hg and 17.16±1.28 mm Hg respectively. However, the mean MAP remained lower than the baseline value in group D. The difference in mean

MAP from the baseline value between group E & C and group D & C was statistically highly significant at T10, Ti and T1i while between group D & E, it was statistically highly significant at time Ti and T1i only (Table 3). The inter group comparison of difference in MAP of three groups was insignificant at time T4i to T10i (Table 3). No significant adverse effects like bradycardia, hypotension, hypertension was observed in any of the group.

Table 1: Demographic variable among different groups

Parameters	Group C (n=70)	Group D (n=70)	Group E (n=70)	p value*
Age (years)	43.18±13.45	39.37±12.57	39.08±14.01	0.085 (NS)
Weight (Kg)	64.22±7.08	65.18±6.76	65.15±6.90	0.415 (NS)
Height (cm)	161.529±4.43	161.029±4.52	162.543±3.68	0.510 (NS)
Sex (M/F)	41/29	48/22	46/24	0.324 (NS)
ASA I/II	60/10	58/12	57/13	0.390 (NS)
Mallampati grading I/II	46/24	50/20	49/21	0.250 (NS)
Duration of laryngoscopy (Seconds)	12.50±2.5	11.26±3.14	12.75±1.75	0.876 (NS)

p value *<0.05 is considered significant, NS- non significant.

Table 2: Comparison heart rate from basal values at different time intervals of study groups

	GROUPC		GROUPD		GROUPE		ANOVA TEST	Ttest P value		
	Mean	SD	Mean	SD	Mean	SD	PVALUE	C*D	C*E	D*E
HR(T0)	83.60	13.52	85.00	7.36	83.07	8.92	0.518	0.761 P=0.448	0.273 P=0.785	1.396 P=0.165
HR(T10)	83.74	9.46	78.01	11.07	83.64	8.39	<0.001	3.292 P=0.001	0.066 P=0.947	3.391 P=0.001
HR(Ti)	101.13	7.44	80.01	8.81	88.07	11.49	<0.001	15.32 P<0.001	7.981 P<0.001	4.656 P<0.001
HR(T1i)	112.09	4.97	83.63	8.43	88.01	11.42	<0.001	24.33 P<0.001	16.163 P<0.001	2.585 P=0.011
HR(T2i)	102.80	10.72	84.13	10.70	89.00	10.69	<0.001	10.315 P<0.001	7.627 P<0.001	2.695 P=0.008
HR(T4i)	91.66	11.03	71.21	5.96	86.80	9.37	<0.001	13.649 P<0.001	2.808 P=0.006	11.744 P<0.001
HR(T6i)	87.01	11.07	68.61	5.01	85.00	8.96	<0.001	12.671 P<0.001	1.183 P=0.239	13.353 P<0.001
HR(T8i)	80.19	7.74	66.43	6.69	79.84	8.21	<0.001	11.252 P<0.001	0.254 P=0.800	10.598 P<0.001
HR(T10i)	76.19	7.95	67.40	6.34	77.70	10.24	<0.001	7.227 P<0.001	0.977 P=0.330	7.156 P<0.001

*pVALUE <0.001= HIGHLYSIGNIFICANT, <0.05=SIGNIFICANT

Table 3: Comparison of mean arterial pressure at different time intervals in all the groups

	GROUPC		GROUPD		GROUPE		ANOVATEST PVALUE	T test P value		
	Mean	SD	Mean	SD	Mean	SD		C*D	C*E	D*E
MAP(T0)	81.16	13.73	81.03	6.08	80.91	8.28	0.990	0.072 P=0.943	0.127 P=0.889	0.093 P=0.926
MA (T10)	87.27	13.09	75.71	9.82	79.04	7.32	<0.001	5.909 P<0.001	4.591 P<0.001	2.274 P=0.024
MAP(Ti)	98.00	14.45	78.77	9.15	87.49	6.10	<0.001	9.405 P<0.001	5.608 P<0.001	6.632 P<0.001
MAP(T1i)	95.70	16.07	80.20	6.52	86.04	7.49	<0.001	7.479 P<0.001	4.557 P<0.001	4.921 P<0.001
MAP(T2i)	89.80	14.23	82.01	11.25	85.10	6.40	<0.001	3.591 P<0.001	2.520 P=0.013	1.995 P=0.048
MAP(T4i)	83.47	12.67	81.46	12.71	83.01	7.90	0.545	0.939 P=0.349	0.256 P=0.798	0.871 P=0.386
MAP(T6i)	79.20	9.21	82.39	15.00	79.10	8.84	0.154	1.514 P=0.132	0.066 P=0.948	1.579 P=0.117
MAP(T8i)	75.21	7.26	82.34	14.82	77.00	8.03	<0.001	3.613 P<0.001	1.380 P=0.170	2.652 P=0.009
MAP(T10i)	75.36	9.27	75.11	12.80	75.00	8.36	0.978	0.129 P=0.898	0.239 P=0.811	0.063 P=0.950

*pVALUE <0.001= HIGHLYSIGNIFICANT, <0.05=SIGNIFICANT

Discussion

Stress response due to laryngoscopy has been well known phenomenon all over the world which may present in the form of tachycardia, hypertension, and arrhythmias as autonomic disturbance. Although this stress response is probably of no significance in healthy patients, but this may be harmful to patients with hypertension and coronary artery disease.[11] Different pharmacological agents have been used in the past to attenuate the hemodynamic response to endotracheal intubation. However, the search for ideal technique or agents for attenuation of this hemodynamic changes continues. So, we conducted this randomized controlled trial to compare the efficacy of IV dexmedetomidine at 1 μg/kg and IV esmolol 1.5 mg/kg along with control, on the stress response to endotracheal intubation in laparoscopic surgical procedures under general anesthesia.

In present study, dexmedetomidine was effective in blunting the stress response to intubation as compared to control group. This finding was in accordance with study conducted by Sulaiman S et al., who studied the effects of dexmedetomidine (0.5 μg/kg) on attenuation of stress response to endotracheal intubation. They found that increase in heart rate and MAP as stress response was statistically significantly lower in dexmedetomidine group than control group at all time intervals from baseline value.[12] Another study done by Reddy SV et al., and Modh DB et al., also found that the increase in heart rate and MAP as stress response to intubation was significantly higher in control group as compared to dexmedetomidine group. [13,14]

In present study, esmolol was also able to attenuate the stress response during intubation as compared to control group and this finding was in concordance with the study conducted by S Gupta et al., who compared normal saline, esmolol (2 mg/kg) and fentanyl (2 µg/kg) for attenuation of pressor response during intubation.[15] They found that there was increase in heart rate from 82.2 ±5.47 at baseline to 101.8±4.34 at T1i min in control group as compared to 85.2 ±7.60 at baseline to 88.33 ±5.28 at T1i min in esmolol group (p value<0.001). MAP also increased in both the esmolol and control group after intubation but this increase was statistically more significant in control group than esmolol group (p value< 0.001).

Our study found that the dexmedetomidine was better in blunting the stress response to intubation than esmolol in terms of better hemodynamic control. Sharma et al., conducted a study where they used esmolol (1.5mg/kg) and dexmedetomidine (1µg/kg) for suppression of stress response to laryngoscopy or endotracheal intubation and found that the heart rate and MAP remained statistically significantly lower (p value < 0.001) in dexmedetomidine group as compared to esmolol at all time intervals which correlate well with our study.[16] Syal et al., compared dexmedetomidine (1**µg**/kg) and esmolol (1mg/kg) to attenuate the hemodynamic pressor response to laryngoscopy and found that in dexmedetomidine group heart rate remained statistically significantly lower than the baseline at all time intervals (p value <0.001).[17]MAP was also statistically significantly decreased in dexmedetomidine group than esmolol group at all time intervals (MAP increased from 117.2±8.8 mm Hg at baseline to 122.6±15.9mmHg T1i min in esmolol group as compared to 114.9±10.0 mm Hg at baseline to 108.8±20.0 mm Hg T1i min in dexmedetomidine group (p value<0.001).Our results are not in corelation with the study of Alagol et al., where esmolol was found to have better hemodynamic control than dexmedetomidine.[18] Theoretically, the hypotension and bradycardia with use of dexmedetomidine, could limits its usage in bradyarrhythmia patient or neurosurgical patient with raised intracranial pressure. In our study, bradycardia was observed in only three patients of group D, which were managed with IV 0.5 mg atropine. However, none of these three patients have reported fall in blood pressure along with bradycardia.

This clinical trial was a small effort to evaluate the efficacy of dexmedetomidine and esmolol to attenuate stress response to endotracheal intubation with few inherit limitations. Firstly, it includes the use of a fixed dosage of study drugs at a fixed interval before intubation. Secondly, we have not assessed plasma catecholamines levels to know the degree of suppression of neurohumoral pathway. Thirdly, as patients with MPG III and IV were excluded from the study, these results may not be generalized to the patients with difficult airway.

Conclusion

We conclude that both dexmedetomidine and esmolol are good agents to blunt the stress response to intubation. However, dexmedetomidine provides consistent and dependable protection against hemodynamic response in form of increase in HR as well as MAP during endotracheal intubation. Therefore, dexmedetomidine is better than esmolol in attenuating stress response to intubation and laryngoscopy in laparoscopic patients.

Conflict of Interest: Declared None

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