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Original Research Article

Effects of lidocaine, fentanyl and esmolol on haemodynamics and bispectral index when used before laryngoscopy and intubation to prevent stress response in patients with etomidate induction

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Abstract: Endotracheal intubation creates a period of hemodynamic instability in normotensive patients. Endotracheal intubation produces stimulation of laryngeal and tracheal sensory receptors, resulting in a marked increase in the elaboration of sympathetic amines leading to hypertensive crisis. The objective of study is to evaluate and compare the efficacy of fentanyl, lidocaine and esmolol in attenuating the stress responses to laryngoscopy and endotracheal intubation in normotensive patients with etomidate induction. We conducted a prospective, randomized, double-blind study in 120 patients posted for laparoscopic surgery. All patients were randomly divided into four groups. The fentanyl group received Fentanyl 2 mcg/kg and lidocaine group received 2mg/kg lidocaine and esmolol group received 1mg/kg esmolol 3 min prior to intubation. BIS and hemodynamic parameters were recorded at baseline, after giving induction agents, and 1 to 5 minutes at each 1 min interval after endotracheal intubation. There were no significant differences between the three groups regarding hemodynamic parameters like heart rate, systolic diastolic and mean arterial blood pressure, but BIS value was better in fentanyl group. Esmolol, lidocaine and fentanyl effectively decreased the stress response to endotracheal intubation. But BIS was better in fentanyl group.
Keywords: Fentanyl, Hemodynamic stress, Intubation, Lidocaine, clonidine.

INTRODUCTION

Endotracheal intubation has become an integral part of anaesthetic management and critical care of the patient. Direct laryngoscopy and endotracheal intubation is almost always associated with haemodynamic changes due to reflex sympathetic discharge, caused by epipharyngeal and laryngopharyngeal stimulation [1]. This increased sympathoadrenal activity results in hypertension, tachycardia and arrhythmias [2, 3]. Transitory hypertension and tachycardia may be hazardous to those with hypertension, myocardial insufficiency and cerebrovascular diseases. The laryngoscopic reactions in such individuals may predispose to pulmonary edema, myocardial insufficiency and cerebrovascular accidents [4]. Pharmacological methods devised to reduce the extent of haemodynamic events include high dose of opioids, local anaesthetics like lignocaine, alpha and beta adrenergic drugs and vasodilator drugs like nitroglycerine [5]. But still the search for ideal agent goes on. The present study was undertaken to determine the efficacy of IV lignocaine 2 mg/kg, IV fentanyl 2mcg/kg and IV esmolol 1 mg/kg in attenuating the sympathetic response to laryngoscopy and intubation. The Bispectral Index is a measure of the hypnotic effect of anaesthesia. The unintentional awake intubation and the explicit memory of such an incident is one of the most consequential concerns during anaesthetic practice. Awareness is an unpleasant and traumatic experience and has the considerable potential for morbidity, including severe emotional stress and post-traumatic stress disorder. To our knowledge, however, little study has been performed on how adjuvants for blunting the tracheal response might be influential on the change in BIS or not.

We had studied the effects of study drugs on haemodynamics and bispectral index during laryngoscopy and intubation in patients with etomidate induction.

METHOD

The study was undertaken in SCB Medical College and Hospital, Cuttack during 2013-15. The study was undertaken after obtaining informed consent from

patients and ethical committee clearance.120 patients of ASA-I and ASA-II grades scheduled for various elective (non cardiac) surgical procedures were selected for a prospective, randomized, single blinded study. The patients were normotensive. The age varied from 20-60 yrs. The patients were selected at random.

All patients were pre-medicated with Tab. clonazepam 0.5mg at bed time the previous day. On the day of surgery, IV line was secured with 18G cannula and infusion of ringers lactate started, Inj. Glycopyrrolate 0.005mg/kg IV, Inj. Midazolam 0.04mg/kg IV and inj. Tramadol 1mg/kg IV 30 min before induction were administered.

Patients were connected to multichannel monitor and heart rate, non-invasive blood pressure, end-tidal Co2, continuous ECG, oxygen saturation and mean arterial pressure, BIS index were monitored. Study population was divided into 4 groups.

Group 1 was the control group and these patients received 10 ml of normal saline 3 minute prior to laryngoscopy.
Group 2 patients received Lidocaine2 mg/kg (diluted to 10 ml) 3min before laryngoscopy and intubation.
Group 3 patients received IV Fentanyl 2 mcg/kg (diluted to 10 ml) 3min before laryngoscopy and intubation.
Group 4 patients received IV Esmolol1.0 mg/kg (diluted to 10 ml) 3min before laryngoscopy and intubation.

All patients were preoxygeneted for 3 minutes with a fresh gas flow of 6lit/min, using a face mask connected to a semi-closed breathing circuit.

Anaesthesia was induced with Inj. Etomidate 0.3mg/kg body weight and Inj. Rocuronium 0.6mg/kg body weight was administered. Intubation was carried out using appropriate sized endotracheal tube. Laryngoscopy and intubation were performed within 10-15 seconds by the anaesthesiologist. Anaesthesia was maintained with 66% nitrous oxide, 33% oxygen, and Isoflurane 1 vol% and was titrated. Adequacy of ventilation was monitored clinically and SP02 maintained at 99-100%.All the raw data were collected and entered into Microsoft excel spread sheet and analyzed using standard statistical software such as Microsoft Excel 2007, Statisstica 6.0 and SPSS 20.

Categorical variables were expressed in terms of no. and proportions. Associations between categorical variables were determined by Chi-square test. Continuous variables were expressed in terms of mean and SD (standard deviation), associations between the groups was determined by ANOVA test. In between the groups association was determined by Bonferroni post hoc analysis.

OBSERVATION

There was no significant difference between four groups regarding age, sex, weight and ASA status. Heart rate increased maximally in the control group reaching a maximum of 41.94 % above baseline at 1 minute after laryngoscopy and intubation which remained at 24.02 % higher even after 5 minutes post intubation

Table 1: Heart rate

Group	Lidocaine		Fentanyl		Esmolol		Control		P value*
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
HR Baseline	79.43	11.007	79.90	8.841	81.10	7.671	80.17	10.952	0.925
HR1min	103.63	13.813	109.80	11.775	84.00	7.647	113.80	14.077	<0.001
HR2min	99.90	13.343	105.40	11.057	81.30	7.316	110.07	13.859	<0.001
HR3min	96.47	13.017	100.97	10.519	78.90	7.378	106.70	13.272	<0.001
HR4min	93.07	12.897	95.00	9.606	77.30	7.082	103.40	13.019	<0.001
HR5min	87.63	10.839	89.67	8.683	76.03	7.199	99.43	12.165	<0.001

*ANOVA test was used

Table 2: Post hoc analysis of heart rate

	Lidocaine vs Control	Fentanyl Vs Control	Esmolol vs Control	Lidocaine Vs Fentanyl	Fentanyl Vs Esmolol	Lidocaine Vs Esmolol
HR Baseline	1.00	1.00	1.00	1.00	1.00	1.00
HR1min	0.009	1.00	<0.001	0.305	<0.001	<0.001
HR2min	0.006	0.747	<0.001	0.425	<0.001	<0.001
HR3min	0.004	0.311	<0.001	0.754	<0.001	<0.001
HR4min	0.002	0.021	<0.001	1.00	<0.001	<0.001
HR5min	<0.001	0.001	<0.001	1.00	<0.001	<0.001

Bonferroni post hoc analysis was used for finding association (P-values) within groups. Inter group

comparison shows control of heart rate was comparable between Lidocaine group and Fentanyl group, but Esmolol group resulted in better control of heart rate as compared to Fentanyl and Lidocaine.

Table 3: SBP

Group	Lidocaine		Fentanyl		Esmolol		Control		P value*
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
SBP baseline	128.60	6.129	128.07	6.797	130.43	7.731	126.53	6.827	0.185
SBP1min	168.50	8.174	157.43	8.386	149.83	8.867	167.60	9.137	<0.001
SBP2min	164.83	8.655	151.87	8.123	146.47	8.665	163.90	8.707	<0.001
SBP3min	161.93	8.436	146.53	7.776	142.97	8.512	159.87	8.500	<0.001
SBP4min	156.17	7.940	140.90	7.796	139.63	8.302	156.60	8.324	<0.001
SBP5min	149.40	7.323	135.17	7.216	136.43	8.123	152.80	8.181	<0.001

Table 4: Post hoc analysis of SBP

	Lidocaine vs Control	Fentanyl Vs Control	Esmolol vs Control	Lidocaine Vs Fentanyl	Fentanyl Vs Esmolol	Lidocaine Vs Esmolol
SBP baseline	1.00	1.00	0.183	1.00	1.00	1.00
SBP1min	1.00	<0.001	<0.001	<0.001	0.005	<0.001
SBP2min	1.00	<0.001	<0.001	<0.001	0.095	<0.001
SBP3min	1.00	<0.001	<0.001	<0.001	0.595	<0.001
SBP4min	1.00	<0.001	<0.001	<0.001	1.00	<0.001
SBP5min	0.545	<0.001	<0.001	<0.001	1.00	<0.001

Bonferroni post hoc analysis was used for finding association (P-values) within groups. Attenuation of SBP is definitely better in Esmolol& Fentanyl group than Lidocaine& Control groupat 1 min, 2 min, 3 min, 4 min, & 5 min. But at 1 minute Esmolol group has lesser rise in SBP than Fentanyl group which is statistically significant (p<0.001).

Table 5: DBP

Group	Lidocaine		Fentanyl		Esmolol		Control		P value*
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
DBP baseline	81.03	5.442	82.73	4.386	83.57	5.361	80.73	4.690	0.089
DBP1min	94.13	6.257	91.77	4.939	92.13	5.912	101.37	5.648	<0.001
DBP2min	92.03	6.014	90.70	4.843	90.67	5.707	97.13	5.237	<0.001
DBP3min	90.37	6.054	89.57	4.651	89.40	5.905	91.97	5.468	0.264
DBP4min	88.90	6.036	87.10	4.405	87.20	5.738	89.73	5.239	0.163
DBP5min	87.10	5.732	84.70	4.427	84.57	5.575	87.80	4.944	0.032

Table 6: Post hoc analysis

	Lidocaine vs Control	Fentanyl Vs Control	Esmolol vs Control	Lidocaine Vs Fentanyl	Fentanyl Vs Esmolol	Lidocaine Vs Esmolol
DBP baseline	1.00	0.740	0.179	1.00	1.00	0.310
DBP1min	<0.001	<0.001	<0.001	0.667	1.00	1.00
DBP2min	0.003	<0.001	<0.001	1.00	1.00	1.00
DBP3min	1.00	0.579	0.454	1.00	1.00	1.00
DBP4min	1.00	0.366	0.428	1.00	1.00	1.00
DBP5min	1.00	0.136	0.105	0.457	1.00	0.369

Bonferroni post hoc analysis was used for finding association (P-values) within groups. The rise in DBP (diastolic blood pressure) was lesser in Esmolol, Lidocaine& Fentanyl group as compared to Control group at 1st min and 2nd min following intubation (p<0.001).at 3rd, 4th ,5th min there was no difference in rise of DBP among all the groups.

Table 7: MAP

Group	Lidocaine		Fentanyl		Esmolol		Control		P value*
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
MAP baseline	95.10	5.115	94.17	4.822	96.00	5.527	94.10	4.795	0.425
MAP1min	117.03	6.536	109.77	5.637	106.73	6.192	120.23	5.935	<0.001
MAP2min	114.67	6.402	106.87	4.995	104.77	6.140	116.13	5.835	<0.001
MAP3min	112.47	6.257	104.27	5.232	103.20	5.892	112.30	5.434	<0.001
MAP4min	109.97	5.933	100.90	4.766	101.07	5.919	108.70	5.434	<0.001
MAP5min	106.83	5.657	97.17	4.956	98.13	5.882	105.87	5.237	<0.001

Table 8: Post hoc analysis

	Lidocaine Vs Control	Fentanyl Vs Control	Esmolol Vs Control	Lidocaine Vs Fentanyl	Fentanyl Vs Esmolol	Lidocaine Vs Esmolol
MAP baseline	1.00	1.00	0.898	1.00	1.00	1.00
MAP1min	0.263	<0.001	<0.001	<0.001	0.336	<0.001
MAP2min	1.00	<0.001	<0.001	<0.001	1.00	<0.001
MAP3min	1.00	<0.001	<0.001	<0.001	1.00	<0.001
MAP4min	1.00	<0.001	<0.001	<0.001	1.00	<0.001
MAP5min	1.00	<0.001	<0.001	<0.001	1.00	<0.001

Bonferroni post hoc analysis was used for finding association (P-values) with in groups. The rise in MAP is definitely lesser in Fentanyl and Esmolol group in comparison to Lidocaine and Control group at 1^{st},2^{nd} ,3^{rd} ,4^{th} ,5^{th} min. following intubation which is statistically significant (p<0.001). But there is no difference between Fentanyl and Esmolol group in MAP following intubation at 1 to 5 min.

Table 9: BIS

Group	Lidocaine		Fentanyl		Esmolol		Control		P value*
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
BIS baseline	95.43	3.702	96.83	1.510	97.03	2.042	97.97	.890	0.001
BIS1min	60.47	3.636	51.57	5.217	55.50	3.866	60.03	2.846	<0.001
BIS2min	60.63	2.659	51.60	5.612	53.70	3.949	60.63	2.748	<0.001
BIS3min	55.67	3.546	48.77	5.230	51.77	3.674	55.57	3.588	<0.001
BIS4min	53.23	3.266	46.63	4.930	49.37	3.000	53.10	2.440	<0.001
BIS5min	50.93	3.676	44.63	5.021	47.33	3.144	52.83	3.152	<0.001

Table 10: Post hoc analysis

	Lidocaine vs Control	Fentanyl Vs Control	Esmolol vs Control	Lidocaine Vs Fentanyl	Fentanyl Vs Esmolol	Lidocaine Vs Esmolol
BIS baseline	<0.127	0.345	0.702	0.117	0.591	0.047
BIS1min	1.00	<0.001	<0.001	<0.001	0.001	<0.001
BIS2min	1.00	<0.001	<0.001	<0.001	0.244	<0.001
BIS3min	1.00	<0.001	0.003	<0.001	0.031	0.002
BIS4min	1.00	<0.001	<0.001	<0.001	0.02	<0.001
BIS5min	0.341	<0.001	<0.001	<0.001	0.043	0.002

Bonferroni post hoc analysis was used for finding association (P-values) within groups. There was no significant difference in baseline BIS values in all the groups. At 1 to 5 min. post intubation BIS values in Fentanyl &Esmolol group were better than Lidocaine& Control group. But however the BIS values were better in Fentanyl group than Esmolol group post intubation.

Esmolol is the better among these groups in attenuating the HR response to intubation followed by Lidocaine, Fentanyl& Control group, and fentanyl was better in comparison to other groups as BIS is concerned.

DISCUSSION

According to Ali *et al.;* in 2010, pre-treatment with lidocaine improves intra- and post-operative hemodynamic stability during laparoscopic surgery without prolonging recovery [6]. Our study was in line

with some previous studies such as Shin *et al.;* that compared the effects of lidocaine, fentanyl, Nicardipine and Esmolol, on the hemodynamic response during intubation and those studies showed that all the agents are effective in producing hemodynamic stability. The administration of lidocaine, fentanyl, or esmolol during induction with etomidate attenuated with a various degree of hemodynamic and BIS responses following tracheal intubation. However, the changes in tracheal response were not coincident with the changes in BIS responses following different adjuvants as per the study conducted by Hyoung Yong Shin *et al.;* [7]. According to Levitt *et al.;* Esmolol and lidocaine have similar efficacies to attenuate moderate hemodynamic responses to intubation in patients with isolated head trauma [8]. Additionally, Malde and Sarode in a 2007 study compared lignocaine and fentanyl efficacy on hemodynamic stability and revealed that lignocaine and fentanyl both attenuated the rise in heart rate; however, fentanyl produced better results. Lignocaine attenuated the rise in blood pressure with intubation while fentanyl inhibited it totally [9]. Feng CK showed that only esmolol could reliably offer protection against the increase in both HR and SBP, low dose of fentanyl (3 micrograms/kg) prevented hypertension but not tachycardia, and 2 mg/kg lidocaine had no effect to blunt adverse hemodynamic responses during laryngoscopy and tracheal intubation [10]. Gurulingappa in his study found that attenuation of presser response is seen both with lignocaine and fentanyl upto different extent. Of the two drugs fentanyl 4microgram i.v. bolus provides a consistent, reliable and effective attenuation as compared to lignocaine 1.5mg/kg iv Bolus [11]. So fentanyl at 2mcg/kg may not be sufficient to blunt the stress response alone. There was no significant difference in baseline BIS values in all the groups. At 1 to 5 min. post intubation BIS values in Fentanyl & Esmolol group were better than Lidocaine& Control group. But however, incidence of BIS values was better in Fentanyl group than Esmolol group.

Although the hemodynamic responses are the most commonly used measures to judge the depth of anaesthesia, they are not precise tools for judging anaesthetic depth. BIS has been widely used to identify and reduce the incidence of awareness during the anaesthetic induction. BIS is highly correlated with the level of sedation and the loss of consciousness for volatile agents and most of the intravenous anaesthetic agents. BIS is a safe and simple measurement to detect the hypnotic component of anaesthesia, however, it may not predict the awareness reaction to intubation in surgical patients and the effectiveness is still questionable. In addition, BISvalue may be changed in response to drugs and stimulations such as cardiovascular or somatic responses. In our study we found the incidence of BIS ≥65 were nil in Fentanyl group, 2 in Esmolol group and 6 in Lidocaine group 1st to 5th min. following intubation. This suggests that the change in BIS after administration of study drugs for suppression of tracheal response is not co-ordinated with the change in the hemodynamics.

Fentanyl, an opioid, is commonly used opioid that combined with hypnotic agents to minimize the hemodynamic responses to tracheal intubation. As per the study of Hyoung Yong Shin *et al.;* [12] fentanyl modified hemodynamic responses due to tracheal intubation but did not affect the BIS responses.

Ugur *et al.;* [12] reported that esmolol had not only attenuation of the hemodynamic responses but also the suppression of BIS arousal reactions due to the laryngoscopy and tracheal intubation in patients anesthetized with propofol. They used a continuous infusion of esmolol and propofol to keep the patients BIS value below 65 during the measuring time. However, in the present study we could not found the BIS suppressing effect of esmolol. In our study BIS value is better in Fentanyl group than Esmolol group.

CONCLUSION

In conclusion, all the adjuvant drugs used in this study attenuated the hemodynamic responses due to the laryngoscopy and tracheal intubation with a various degree. However, the study could not find the correlation between the changes of haemodynamics and BIS values after tracheal intubation. Appropriate adjuvant drug therapy during anaesthetic induction can be used for better quality of anaesthesia.

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