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A Comparative Study of Effect of Etomidate, Propofol and Etomidate Plus Propofol Induction on Hemodynamic Response to Endotracheal Intubation: A Prospective Randomized Controlled Study

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Abstract: ***Aim: The primary objective of this current study was to compare the efficacy of three different anaesthesia induction approach (Inj. Etomidate, Inj. Propofol,and Inj. Etomidate plus Inj. propofol) in maintaining hemodynamic stability during induction followed by endotracheal intubation in patients undergoing elective surgeries. Material and methods: Total 90 patients, aged 16 to 65 years of both sex and ASA physical status I or II scheduled for elective surgeries under general anaesthesia were taken for this present study. After taking both written and informed consent, the patients were randomly placed into three groups. Group E with Inj. Etomidate (0.3 mg/kg) intravenously, Group P induced with Inj. Propofol (2.5 mg/kg) intravenously, and Group PE with Inj. Etomidate (0.2 mg/kg) plus Inj. Propofol (1.5 mg/kg) intravenously. Patient's Heart rate (HR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial blood pressure (MAP), and Saturation percentage of Oxygen (SPO2) were noted at different time interval. Results: In all the study groups Heart rate (HR) decreases after induction, and it is more in group P when compared to group E and PE. Among all the three groups MAP decreases after induction, and it was more in group P than group E and PE. MAP increases significantly at 1 min after intubation in all the three study groups, but this increase is not sustained and returned to baseline in group E and PE. Conclusion: Hemodynamic stability is better with the combination of etomidate plus propofol than that of etomidate alone at 1 min after intubation, even though etomidate is equally stable at other points of time. The combination has proved to be significantly better than the administration of etomidate or propofol individually.***

Keywords: Etomidate; Propofol; Heart rate; Mean arterial pressure; Laryngoscopy

1. Introduction

Airway management and Patient safety are themost important aspects of patient management in general anaesthesia. Endotrachealintubation is considered as the gold standard and safest method for protecting theairway and delivering anaesthetic gases[1,2].

The unavoidable effects of laryngoscopy and tracheal intubation induced stress response includes dysrhythmia, hypertension, tachycardia myocardial ischemia, infarction, laryngospasm, and bronchospasm. Till now, no ideal induction agent has been found in terms of providing a stable haemodynamics during laryngoscopy and intubation. Also there are veryfew published studies which have compared thephysiological effect of various induction agents during laryngoscopyand intubation.

Propofol is one the commonly used short acting iv inducing agent for induction of general anaesthesia. Recommended dose of propofol for induction is 1-2.5 mg/kg. Propofol can lead to bradycardia and hypotension by increasing the production and release of nitric oxide and also causes pain at injection site[3-5].

Etomidate is a short acting hypnotic agent used for induction and maintenance of anaesthesia[6,17].It is cardio-stable with no release of histamine. Dose is 0.3mg/kg. Induction with Etomidate would lead to astable hemodynamic condition for performing laryngoscopy and endotracheal intubation [8.9,11].Nausea and vomiting are side effects. Iv injection cause a burning sensation[7]. Suppression of steroids production by reversible inhibition of 11 beta-hydroxylase enzyme is a rare but important adverse effect[9.10].

The Primary objective of this study was to compare the efficacy of 3 different approaches of anaesthesia induction (inj. Propofol, inj. Etomidate and inj. Propofol plus inj. Etomidate) in maintaining hemodynamic stability during induction and following endotracheal intubation in elective surgeries.

2. Material and Methods

This randomized double blind clinical trial was conducted at Department of Anaesthesiology, GOVT.General Hospital, Kakinada. Study period was from December 2018 to September 2019.

After approval from institutional ethical committee, 90 patients aged between 16 to 65 years of either sex and ASA physical status I and II scheduled for elective surgeries under general anaesthesia were taken for study. Written informed consent was taken. The patients were randomly

divided into three groups. Randomization was done by computer generated random number tables.

- Group P induction with inj. Propofol (2.5 mg/kg) iv.
- Group E induction with inj. Etomidate (0.3 mg/kg) iv.
- Group PE induction with inj. Propofol (1.5 mg/kg) plus inj.Etomidate (0.2 mg/kg) iv.

Exclusion Criteria

- ASA physical status iii and iv.
- Emergency surgery.
- History of hypersensitivity to propofol /etomidate.
- Mouth opening <2.5 cm.
- Patients with cardiovascular, respiratory diseases.
- Mallampatigrade 3 and 4

Complete clinical history was taken, general and systemic examinations were done in detail. Routine laboratory investigations such as complete hemogram, bleeding time, clotting time, blood sugar, blood urea, serum creatinine and urine analysis, electrocardiography (ECG), and chest X-ray were carried out in all patients.

Patient kept Nil per orally for 8 hours prior to surgery.On arrival at Operation Theatre standard anaesthesia monitors including electrocardiogram (ECG), non-invasive blood pressure (NIBP) and pulse oximetry were attached and hemodynamic parameters were recorded.All study drugs were prepared by an anaesthesiologist who was unaware of the details of the study.Patients were given the study drugs during induction.Heart rate, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure and oxygen saturation were continuously monitored and recorded before induction, after induction and at 1 minute, 2 minute, 3 minute, 5 minute after intubation.Inj. Vecuronium (0.1 mg/kg) was given, laryngoscopy and endotracheal intubation was done. Duration of laryngoscopy was kept less than 15 seconds. Trachea was intubated with adequate size endotracheal tube and placement was confirmed by capnography and bilateral auscultation of chest. Anaesthesia was maintained by sevoflurane 1-1.5% and equal mixtures of oxygen-nitrous oxide (4 L/ min) along with intermittent bolus of vecuronium as required throughout the surgery.At the end of the surgery residual neuromuscular block was antagonized with inj. Neostigmine (0.05 mg/kg) IV and inj. Glycopyrolate (0.01 mg/kg) IV and extubation was performed.

3. Statistical Analysis

The obtained data were analysed using SPSS 16.Descriptive data was compared and presented as mean ± SD for continuous variables and as percentage for nominal variable. The various categorical variables studied during observation period were compared using chi-square Test. The various hemodynamic variable parameters studied during observation period were compared using ANOVA test and inter group comparison of hemodynamic variables. The critical value of 'p'indicating the probability of significant difference was taken as <0.05 for comparison.

4. Results

There was no statistically significant difference was observed between the groups regarding Patient characteristic and ASA score.

Baseline and pre-induction HR,SBP,DBP and MAP were comparable among all three groups with no statistical significant differences (p>0.05). Inter group comparison showed that there are significant differences (p<0.05) in heart rate among all three groups at time interval (after induction and 1, 2, 3 min after intubation). At 5min after intubation there are significant differences among groups except between group E and group PE

SpO2 was 100% throughout the study period in all groups

SBP, DBP and MAP of three groups after induction and at 1, 2, 3, 5 minute after intubation were different both clinically and statistically, with p value <0.05.Inter group comparison of SBP, DBP and MAP (mean ± SD) revealed significant differences among various groups at different points of time except that among group E and group PE. Regarding SBP,DBP and MAP between groups E and PE, there was significant difference only at 1 min after intubation.

Table 1: Demographic data

	Group P	Group E	Group PE	*p*-value
Age (Y)	33.68 ± 6.26	34.26 ± 6.57	37.30 ± 9.39	0.149
BMI (kg/m)	23.72 ± 2.67	22.38 ± 2.62	23.46 ± 2.89	0.137
Gender (M/F)	12/18	13/17	16/14	0.268
Height (feet and inches)	5.36 ± 0.51	5.42 ± 0.46	5.43 ± 0.49	0.835

BMI: Body Mass Index; M/F: Male/Female; ASA: American Society of Anesthesiologist; Data presented as Mean ± SD or frequencies

Table 2 (a): Mean HR (Heart Rate) in (beats per minute)

Time Interval	Group P	Group E	Group PE	f-value	*p*- value
Baseline HR	76.42 ± 6.482	77.36 ± 6.387	78.24 ± 5.678	0.648	0.526
HR pre induction	88.74 ± 6.134	89.04 ± 6.564	89.41 ± 5.894	0.288	0.916
HR after induction	70.56 ± 5.343	89.36 ± 7.326	81.48 ± 6.916	101.758	P<0.001
HR 1min after intubation	78.64 ± 4.746	99.48 ± 6.135	94.85 ± 6.764	126.623	P<0.001
HR 2mins after intubation	81.24 ± 4.836	97.47 ± 6.116	90.86 ± 6.936	107.742	P<0.001
HR 3mins after intubation	84.36 ± 5.161	95.56 ± 5.794	91.28 ± 5.793	48.358	P<0.001
HR 5mins after intubation	85.65 ± 4.446	91.67 ± 6.101	88.49 ± 5.760	21.547	P<0.001

Table 2(b): Group comparisons mean HR.

Time Interval	*Group Pvs. E*	*Group Pvs. PE*	*Group Evs. PE*
Baseline HR	0.329	0.649	0.618
HR pre induction	0.458	0.524	0.936
HR after induction	P<0.001	P<0.001	0.001
HR 1min after intubation	P<0.001	P<0.001	P<0.001
HR 2mins after intubation	P<0.001	P<0.001	0.002
HR3mins after intubation	P<0.001	P<0.001	0.017
HR 5minsafter intubation	P<0.001	0.009	0.205

Table 3(a): SBP (systolic blood pressure) in (mmHg).

Time Interval	Group I	Group II	Group III	f-value	*p*-value
Baseline SBP	128.97 ± 6.257	128.74 ± 5.648	128.86 ± 7.316	0.465	0.910
SBP pre induction	126.85 ± 6.154	122.96 ± 6.037	124.54 ± 7.231	0.825	0.710
SBP after induction	101.74 ± 8.516	116.47 ± 5.924	117.64 ± 6.218	47.257	P<0.001
SBP 1min after intubation	112.57 ± 6.143	132.56 ± 5.246	130.39 ± 5.104	186.685	P<0.001
SBP 2mins after intubation	116.15 ± 6.815	128.83 ± 4.115	125.98 ± 4.101	78.267	P<0.001
SBP 3mins after intubation	120.98 ± 4.697	126.15 ± 4.351	124.91 ± 3.969	32.289	P<0.001
SBP 5mins after intubation	125.96 ± 3.381	121.76 ± 5.326	122.86 ± 4.556	20.758	P<0.001

Table 3(b): Group comparison SBP

Time Interval	Group I *vs.* II	Group I *vs.* III	Group II *vs.* III
Baseline SBP	0.238	0.196	0.978
SBPpreinduction	0.278	0.824	0.469
SBPafter induction	P<0.001	P<0.001	0.750
SBP 1min after intubation	P<0.001	P<0.001	0.058
SBP 2mins after intubation	P<0.001	P<0.001	0.157
SBP 3mins after intubation	0.003	0.004	0.987
SBP 5mins after intubation	0.002	0.007	0.426

Table 4(a): DBP (Diastolic Blood Pressure) in (mmHg).

Time Interval	Group I	Group II	Group III	f-value	*p*-value
Baseline DBP	76.42 ± 5.914	75.16 ± 4.923	74.89 ± 5.242	0.692	0.503
DBP pre induction	72.82 ± 6.216	72.39 ± 4.125	70.78 ± 5.142	1.268	0.287
DBP after induction	60.65 ± 3.213	67.94 ± 3.102	67.84 ± 2.024	25.369	P<0.001
DBP 1min after intubation	64.86 ± 2.846	77.46 ± 3.152	72.84 ± 2.241	78.536	P<0.001
DBP 2mins after intubation	68.14 ± 2.768	72.98 ± 3.946	71.88 ± 1.938	49.667	P<0.001
DBP 3mins after intubation	69.21 ± 1.026	71.98 ± 2.136	70.96 ± 1.684	37.786	P<0.001
DBP 5mins after intubation	73.38 ± 1.124	72.58 ± 2.187	69.89 ± 1.116	15.427	P<0.001

Table 4(b): Group comparison DBP (mmHg)

Time Interval	*Group I vs. II*	*Group I vs. III*	*Group II vs. III*
Baseline DBP	0.514	0.628	0.726
DBPpreinduction	0.486	0.414	0.912
DBPafter induction	P<0.001	P<0.001	0.687
DBP 1min after intubation	P<0.001	P<0.001	0.006
DBP 2mins after intubation	P<0.001	P<0.001	0.620
DBP 3mins after intubation	P<0.001	0.007	0.428
DBP 5mins after intubation	0.368	0.029	0.276

Table 5(a): Mean (Mean arterial BP) MAP (mmHg).

Time Interval	*Group I*	*Group II*	*Group III*	*f-value*	*p-value*
Baseline Mean BP	92.68 ± 5.496	91.97 ± 4.863	90.91 ± 5.889	0.807	0.450
Mean BP pre induction	88.79 ± 5.265	87.89 ± 5.234	88.68 ± 5.976	0.239	0.788
Mean BP after induction	72.69 ± 3.842	82.49 ± 3.184	84.28 ± 3.501	47.150	P<0.001
Mean BP 1min after intubation	81.27 ± 2.454	93.60 ± 3.674	90.68 ± 3.345	156.495	P<0.001
Mean BP 2mins after intubation	82.68 ± 2.418	90.60 ± 2.349	88.96 ± 2.467	90.130	P<0.001
Mean BP 3mins after intubation	84.76 ± 1.987	90.07 ± 1.865	88.75 ± 2.566	57.246	P<0.001
Mean BP 5mins after intubation	89.86 ± 1.874	87.36 ± 1.811	86.10 ± 2.123	25.210	P<0.001

Table 5(b): Group comparison mean (mean arterial BP).

Time Interval	*Group I vs. II*	*Group I vs. III*	*Group II vs. III*
Baseline Mean BP	0.289	0.147	0.746
MeanBPpre induction	0.467	0.963	0.449
Mean BP after induction	P<0.001	P<0.001	0.772
Mean BP 1min after intubation	P<0.001	P<0.001	0.002
Mean BP 2mins after intubation	P<0.001	P<0.001	0.289
Mean BP 3mins	P<0.001	P<0.001	0.496
Mean BP 5mins after intubation	0.008	0.004	0.624

5. Discussion

In our study, combinations of various anaesthetic agents have been used which results in reduction in anaesthetic medication, side effects.

Hosseinzadeh et al. [12]comparing hemodynamic changes during placement of laryngeal mask airway (LMA) using propofol, etomidate and etomidate-propofol combination. In their study, group one was given inj. propofol 2.5 mg/kg, group two received inj etomidate 0.3 mg/kg and group three 1 mg/kg propofol+0.2 mg/kg etomidate. LMA placement was done after loss of eyelash reflex and no response to verbal command. The main finding of the study was that more stable hemodynamics was provided by combination of propofol and etomidate compared to propofol and etomidate and alone similar to our study.

Yagan Ö et al. [13] conducted a study in which patients were randomly divided into three groups as group P (n=30, propofol 2.5 mg/kg), group E (n=30, etomidate 0.3 mg/kg) and group PE (n=30, propofol 1.25 mg/kg+etomidate 0.15 mg/kg). Measurement of the heart rate (HR) and mean arterial pressure values were defined as baseline, after the induction, before the intubation, immediately after the intubation and 1, 2, 3, 4, 5 and 10 minutes after the intubation. They found that etomidate-propofol combination may be a valuable alternative when extremes of hypotensive and hypertensive responses due to propofol and etomidate are best to be avoided.In our study we administered propofol 1.5mg/kg + etomidate 0.2mg/kg together instead of propofol 1.25mg/kg + etomidate 0.15mg/kg respectively.

Harris et al. [14] compared the hemodynamic response to tracheal intubation in 303 patients in whom anaesthesia was induced with either thiopentone 4 mg/kg, etomidate 0.3 mg/kg or propofol 2.5 mg/kg with or without fentanyl 2 µg/kg.After propofol alone, there was a significant decrease in arterial blood pressure, which did not increase above control value after intubation. Significant increase in arterial pressure followed intubation in patients induced with thiopentone or etomidate alone. Increases in heart rate occurred with all agents after laryngoscopy and intubation. The use of fentanyl resulted in arterial Pressure lower than those after the induction agent alone and in an attenuation, but not abolition, of responses to laryngoscopy and intubation.

Möller et al.[15] which used propofol and etomidate in general anaesthesia induction accompanied by Bis monitoring, found in the propofol group and a significantly high level of hypertension incidence in the etomidate group. Compared with etomidate, the use of propofol was determined to have caused less hypertension and tachycardia after intubation.

Muriel et al. [16], a comparison was made of propofol(2 mg/kg), thiopental (5 mg/kg) and etomidate (0.3 mg/kg) inanaesthesiainduction.Astatistically significant increase wasdetermined in systolic and diastolic arterial pressure and HR in theetomidate and thiopental group after intubation and the highest rate ofcomplication was reported in etomidate group.

Limitations: Not using BIS to measure the depth of anaesthesia is a major limitation of our study. Another limitation is not measuring plasma cortisol and adrenocorticotropin hormone level. But it has been reported that adrenal suppression after single dose of etomidate is transient and clinically not important[18].

6. Conclusion

The combination of etomidate plus propofol has better hemodynamic stability than etomidate alone at 1 min after intubation, though etomidate was equally stable at other points of time. and, the combination proved to be significantly better in maintaining uniform haemodynamic stability without any extremes than either propofol or etomidate alone .

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