ORIGINAL RESEARCH PAPER

Anaesthesiology

A CLINICAL COMPARATIVE STUDY OF EFFECT OF PROPOFOL, ETOMIDATE AND COMBINATION OF PROPOFOL AND ETOMIDATE ON ATTENUATION OF HAEMODYNAMIC RESPONSE TO ENDOTRACHEAL INTUBATION

KEY WORDS: Propofol, Etomidate, hemodynamic response, mean arterial pressure, heart rate, laryngoscopy

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ABSTRACT

Aim and objective: The aim of this study was to compare the effect of Propofol and Etomidate separately and in a combination with reduced doses of the two drugs in attenuating the hemodynamic response following laryngoscopy and intubation.

Methods: After taking ethical committee clearance, A prospective randomized double blinded study involving 90 patients aged 18-60 years of either sex and ASA physical status I or II scheduled for elective surgery under general anesthesia were randomly placed into three groups. Group A induced with Inj.Propofol (2.5 mg/kg), Group B with Inj. Etomidate (0.3 mg/kg) and Group C with Inj.Propofol (1.5 mg/kg) plus Inj.Etomidate (0.15 mg/kg). Heart rate (HR), mean arterial pressure (MAP) were recorded at baseline, after induction, before intubation, immediately after intubation and then at 1min, 3 min, 5 min and 10 min. ANNOVA and chi-square test were used for statistical analysis.

Result: Heart rate in all study groups decreases after induction and it was more in group A compared to group C ($p<0.045$) and after intubation HR increases in all three groups but this increase was greater in group B than A and C ($p<0.000$, $p<0.001$). MAP among all three groups decreases after induction and it was more in group A than group B and C ($p<0.000$, $p<0.000$). MAP was increased after intubation in all groups, more in group B than A and C (p 0.000, p 0.010).

Conclusion: The combination of propofol plus Etomidate has better hemodynamic stability than propofol and etomidate alone.

INTRODUCTION

Laryngoscopy and endotracheal intubation is now one of the frequently performed procedures in the practice of anaesthesia.

The hemodynamic responses to laryngotracheal stimulation are well known since 1940 (Reid & Brace)[1]. Change in the nervous system activity in the cervical sympathetic efferent fibres by the mechanical stimulation of the respiratory tract is shown in the study by Tomori & Widdicombe (1969)[2]. King et al (1951) have explained the circulatory responses to laryngeal and tracheal stimulation following laryngoscopy and tracheal intubation as reflex sympathoadrenal stimulation[3].

The process of laryngoscopy and endotracheal intubation is a marked noxious stimuli, and constitute a period of extreme haemodynamic stress and is associated with intense sympathetic activity marked by tachycardia and hypertension[1]. Although the elevation in blood pressure and heart rate due to laryngoscopy and intubation are brief, they may have detrimental effects in high risk patients such as patient with myocardial infarction, cardiac failure, intracranial haemorrhage and increase in intracranial pressure.

The need for an anaesthetic technique where the cardiovascular response to laryngoscopy and intubation can be attenuated has drawn the attention of many anaesthetists all over the world. Various pharmacological and non-pharmacological methods have been used to attenuate the haemodynamic response to laryngoscopy & endotracheal intubation[4].

The other factors which contribute to increased sympathoadrenal response from upper airway manipulation are mismatched endotracheal tube, large endotracheal cuff volume, use of stylletes and bougies and airway suctioning[5].

Many strategies that have been advocated and aimed at different levels of the reflex are:-

1) Blockade of the peripheral sensory receptors and afferent input – by topical application and infiltration of local anaesthetic to superior laryngeal nerve[6] and blocking Glossopharyngeal nerve.
2) Blockade of central mechanism of integration and sensory input – by the use of fentanyl, morphine, etc.
3) Blockade of efferent pathway and effecter sites – by the use of i.v. lignocaine, β blockers, calcium channel blockers, hydralazine, etc.

The non-pharmacological methods like smooth & gentle intubation with a shorter duration of laryngoscopy and insertion of LMA instead of endotracheal tube[4] have been used to attenuate the cardiovascular response to laryngoscopy and endotracheal intubation.

Pharmacological methods that have been adopted to attenuate the cardiovascular response to laryngoscopy and intubation are use of inhalational anaesthetics[7], topical and intravenous lidocaine[8,9,10] narcotics[11,12,13] ,β-blockers[14,15,16] , calcium channel blockers[17,18,19] , and vasodilators[20,21].

Different induction agents have been used over last few decades and their influence on the reflex sympathetic activity following laryngoscopy and endotracheal intubation has been widely studied. An ideal induction agent for general anaesthesia should have hemodynamic stability, minimal respiratory side effects and rapid clearance. Presently etomidate and propofol are popular rapid acting inducing agent.

Propofol is the most commonly used drug for induction of general anaesthesia. It is an alkylphenol currently formulated in lipid emulsion. It provides a rapid onset and offset with context-sensitive times of approximately 10 minutes when infused for less than 3 hours and of less than 40 minutes when infused for upto 8 hours. Its mechanism of action is likely the enhancement of gamma-aminobutyric acid (GABA) induced chloride currents. Propofol causes a dose dependent decrease in arterial blood pressure through decrease in

cardiac output and systemic vascular resistance and produces moderately respiratory depression. Other side effects of propofol are pain on injection, apnea and rarely thrombophlebitis of the vein into which propofol is injected. Propofol infusion syndrome is a rare but lethal syndrome associated with infusion of propofol at 4mg/kg/hour or more for 48 hours or longer. A unique action of propofol is its antiemetic effect, even at a concentration less than those producing sedation[22].

Etomidate is a carboxylic imidazole containing compound characterized by hemodynamic stability, minimal respiratory depression and cerebral protective effects[22]. Its lack of effect on sympathetic nervous system, baroreceptor reflex regulatory system[20] and its effect of increased coronary perfusion even on patients with moderate cardiac dysfunction make it an induction agent of choice. Propofol decreases blood pressure, cardiac output and systemic vascular resistance due to inhibition of sympathetic vasoconstriction and impairment of barorceptor reflex regulatory system. These effects may be exaggerated in hypovolemic and elderly patients with compromised left ventricular function due to coronary artery diseases. It produces dose dependent depression of ventilation. However the adverse effects such as pain on injection, thrombophlebitis and myoclonus for both the agents have been corrected by premedicating with the fentanyl. This study is an attempt to compare hemodynamic effect of both the drugs separately and in a combination of reduced dose so that we can choose a safe induction agent.

MATERIALS AND METHOD

The study was undertaken at Silchar Medical College and Hospital, Silchar, Assam, from June 1st, 2018 to May 31st, 2019 after obtaining Institutional Ethical Committee clearance and written informed consent from the patients. A prospective randomized double blinded study involving 90 patients of both sexes requiring endotracheal intubation and general anaesthesia for various elective surgical procedures belonging to ASA grade I and II were included in the study. The study population was divided into 3 groups with 30 patients in each group.

Inclusion criteria:

1. Patients aged between 18-60 years,
2. Patients of either sex,
3. Patients with ASA grade I and II,
4. Patients scheduled for elective surgical procedure under general anaesthesia,
5. Mallampati I and II

Exclusion criteria:

1. Patient refusal
2. ASA physical status III and IV
3. Emergency surgery
4. Patient with history of allergy to propofol/etomidate
5. Mouth opening < 2.5cm
6. Patients with cardiovascular diseases like ischemic heart disease or hypertension
7. Bronchial asthma
8. Mallampati grade III and IV
9. Existance of any pathology in larynx or pharynx
10. Patients with GERD
11. Patient with anticipated difficult airway,
12. Pregnant and lactating women

On the day prior to the scheduled date of proposed surgery, a thorough clinical examination of all the patient was performed, assessing the general physical Status & systemic examination. ASA grading was assessed. Airway assessment like mouth opening, mallampati grading, dentition, neck extension was done.

All patients were explained about the anaesthesia technique & written informed consent was taken. Patients were kept nil per oral (NPO) for 8 hours prior to surgery. All the patients were given Tablet Alprazolam 0.25mg orally at bed time on the previous night of the surgery.

All routine pre op investigations were checked.

90 patients, aged between 18 to 60 years, belonging to ASA grade I & II were randomly divided into 3 groups and each group consisted 30 patients.

1) Group A received Inj. propofol 2.5 mg/kg body weight i.v.
2) Group B received Inj. etomidate 0.3mg/kg body weight i.v.
3) Group C received inj. propofol 1.5mg/kg and inj. etomidate 0.15 mg/kg given in two separate syringes, first propofol and after 30 seconds etomidate

All standard monitors were connected for continuous monitoring. The baseline pulse rate, MAP, SpO2 %, respiration rate was recorded (T1). Continuous monitoring of the vital parameters was done thereafter. An IV line was secured with an appropriate sized cannula and i.v. fluids were started with 500ml of Ringer lactate in all patients.

Patients were pre-medicated with Inj. fentanyl 1mcg/kg i.v stat. and Inj. Glycopyrrolate 0.2 mg i.v stat After pre-oxygenation with 100% oxygen for 3 minutes with facemask of appropriate size using Mapleson D circuit. Then the study drugs were given, followed by injecting muscle relaxant – inj. Vecuronium at a dose of 0.1 mg/kg. Patient was then ventilated with bag and mask for 3 minutes till proper relaxation was achieved. Laryngoscopy was done with rigid laryngoscope and standard Macintosh blade of right size. Patients were intubated with appropriate sized cuffed endotracheal tube and after confirming bilateral equal air entry by chest auscultation, endotracheal tube was secured and the EtCO2 probe was attached for monitoring end-tidal carbon dioxide gas. Oral intubation was done in all patients and intubation was accomplished within 15 to 20seconds. Anaesthesia was maintained with mixture of N2O and O2 gas at 66% and 33% respectively along with Sevoflurane, and muscle relaxation was maintained with intermittent dosage of Inj. vecuronium. Intra-venous fluid was given as Ringer's lactate and Normal Saline 0.9% at the rate of 4-6ml/kg/hr. inj. ondensatron and inj. ranitidine were given half an hour before completion of surgery.

No surgical or any other stimulus was allowed to give to the patient following intubation during the study period.

All patients were monitored for systolic and diastolic blood pressure, mean arterial pressure, pulse rate, respiration rate, SpO2, EtCo2 at the following interval:

T1- baseline
T2- after induction
T3- before intubation
T4- immediately after intubation
T5- 1 minute after intubation
T6- 3 minutes after intubation
T7- 5 minutes after intubation
T8- 10 minutes after intubation

At the end of surgery, when patients had respiratory efforts, residual neuromuscular blockade was reversed with Inj. Neostigmine 0.05 mg/kg i.v. & Inj. Glycopyrrolate 0.01 mg/kg i.v. recovery assessement & extubation were done after thorough laryngeal suction.

Post Operative Nausea And Vomiting (PONV):

It was noted as either Yes or No, and if present, then it was treated with Inj. Ondansetron 0.1 mg/kg i.v. stat.

Statistical Method Employed

All data are presented as Mean ± SD (Standard Deviation). All Quantitative data are assessed using ANNOVA test to analyze changes over a period of time. Qualitative data are assessed using Chi- square test.

- p>0.05 – Statistically Not Significant (NS)
- p<0.05 – Statistically Significant (S)
- p<0.001 – Statistically highly Significant (HS)
- p<0.0001 - Statistically Extremely Significant (ES)

Statistical Software Employed

The statistical software **SPSS** was used for the analysis of data and **Microsoft Word** and **Microsoft Excel** have been used to generate graphs, tables etc.

RESULT

The present study consists of 90 adult patients who are divided into 3 groups of 30 each; where Group A has received Inj. Propofol 2.5mg/kg, Group B received Inj.Etomidate 0.3mg/kg and Group C received both inj Propofol 1.5mg/kg and Etomidate 0.15mg/kg in separate syringes.

There was no statistically significance difference among the groups regarding demographic profile and ASA score.

Table 1: patient's characteristics

	Group A	Group B	Group C	p-value
Age (years)	36.80±11.719	37.70±11.426	37.33±10.280	0.952
Gender (M/F)	8/22	13/17	11/19	0.398
Weight (kg)	50.90±6.885	51.40±9.579	51.80±7.761	0.912
ASA(I/II)	25/5	25/5	24/6	0.927

Hemodynamic variables

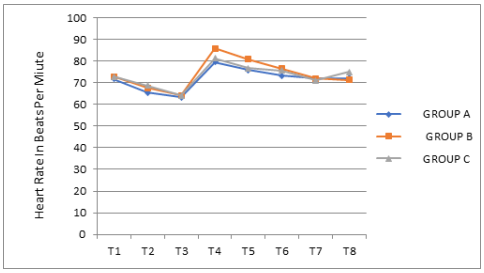
Table 2: Comparison of mean heart rate between three groups

Study Time	Heart Rate (beats/min)						P value
	Group A		Group B		Group C		
	Mean	SD	Mean	SD	Mean	SD	
T1	71.6	6.82	72.73	7.03	72.87	5.44	0.708
T2	65.4	6.76	67.67	6.94	68.57	5.11	0.142
T3	63.2	7.01	64.2	6.74	64.1	4.70	0.792
T4	79.47	7.05	85.8	5.71	81.2	4.70	0.000
T5	75.73	6.90	80.87	5.78	76.8	5.08	0.003
T6	73.13	6.34	76.47	6.09	75.63	6.19	0.102
T7	71.83	6.27	71.97	6.08	71.03	6.01	0.816
T8	72.1	6.86	71.33	6.20	74.9	6.96	0.100

The baseline heart rate was comparable in all three groups. At T2 and T3 i.e. after induction and before intubation respectively, the heart rate were decreased from baseline in all the three groups. At T4, i.e. immediately after intubation, heart rate in all the three groups were increased. This increase was maximum in the Etomidate group (GROUP B). Subsequently, heart rate in all the groups started to decrease.

Table 3: Inter Group comparison of mean Heart rate

TIME INTERVAL	GROUP A vs B	GROUP A vs C	GROUP B vs C
T1	0.529	0.430	0.935
T2	0.205	0.045	0.570
T3	0.576	0.562	0.947
T4	0.000	0.267	0.001
T5	0.003	0.498	0.005
T6	0.042	0.128	0.601
T7	0.934	0.616	0.553
T8	0.652	0.122	0.041



Graph 1: Line diagram showing changes of mean heart rate of the three groups at different time intervals

CHANGES IN MEAN ARTERIAL PRESSURE

Table 3: Comparison of mean arterial pressure (MAP) between the three groups

Time Interval	Mean Arterial Pressure (mmHg)						p value
	Group A		Group B		Group C		
	Mean	SD	Mean	SD	Mean	SD	
T1	78.90	7.024	77.73	5.789	80.60	5.568	0.199
T2	64	6.628	75.30	5.706	75.10	6.019	0.000
T3	57.90	7.063	72.53	7.710	72.10	6.445	0.000
T4	83.20	8.277	98	7.278	93.17	6.833	0.000
T5	81.50	6.704	92.90	6.764	86.13	6.469	0.000
T6	77.57	7.338	83.70	6.508	84.63	5.980	0.000
T7	76.70	7.813	74	5.907	79.73	6.170	0.006
T8	74.90	8.092	71.93	6.040	76.63	5.933	0.029

The baseline mean arterial pressure in all the groups were comparable. The MAP values in all 3 groups at T2 and T3 after induction were statistically significantly lower compared to the basal values. In comparison between the MAP values of the groups at T2 and T3, in group A were determined to be statistically significantly lower compared to group B, and group C .

At the T4, MAP values of all groups were significantly increased compared to the basal values. In the comparison between the groups at T4, the MAP values of the group E were statistically significantly higher than those of group B and group C.

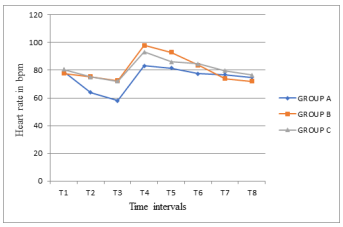
In group A, MAP values were found to be significantly lower than those of group B at T5, T6 and of group C at T5 and T6

In comparison between group B and group C, MAP of group B was statistically significantly higher than group C at T5 and statistically significantly lower than group C at T7 and T8.

Table 4: Inter group comparison of MAP

TIME INTERVAL	GROUP A vs B	GROUP A vs C	GROUP B vs C
T1	0.485	0.303	0.055
T2	0.000	0.000	0.895
T3	0.000	0.000	0.784
T4	0.000	0.000	0.010
T5	0.000	0.009	0.000
T6	0.001	0.000	0.565
T7	0.137	0.101	0.001
T8	0.113	0.348	0.004

Graph 2: line diagram showing changes of MAP of three groups at different time intervals



DISCUSSION

Although the effects of sympathetic stimulation such as hypertension, tachycardia etc. last for short duration, but these can produce deleterious effects such as myocardial ischemia or increased intracranial tension in certain patients with risk factors. These effects are usually well tolerated in normal healthy persons without any risk factors.

The present study was aimed at comparing the effect of propofol, etomidate and combination of propofol and etomidate on attenuation of haemodynamic response to endotracheal intubation.

DEMOGRAPHIC CHARACTERISTICS

The mean age, weight, and sex of the groups were comparable. There was no significant difference amongst the groups with regard to demographic variables (P value>0.05).

HEMODYNAMIC VARIABLES

HEART RATE

The mean baseline heart rate in group A was 71.6 ± 6.82 bpm, in group B it was 72.73 ± 7.03 bpm and in group C it was 72.87±5.44 which was not significant on comparison (p value = 0.0.708). Immediately after drug administration, in group A the heart rate decreased to 65.4±6.76 bpm, in group B, heart rate decreased to 67.67±6.94 bpm and in group C heart rate decreased to 68.57±5.11. On intergroup comparison this decrease in heart rate was significantly low in group A compared to group C (p value 0.045). Heart rate decreases further till just before intubation and it becomes 63.2±7.01 in group A, 64.2±6.74 in group B and 64.1±4.70 in group C. On Intergroup comparison there was no significant difference at this point. Immediately after intubation, the heart rate in all the three groups were increased from their respective baseline values. Mean heart rate in group A after intubation was 79.47±7.05, in group B it was 85.8±5.71, in group C it was 81.2±4.70.this increase was statistically significantly higher in group b compared to group A (0.000) and group C (0.001). There were also statistically significant difference in heart rate at T5 and T6 between group A and group B and at T5 and T8 between group B and group C.

MEAN ARTERIAL PRESSURE (MAP)

The mean baseline MAP in group A was 78.90 ± 7.024 mmhg, in group B it was 77.73 ± 5.789 mmhg and in group C it was 80.60±5.568mmhg which was not significant on comparison (p value = 0.199). Immediately after drug administration, in group A the MAP decreases to 64±6.628 mmhg, in group B, MAP decreased to 75.30±5.706 mmhg and in group C MAP decreased to75.10±6.019. On intergroup comparison this decrease in MAP was significantly low in group A compared to group B (p value 0.000) and group C (p value 0.000). MAP decreases further till just before intubation and it becomes 57.90±7.063 in group A, 72.53±7.710 in group B and 72.10±6.445 in group C. This decrease was again significantly low in group A compared to group B (P value 0.000) and group C (p value 0.000). Immediately after intubation, the MAP in all the three groups was increased from their respective baseline values. MAP in group A after intubation was 83.20±8.277, in group B it was 98±7.278, in group C it was 93.17±6.833.This increase was statistically significantly higher in group B compared to group A (0.000) and group c (0.010). The increase in MAP in group C was also statistically significantly higher compared to group A (p value 0.000). In group A, MAP values were found to be significantly lower than those of group B at T5, T6 and of group C at T5 and T6

In comparison between group B and group C, MAP of group B was statistically significantly higher than group C at T5 and statistically significantly lower than group C at T7 and T8.

Meena K. et al[23], in 2016 conducted a study to compare the efficacy of 3 different anesthesia induction approach (Inj. Propofol, Inj. Etomidate and Inj. propofol plus Inj Etomidate) in maintaining hemodynamic stability during induction and following endotracheal intubation in elective surgery. 90 patients aged 15 to 60 years. 3 groups were made randomly Group I induced with Inj. Propofol (2.5 mg/kg) intravenous, Group II with Inj. Etomidate (0.3 mg/kg) intravenous and Group III with Inj. Propofol (1 mg/kg) plus Inj. Etomidate (0.2 mg/kg) intravenous. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP) and oxygen saturation (SPO2) were noted at different time interval. They concluded that 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. The combination proved to be significantly better than either propofol or etomidate alone. Our results were comparable to this study in attenuation of haemodynamic response to endotracheal intubation by our study drugs.

Yagan O. et al[24], in 2015 conducted a study to compare the haemodynamic responses to a etomidate-propofol combination used for anaesthesia induction and to compare the haemodynamic responses with the separate use of each drug. The patients were randomly divided into three groups as group P (n = 30, propofol 2.5 mg kg-1), group E (n = 30, etomidate 0.3 mg kg-1) and group PE (n = 30, propofol 1.25 mg kg-1 + etomidate 0.15 mg kg-1). They concluded that Etomidate-propofol combination may be a valuable alternative when extremes of hypotensive and hypertensive responses due to propofol and etomidate are to be avoided. The results of our study were comparable to that of this study.

S. Fatma et al[25], in 2011 conducted a study to compare etomidate-lipuro and propofol and 50%, (1:1) admixture of these agents at induction with special reference to injection pain, hemodynamic changes, and myoclonus. They concluded that 1:1 admixture of etomidate-lipuro and propofol is a valuable agent for induction. The hemodynamic findings of our study was comparable with this study

SIDE EFFECTS

In our study postoperative nausea and vomiting was complained by 11 patients in the Group who received Etomidate, by 9 patients who received propofol and by 8 patients who received the combination of the two drugs. No other significant side effects were seen.

CONCLUSION

The combination of Etomidate plus propofol has better hemodynamic stability and this combination may be a valuable alternative when extremes of hypotensive and hypertensive responses due to propofol and Etomidate are best to be avoided. Further studies are required to decide the optium dose of the drugs when used in combination.

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