Comparative Study of Effect of Etomidate Versus Propofol plus Ketamine on Haemodynamic Response to Laryngoscopy and Endotracheal Intubation

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ABSTRACT

BACKGROUND

Laryngoscopy and endotracheal intubation, a painful procedure, frequently used in airway management is commonly associated with undesired haemodynamic changes like hypertension, tachycardia and arrythmias. Thus, this study was designed to compare haemodynamic stability to laryngoscopy and intubation using single drug induction with etomidate and combined drug induction with propofol and ketamine.

METHODS

This was a double blind randomised controlled trial, a total of 90 patients of both sexes, aged between 18 - 60 years, who were scheduled for elective surgeries under general anaesthesia in regional institute of medical sciences (RIMS) operation theatre (OT) were divided into two groups. Group PK received propofol (1.5 mg / kg) + ketamine (0.5 mg / kg) and Group E received etomidate (0.3 mg / kg) as induction agents. The haemodynamic parameters (systolic blood pressure-SBP, diastolic blood pressure-DBP, mean arterial pressure-MAP, heart rate-HR) were recorded before induction, immediately after induction, 1, 3 and 5 mins after intubation. Side effects like myoclonus and post-operative nausea and vomiting were also noted.

RESULTS

SBP, DBP, MAP which were recorded, before induction considered as the baseline, and after induction, were comparable between the two groups. SBP, DBP and MAP compared at 1, 3 and 5 mins after intubation showed statistically significant difference between the two groups with propofol-ketamine group showing better haemodynamic stability. The HR between both the groups at various time intervals were comparable and not considered statistically significant. The side effect associated after induction was myoclonus in 14 patients in Group E i.e. 31 % and post-operative nausea vomiting was observed in 8 patients in Group E i.e. 18 %.

CONCLUSIONS

Thus, in view of haemodynamic stability during laryngoscopy, intubation and side effect profile; propofol and ketamine combination proves to be a better alternative compared to etomidate according to our study.

KEYWORDS

Propofol, Ketamine, Etomidate, Haemodynamic Stability

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BACKGROUND

The principal goal of anaesthesia is to maintain autonomic and cardiovascular stability in response to stress in surgical patients. Laryngoscopy and tracheal intubation are a painful procedure, commonly used for airway management during general anaesthesia is associated with undesirable haemodynamic changes like hypertension, tachycardia and arrythmias. Conversely general anaesthesia induction agents may decrease the arterial blood pressure via myocardial depression, vasodilation and attenuation of autonomic nervous system activity.[1] Propofol (2 - 6 di-isopropyl phenol) developed in Europe in 1970's is an ultra-short acting sedative hypnotic agent widely used for induction during general anaesthesia. It causes dose dependent hypertension and respiratory depression.[2] Ketamine, an intravenous anaesthetic agent developed in 1960's from its precursor phencyclidine acts by causing dissociative anaesthesia. It is used for both induction and maintenance of general anaesthesia. Unlike many anaesthetics it stimulates the cardiovascular system causing increase in heart rate, blood pressure and cardiac output.[3] Propofol and ketamine combination is believed to provide both sedation and analgesia, with fewer cardiovascular effects due to opposing effect of each drug[4]. Etomidate is used as an induction agent with minimal cardiovascular effects. It also possesses unique desirable properties such as rapid onset and short duration of action, relative cardiovascular and respiratory stability as well as neuroprotective effects making it an attractive induction agent to facilitate endotracheal intubation. But the disadvantage associated with it is profound and persistent adrenocortical suppression by inhibiting mitochondrial 11-beta hydroxylase enzyme of adrenal steroid synthetic pathway and myoclonus movements in 30 - 40 % of the patients.[5] Theoretically, combined use of drugs may balance opposing haemodynamic effects. The latest research shows administration of several anaesthetic agents (co-induction) during induction of general anaesthesia has distinct advantages over monotherapy. This technique is applied to produce the desired outcome with fewer adverse effects compared to single drug use.

Objectives

The attenuation of haemodynamic response to laryngoscopy and endotracheal intubation is extremely important as it is an inevitable procedure during general anaesthesia. The paucity of information in literature comparing etomidate and propofol ketamine combination as induction agents in attenuating haemodynamic response motivated us to compare the effects of these induction agents on haemodynamic response to laryngoscopy and endotracheal intubation.

METHODS

After obtaining approval from institution ethics committee and informed consent from patients, a total of 90 patients of both sexes aged between 18 - 60 years, with American Society of Anaesthesiologist scheduled for elective surgery under general anaesthesia in regional institute of medical sciences Imphal were enrolled in the prospective double blinded randomised control trial. The study was conducted between September 2018 and August 2020.

The sample size was calculated using a study conducted by Shah S.B.[6] in a similar background using the formula:

$$N = \frac{[\mathrm{u} + v]^2\,[{s_1}^2 + {s_2}^2]}{[m_1 - m_2]^2}$$

u = 0.84 (power at 80 %)
v = 1.96 (significance level at 5 %)
s_1 = 11.705 (standard deviation of heart rate using etomidate)
$s_{2.}$ = 8.265 (standard deviation of heart rate using propofol)
m_1 = 72.23 (mean of heart rate using etomidate)
m_2 = 78.30 (mean of heart rate using propofol)

Calculated sample size in each group was 43, considering dropout of 5 % we recruited 45 patients in each group.

Patients with history of diabetes, asthma, hypertension, adrenal insufficiency, difficult airway, receiving steroid in the last six months, pregnancy, allergic to propofol, ketamine, etomidate, egg and soya, serious endocrine, psychiatric or neurological illness were excluded from the study. Participants meeting the inclusion criteria were randomly allocated into two groups (group PK and group E) by an anaesthetist who was unaware of the study groups.

All the patients included in the study received tab. alprazolam 0.25 mg the night before surgery. The patients were kept nil per oral for 6 hours before the surgery. In the pre-op holding area, intravenous access was secured, and the patients were pre-medicated with inj. glycopyrrolate 0.004 mg / kg and haemodynamic parameters were recorded considering the baseline value. On arrival to the operation theatre, monitoring of pulse rate, noninvasive blood pressure, oxygen saturation and electrocardiogram were started. Care was taken to maintain normothermia of the patient. After preoxygenation for 3 minutes with face mask, all patients received intravenous butorphanol (10 mcg / kg) and patients allotted in group PK received propofol (1.5 mg / kg) and ketamine (0.5 mg / kg) and group E received etomidate (0.3 mg / kg) as induction agents.

After confirming bag and mask ventilation, succinylcholine (1.5 mg / kg) was given intravenously to facilitate endotracheal intubation. One minute later, laryngoscopy was performed by an anaesthesiologist blinded to the study groups. Immediately after induction, 1 min, 3 mins and 5 mins after intubation, the haemodynamic parameters (SBP, DBP, MAP, HR) were measured. Moreover, anaesthesiologist who was unaware of the study groups recorded the occurrence of myoclonus after hypnotic drug administration and incidence of nausea and vomiting during recovery in both the study groups.

Statistical Analysis

Data was analysed using SPSS statistics version 21. It was then summarised using descriptive statistics like mean,

percentage and standard deviation. Chi-square test was used for comparison of categorical variables. An independent t-test was used to compare means between the study groups and a P-value of < 0.05 was considered as significant.

RESULTS

A total of 102 patients were assessed for eligibility out of whom 7 patients didn't meet the inclusion criteria and 5 patients declined to participate in the study. The remaining 90 patients were randomly allocated into two groups. All of these patients completed the study and their data was analysed (Figure 1). The demographic and clinical characteristics of the patients in both the groups are presented in Table 1, there was no statistically significant difference between both the groups. Analysing the results of our study the haemodynamic parameters (SBP, DBP, MAP, HR) which was recorded before induction considered the baseline value and also after induction were comparable between the study group and are statistically insignificant with a P-value of > 0.05. The systolic blood pressure measured at 1, 3 ,5 mins after intubation showed statistically significant difference between the study groups with group PK showing better haemodynamic stability. DBP measured at 1, 3 minutes after intubation showed significant difference between the study groups in which group PK is found superior at 1 minute and group E showing better haemodynamic stability at 3 mins. DBP at 5 mins were comparable between the groups. MAP at 1, 3, 5 minutes after intubation between the study groups showed significant difference, with group PK showing better haemodynamic stability. HR between the study groups at various time intervals were comparable and are statistically insignificant. Table 2 shows mean and 95 % CI of haemodynamic variables in both the groups at baseline, after induction and three-time intervals after intubation.

Background Characteristics		Propofol-Ketamine Group (N = 45) N (%)	Etomidate Group (N = 45) N (%)	P Value
	Age (Mean ± SD)	34.44 ± 10.96	32.47 ± 11.62	0.405
Gender	Male	29 (64)	29 (64)	0.589
	Female	16 (36)	16 (36)	
Weight	40 - 50	19 (42)	14 (31)	
	51 - 60	10 (22)	15 (33)	0.236
	61 - 70	16 (36)	16 (36)	

Table 1. Demographic and Clinical Characteristics of Patients in Both the Groups

	Variables	Propofol-Etamine	Etomidate	P-Value
Baseline	SBP	118.13 ± 8.97	119.47 ±10.68	0.523
	DBP	76.31 ± 8.34	76.42 ± 8.63	0.717
	MAP	87.62 ± 8.8	89.64 ± 10.61	0.072
	PR	82.33 ± 13.64	85.64 ± 12.51	0.234
1 min after intubation	SBP	138.56 ± 11.37	141.96 ± 17.80	0.009
	DBP	91.96 ± 8.84	93.18 ± 12.49	0.021
	MAP	105.20 ± 9.02	109.78 ± 15.60	0.003
	PR	95.84 ± 14.89	101.38 ±15.02	0.830
3 mins after intubation	SBP	118.49 ± 8.87	120.27 ± 14.41	0.034
	DBP	79.62 ± 9.48	74.80 ±13.18	0.045
	MAP	90.89 ± 8.91	90.02 ±13.06	0.055
	PR	90.96 ± 12.47	89.80 ± 12.70	0.665
5 mins after intubation	SBP	113.31 ± 10.47	114.27 ± 13.46	0.023
	DBP	71.09 ± 9.88	69.24 ± 12.45	0.100
	MAP	83.47 ± 10.20	85.09 ± 12.90	0.027
	PR	86.16 ± 12.70	87.30 ± 12.15	0.655

Table 2. Haemodynamic Variables in Both the Groups, Mean and 95 % CI

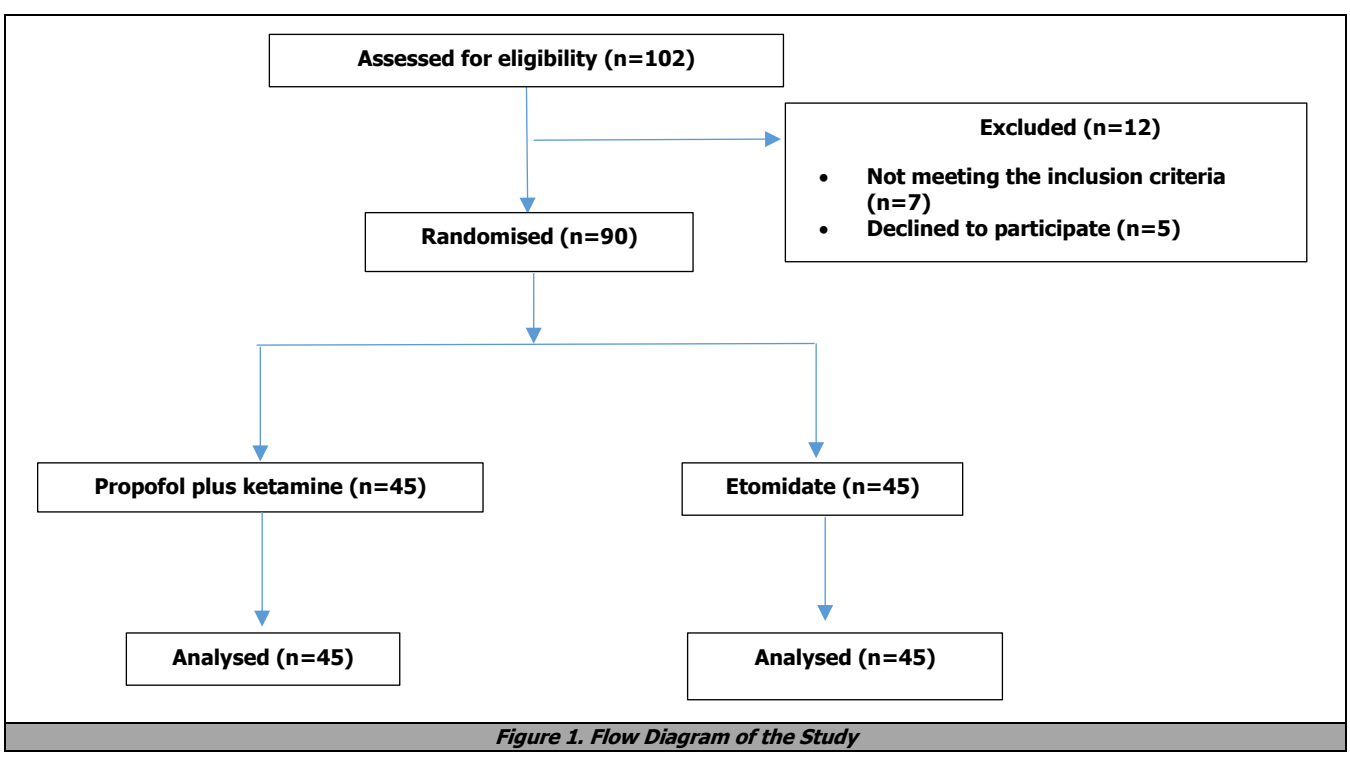

Figure 1. Flow Diagram of the Study

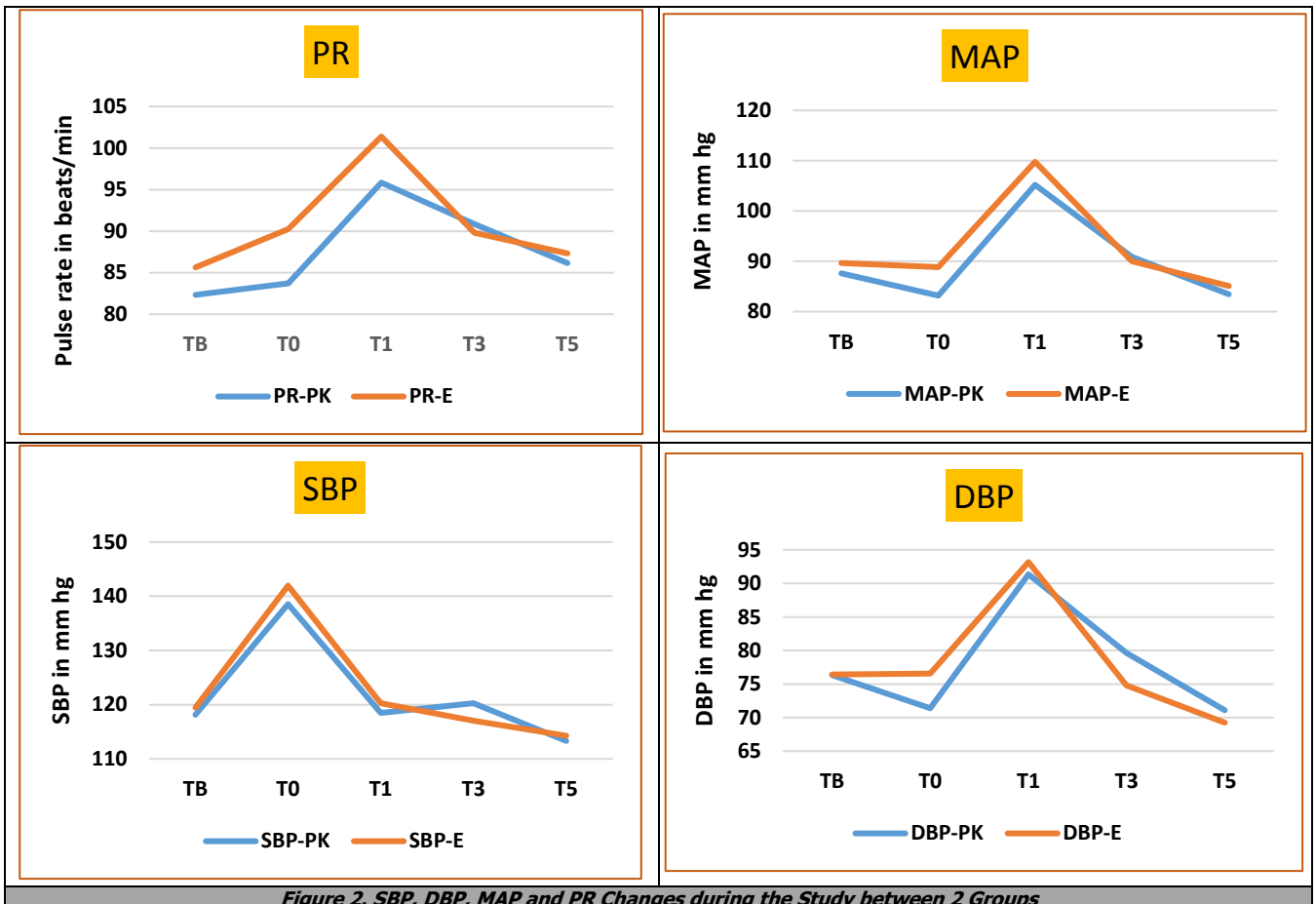

Figure 2. SBP, DBP, MAP and PR Changes during the Study between 2 Groups

Abbreviations: TB - Baseline, T0: After induction T1: 1 min after intubation T3: 3 mins after intubation T5: 5 mins after intubation. PK: Propofol plus ketamine E: Etomidate. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, PR: Pulse rate.

Figure 2 shows changes in SBP, DBP, MAP and HR during the different time intervals between two groups.

	Propofol + Ketamine (N = 45) N (%)	Etomidate (N = 45) N (%)
Myoclonus	0	14 (31 %)
Post-operative nausea and vomiting	0	8 (18 %)

Table 3. Prevalence of Side Effects in Both the Study Groups

From Table 3 we see that the side-effects such as myoclonus and post-operative nausea and vomiting was more prevalent among patients who received etomidate as induction agent. No adverse effects were reported in the propofol-ketamine group.

DISCUSSION

Anaesthesia induced haemodynamic fluctuations are a matter of concern for anaesthesiologist. Research evidence indicates that these haemodynamic alterations are independently associated with postoperative complications in patients undergoing surgery. Therefore, many induction agents have been used by anaesthesiologist to minimise the haemodynamic alterations.[7] Propofol, ketamine and etomidate has been addressed with great success in anaesthesiology for many years. The widely used induction agent during general anaesthesia is propofol. It results in larger decrease in blood pressure after induction by decreasing the systemic vascular resistance and myocardial contractility. Vagotonic effects of propofol reduces the heart rate that may cause severe bradycardia, complex atrioventricular block and can even cause cardiac arrest.[8] Ketamine, a phencyclidine derivative as an anaesthetic agent produces sympathetic stimulation leading to increase in myocardial contractility and vascular resistance which in turn leads to increase in arterial pressure and heart rate. Increase in plasma concentration of epinephrine and norepinephrine occurs as early as two minutes after intravenous administration of ketamine and return to control levels 15 minutes later.[9] Ketamine and propofol are time tested agents but with disadvantages. Thus, combination of propofol and ketamine might be a better alternative. This assumption has been confirmed by various studies. Aboeldahab H et al.[10] compared propofol, ketamine and their combination ketofol as induction agents and concluded that ketofol provided better haemodynamic stability compared to inducing with propofol or ketamine as sole induction agent. "Studies conducted by Regmi NK et al.[11] Yousef GT et al.[12] and Ozgul U[13] et al. showed that propofol and ketamine combined in various proportions provided better haemodynamic stability and decreased side effects compared to induction with either of the agents used individually. Studies conducted by Shivanna S et al. Kaushal RP et al.[14] Kabir K et al.[15] Singhal,[16] Agarwal S et al.[17] on comparing haemodynamic effects of propofol and etomidate

as induction agents concluded etomidate to provide superior haemodynamic stability compared to propofol. Etomidate is a unique induction agent with minimal haemodynamic effects and wide safety margins. In spite of its potential benefits etomidate can suppress adrenocortical steroid synthesis and also increased post-operative nausea and vomiting. Lundy JB et al.[18] reported one case of adrenal insufficiency after administration of single dose of etomidate for anaesthesia induction.

Unfavourable effects of etomidate and importance of co-induction to promote induction of anaesthesia in patients undergoing surgery encouraged us to evaluate combination of some anaesthetic agents with opposing haemodynamic effects, on haemodynamic response to laryngoscopy and endotracheal intubation in patients undergoing surgery. Considering the opposing effects of propofol and ketamine on haemodynamic parameters, it seems that combination of them at a lower dose can decrease the overall side effects and summate the advantage of each agent.

Thus, analysing the results of our study statistically we conclude that the patients who received propofol plus ketamine as induction agents showed better haemodynamic stability with no side effects than the patients who received etomidate. The inference from our study co-related well with the study conducted by Baradari AG et al.[6] who in their study compared the effect of etomidate versus combination of propofol-ketamine and thiopentone-ketamine on haemodynamic response to laryngoscopy and endotracheal intubation and concluded that propofol ketamine combination showed better haemodynamic stability compared to other study groups.

But the difference noted between the study conducted by us and Baradari AG et al. was that, in our study haemodynamic parameters fluctuations between the baseline value and after intubation was noted which was considered statistically significant based on paired t-test but the study conducted by Baradari AG et al. did not show statistically significant changes in the haemodynamic variables at various time intervals.

The difference noted could possibly be because of the different analgesics used, where in our study was butorphanol 10 μg / kg whereas Baradari et al. used fentanyl 3 μg / kg. This assumption is supported by the study conducted by Anand et al.[19] who compared two opioids, iv fentanyl and iv butorphanol in propofol based anaesthesia to attenuate haemodynamic response in abdominal surgical cases and concluded that there was statistically significant difference in haemodynamic parameters between the study groups with fentanyl based induction offering better haemodynamic stability with laryngoscopy, intubation and skin incision. Our study also showed that no patients in propofol plus ketamine group developed myoclonus and post-operative nausea and vomiting whereas patients who received etomidate as induction agents had myoclonus in 31 % and postoperative nausea and vomiting (PONV) in 18 %.

Propofol is known to have antiemetic properties with the mechanism not well elucidated, but it may be because of its modulation of subcortical pathway or probably due to its weak serotonin antagonistic effect. A study conducted by Sumer et al.[20] concluded that the incidence of PONV is more in etomidate than the propofol group.

CONCLUSIONS

Propofol plus ketamine can be recommended as a safe and effective combination for induction to attenuate haemodynamic responses to laryngoscopy and intubation, with superior haemodynamic stability compared to induction with etomidate alone. Further randomised clinical trials are required to check the efficacy and safety in patients with cardiovascular disease and critically ill patients.

Limitations

Limitations of our study was that different doses of propofol, ketamine and etomidate were not compared. Fixed dosage of the induction agents was given rather than applying approved end point for induction which could have possibly influenced the haemodynamic parameters and have been a confounding variable.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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REFERENCES

[1] Valeshabad AK, Nabavian O, Nourijelyani K, et al. Attenuation of hemodynamic responses to laryngoscopy and tracheal intubation: propacetamol versus lidocaine - a randomized clinical trial. Anesthesiol Res Pract 2014;2014:170247.
[2] Saricaoglu F, Uzun S, Arun O, et al. A clinical comparison of etomidate-lipuro, propofol and admixture at induction. Saudi J Anaesth 2011;5(1):62-66.
[3] Strayer RJ, Nelson LS. Adverse events associated with ketamine for procedural sedation in adults. Am J Emerg Med 2008;26(9):985-1028.
[4] Andolfatto G, Willman E. Prospective case series single-syringe ketamine-propofol (ketofol) for emergency department procedural sedation and analgesia in adults. Acad Emerg Med 2011;18(3):237-245.
[5] Shivanna S, Priye S, Jagannath S, et al. A comparative study of haemodynamic effects of propofol and etomidate as an induction agent in coronary artery surgery. JEMDS 2015;4(4):598-607.
[6] Baradari AG, Firouzian A, Kiasari ZA, et al. Effect of etomidate versus combination of propofol-ketamine and thiopental-Ketamine on haemodynamic response to laryngoscopy and intubation: a randomised double blind clinical trial. Anesth Pain Med 2016;6(1):e30071.
[7] Hosseinzadeh H, Eidy M, Golzari SE, et al. Hemodynamic stability during induction of anaesthesia in elderly patients: propofol+ ketamine versus

propofol+ etomidate. J Cardiovasc Thorac Res 2013;5(2):51-54.
[8] Kayhan GE, Yucel A, Colak YZ, et al. Ketofol (mixture of ketamine and propofol) administration in electroconvulsive therapy. Anaesth Intensive Care 2012;40(2):305-310.
[9] Tweed WA, Minuck MS, Mymin D. Circulatory response to ketamine anaesthesia. Anaesthesiology 1972;37(6):613-619.
[10] Aboeldahab H, Samir R, Hosny H, et al. Comparative study between propofol, ketamine and their combination (ketofol) as an induction agent. Egypt J Anaesth 2011;27(3):145-150.
[11] Regmi NK, Khatri S, Datta PK. Comparison of propofol-ketamine combination with propofol-butorphanol combination for total intravenous anaesthesia on short surgical procedures. JNGMC 2014;12(2):34-39.
[12] Yousef GT, Elsayed KM. A clinical comparison of ketofol (ketamine and propofol admixture) versus propofol as an induction agent on quality of laryngeal mask airway insertion and hemodynamic stability in children. Anesth Essays Res 2013;7(2):194-199.
[13] Ozgul U, Begec Z, Karahan K, et al. Comparison of propofol and ketamine-propofol mixture (ketofol) on laryngeal tube-suction ii conditions and hemodynamics: a randomized, prospective, double-blind trial. Curr Ther Res Clin Exp 2013;75:39-43.
[14] Kaushal RP, Vatal A, Pathak R. Effect of etomidate and propofol induction on hemodynamic and endocrine response in patients undergoing coronary artery bypass grafting/mitral valve and aortic valve replacement surgery on cardiopulmonary bypass. Ann Card Anaesth 2015;18(2):172-178.
[15] Kabir K, Acharya G, Banjare M, et al. A prospective comparative study to compare cardiovascular response to laryngoscopy and intubation after induction of anaesthesia by propofol and etomidate. Indian J Clin Anaesth 2017;4(1):41-45.
[16] Singhal S. Comparative study of haemodynamic changes and blood sugar levels before and after induction of general anaesthesia with etomidate and propofol. Int J Adv Res 2018;6(5):721-726.
[17] Aggarwal S, Goyal VK, Chaturvedi SK, et al. A comparative study between propofol and etomidate in patients under general anesthesia. Rev Bras Anestesiol 2016;66(3):237-224.
[18] Lundy JB, Slane ML, Frizzi JD. Acute adrenal insufficiency after a single dose of etomidate. J Intensive Care Med 2007;22(2):111-117.
[19] Anand SN, Suryavanshi V. Study on comparison of two opiods iv fentanyl with iv butarphanol in propofol based anaesthesia to attenuate haemodynamic responses in abdominal surgical cases. IJMCR 2017;4(10):2139-2143.
[20] Sumer C, Erhan OL, Ozer AB, et al. Effects of etomidate on blood cortisol, insulin and glucose levels and ponv rates in smokers. Turkish J Med Sci 2012;42(5):810-815.