Haemodynamic effects of etomidate, propofol and their combination on induction and intubation: A prospective randomized clinical trial

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Abstract

Introduction and Aims: Co-induction benefits of etomidate-lipuro and propofol have been studied in previous literatures. Here we tested the hypothesis that combination of etomidate and propofol have better haemodynamic stability during induction and intubation than their individual effect in patients undergoing surgeries under general anaesthesia.

Materials and Methods: Sixty American Society of Anesthesiologist (ASA) I and II patients scheduled for surgeries under general anaesthesia were randomly allocated into three groups of twenty each. Patients in group E and P received 20ml of the study drug {Inj etomidate 0.3mg/kg in group E, inj.propofol 2mg/kg in group P} intravenously over 1minute during induction. While those in group EP, received 20ml of 1:1 mixture of etomidate and propofol intravenously over 1 minute during induction. Depth of anaesthesia was monitored using bispectral index (BIS). ANOVA and Chi-square test were used for statistical analysis. Changes in heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial Pressure (MAP) during induction and intubation were observed as primary objectives and incidence of pain on injection and myoclonus were observed as secondary outcome.

Results: Demographic characteristics were indistinguishable in all the three groups. The gradient of fall in SBP, DBP, MAP and HR was more in propofol group. Group EP had better haemodynamic stability during induction and intubation. Incidence of pain on injection was relatively higher (60%) in group P and myoclonus was observed only in etomidate group.

Conclusions: The 1:1 mixture of etomidate and propofol provides a better haemodynamic stability compared to either etomidate or propofol alone. Hence it can be preferred as a cost effective induction agent of choice.

Keywords: Propofol, Etomidate, Stress response.

Introduction

Post induction hypotension following general anaesthesia is usually associated with increased morbidity and mortality. Patients who had experienced hypotension for more than 5 minutes after induction had a 13.3% increase in hospital length of stay and an 8.6% increase of death.[1] Conversely laryngoscopy and endotracheal intubation elicited cardiovascular responses like hypertension, tachycardia and dysrhythmias.[2]

Since the introduction of general anaesthesia, no ideal induction agent has been discovered in terms of providing a stable haemodynamics during endotracheal intubation.

Propofol (Propofol 1% fresenius, Fresenius Kabi AB, Germany) is the most commonly used induction agent owing to its favourable characteristics of rapid, smooth induction and recovery and decrease incidence of nausea and vomiting. However decrease in blood pressure, dose dependent depression of ventilation and pain on injection are some of its adverse effects.[3]

Etomidate (Amidate, Hospira, Lake Forest, USA) is a carboxylated imidazole with its characteristic haemodynamicstability, minimal respiratory depression and cerebral protective effects. However pain on injection, thrombophlebitis, adrenocortical suppression and myoclonus are some of its undesirable adverse effects.[4]

The rationale behind the concept of co-induction is that drug combination produces desired effects in more appropriate and balanced manner with fewer side effects. Here we aimed to prove the hypothesis that the 1:1 mixture of propofol and etomidate had a better haemodynamic stability during induction and intubation than their individual effect in patients undergoing surgeries under general anaesthesia. Objectives like changes in blood pressure and heart rate during induction and intubation were considered as primary outcome whereas incidence of pain on injection and myoclonus were observed as secondary objectives.

Materials and Methods

After obtaining permission from institutional human ethics committee and written informed consent from the participants, this prospective, double blinded study was conducted in the department of anaesthesiology. Sixty American Society of Anesthesiologists (ASA) grade I and II patients in the age group 18-60 years of either sex were randomly divided into three groups containing twenty each. Surgeries like head and neck surgeries, breast surgeries and abdominal surgeries scheduled under general anaesthesia were included in this study. Patients with known allergy/ hypersensitivity to propofol and etomidate, those with peripheral vascular diseases and pregnant patients were excluded from this study.Randomisation was done by computer generated randomization code.

Patients in group E received 20ml of injection etomidate (0.3mg/kg) IV during induction and those in group P received 20ml of injection propofol (2mg/kg) IV during induction. While in group EP, 20ml of 1:1 mixture of injection

etomidate and injection propofol was given intravenously at the time of induction.

The study drug was initially loaded in terms of per kilogram body weight and then reconstituted to 20ml using normal saline in a 20ml syringe. In Group EP, Inj.etomidate and Inj. propofol were reconstituted to 20ml in two separate 20ml syringes. Ten millilitre of the study drug from each 20ml syringe was withdrawn and reconstituted to 20ml in a new 20ml syringe.

All the selected patients underwent standard pre-anaesthetic assessment. Written informed consent was taken from the patients after explaining the procedure and they were kept unaware of group allocation. All of them were allowed to fast for 8 hours prior to surgery. They were pre-medicated with tablet diazepam 5mg and tablet ranitidine 150mg in the night before and on the morning of surgery.

On shifting the patient to operation room, standard monitoring with pulse oximetry, non-invasive blood pressure and electrocardiograph were instituted. The bispectral index(BIS) sensor(Aspect Medical Systems, Newton, MA,USA) was placed on the patient's forehead and BIS values were monitored at baseline, at 1minute interval till post intubation and at 2minute interval till 5 minutes. Intravenous access using 18G cannula was secured and an IV infusion of Ringer lactate was initiated. Baseline recording of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and oxygen saturation (SpO2) were noted before induction. All patients were pre oxygenated with 100% oxygen over a period of 3 minutes. Patients were administered with injection fentanyl 2mcg/kg IV and injection ondansetron 4mg IV before induction. The study drug was prepared by an anaesthesiologist who was not involved in this study. 20 ml of the study drug was injected intravenously over a period of 1minute during induction. The observer and the anaesthesiologist injecting the drug were both blinded about the group and study drug. Observation for pain during drug injection and myoclonus if present, were noted.

Following induction with the study drug and confirming successful bag and mask ventilation, neuromuscular blockade was achieved with injection atracurium 0.5mg/kg IV. Direct laryngoscopy was performed using appropriate sized macintosh blade and trachea was intubated with appropriate size cuffed endotracheal tube. The appearance of end tidal carbon dioxide trace on anaesthesia workstation and bilateral auscultation of chest confirmed the successful intubation.

Anaesthesia was maintained with oxygen, air, isoflurane {1minimal alveolar concentration (1MAC)} and intermittent dose of Injection atracurium (0.1mg/kg). Patients were mechanically ventilated with a tidal volume of 8ml/kg and at a respiratory rate of 12 /min. Volume controlled positive pressure ventilation was used to achieve an end tidal carbondioxide of 35- 45 mmHg and oxygen saturation of 100%.

The haemodynamic variables like systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate and saturation of oxygen were monitored at baseline (0 minute), at 1minute interval till post intubation and at 2 minute interval till 5 minutes. BIS value of 40-60 was considered as an adequate depth of anaesthesia and it was achieved throughout the surgery by maintaining the plane of anaesthesia with isoflurane.[5-7] Extubation was performed at the end of surgery after reversal of neuromuscular blockade with injection glycopyrrolate 0.01mg/kg IV and injection neostigmine 0.05mg/kg IV. Post operatively patients were shifted to recovery room. Adverse events, if any were noted.

The primary objective of the study was to compare the effect of etomidate, propofol, and a 1:1 mixture of propofol and etomidate on haemodynamic stability during induction and intubation. So the mean arterial pressure at 1 minute was assumed as the reference point for calculation of sample size. From the reference study,[2] we have taken mean arterial pressure at 1 minute in propofol group as 81.67+3.69mmHg and in a 1:1 mixture group as 92.77+4.07 mmHg for the calculation of sample size. Using two tailed distribution with a power of 80%, allocation ratio of 1:1:1 and an effect size of 0.92, the required sample size was found to be 20 cases in each group. The sample size was worked out using the software G*power 3.1.9.2.

Datas were represented as the mean (S.D.). Physical characteristics, systolic blood pressure, diastolic blood pressure, mean arterial pressure and BIS values were analysed using a one-way ANOVA after normal distribution had been ascertained by Kolmogorov− Simirnov test. $\chi 2$-test was used to compare categorical data like the incidence of myoclonus. All differences were considered to be significant at $p< 0.05$. Statistical analysis was performed using SPSS 13.0.

Results

The demographic characteristics like age, gender, BMI and ASA status were comparable in all the three groups [Table 1]. The rate of fall in systolic blood pressure, diastolic blood pressure and mean arterial pressure [Fig. 1] was higher in group P(83±14.4, 106.4±7.1, 61.9±8.1, 76.8±6.6) during induction compared to group E(87.1±14.9, 114.4±12.1, 70.1±13.2, 84.8±12.1) and group EP (80.4±12.1, 117.2±10.4, 72.2±12.3, 87.2±10.7) respectively. Group EP had a better haemodynamic stability during induction and 1 minute after intubation [HR-85.1±10.4, SBP-119.2±15, DBP-73.3±15.5, MAP-88.6±14.7) [Table 2] compared to other groups.

BIS index of 40-60 was achieved at 1minute after induction in all the three groups [Fig. 2] and was maintained throughout the surgery via isoflurane. The incidence of pain on injection of study drug was higher in group P (60%) compared to group E (40%) and group EP (10%) [Fig. 3]. But myoclonus was observed only in group E (15%) [Table 3].

Table 1: Demographic characteristics of patients

		Group E	Group P	Group EP	p-value
Age(yrs)		33.2±12.2	35.7±9.3	35.4±11.1	0.732
Gender(M/F)		10/10	12/8	11/9	0.817
BMI (kg/m^2)		26.4+1.04	26.6+0.7	26.8 + 0.7	0.342
ASA	I	11	13	16	0.241
	II	9	7	4	

The demographic characteristics of the patients undergoing surgery were comparable in all the groups & was non-significant (p>0.05).

Table 2: Comparison of haemodynamic variables among study groups

		Group E	Group P	Group EP	p value
Heart rate	Baseline HR	86.4+12.9	87.5+16.7	78.9 + 9.7	0.095
	HR after premedication	87.8 + 17.1	84.6+14.2	79.9 + 12.3	0.241
	HR after 1 min induction	87.1+14.9	83.0+14.4	80.4 +12.1	0.309
	HR 1min after intubation	90.4+20.1	84.6+11.0	85.1+10.4	0.386
	HR 3min after intubation	93.3+19.1	85.7+15.1	83.2+9.0	0.095
	HR 5min after intubation	89.6+15.9	84.5+15.7	82.6+9.5	0.275
SBP	Baseline SBP	118.6+11.8	123.1+14.7	117.9+9.4	0.347
	SBP after premedication	116.5+14.2	116.9+12.4	116.8+9.4	0.995
	SBP 1 min after induction	114.4+12.1	106.4+7.1	117.2+10.4	0.004*
	SBP 1min after intubation	118.2+10.7	115.3+14	119.2+15	0.63
	SBP 3min after intubation	114.9+11.7	114.8+15.7	114.8+12.8	1.00
	SBP 5min after intubation	110.8+10.3	112.6+14.8	115.3+11.5	0.521
DBP	Baseline DBP	73.3±11.5	73.4±12.1	71.1±9.7	0.767
	DBP after premedication	72.4±13.3	69.1±10.8	71.4±10.2	0.661
	DBP 1 min after induction	70.1±13.2	61.9±8.1	72.2±12.3	0.016*
	DBP 1min after intubation	71.1±13.3	68.6±13.1	73.3±15.5	0.579
	DBP 3min after intubation	69.0±10.1	68.4±12.7	70.4±11.1	0.842
	DBP 5min after intubation	67.9±10.1	67.7±13.2	69.6±12.5	0.863
MAP	Baseline MAP	88.4±11	90.0±11.6	86.7±8.7	0.623
	MAP after premedication	87.1±13.2	85±10.4	86.5±9.1	0.831
	MAP 1 min after induction	84.8±12.1	76.8±6.6	87.2±10.7	0.005*
	MAP 1min after intubation	86.8+11.6	84.2+12.6	88.6+14.7	0.567
	MAP 3min after intubation	84.3+9.9	83.8+13.0	85.2+11	0.929
	MAP 5min after intubation	82.2+9.2	82.6+12.9	84.8+11.7	0.744

Table 3: Comparison of incidence of myoclonus in the study groups

Myoclonus		Group (%)		p value
	E	P	EP	
Present	15%	0%	0%	0.043*
Absent	85%	100%	100%	

*p value significant (<0.05)

Only 3(15.0%) cases had myoclonus in Group E. There was no myoclonus observed in other two categories. The incidence of myoclonus was statistically significant (p-value 0.043) among the study groups.

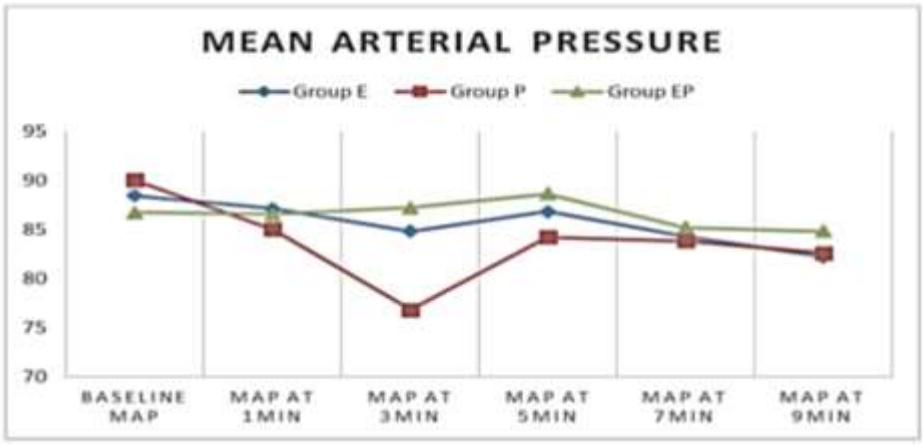

Fig. 1: Comparison of mean arterial pressure (mmHg) among the study groups

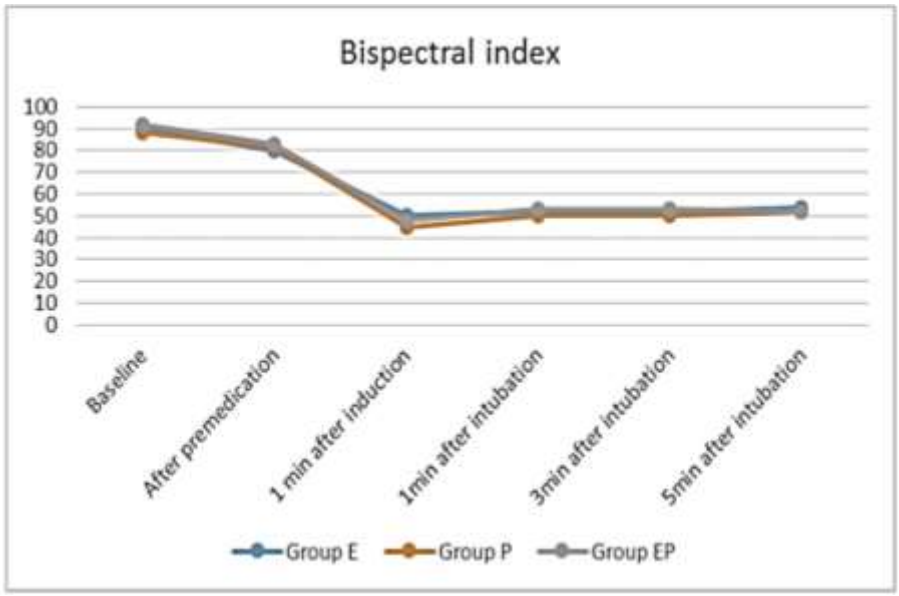

Fig. 2: Comparison of BIS index among 3 groups

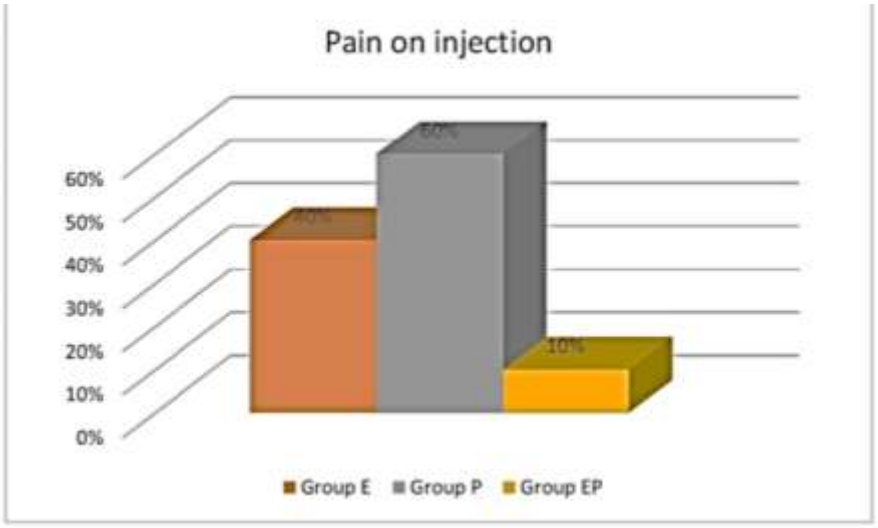

Fig. 3: Comparison of incidence of pain on injection among study groups

Discussion

Haemodynamic stability of etomidate-lipura and propofol combination has been proved in many studies.[8] Etomidate is a substituted imidazole induction agent that is associated with hemodynamic stability.[9] But it failed to gain it's popularity owing to its solvent propylene glycol which caused pain on injection.

The decrease in pain with etomidate lipuro injection was considered to be contributed by the lipid solvent which inturn decreases the propofol concentration in the Etofol group.[10,11] Thus, it may be possible to reduce pain on injection either by reducing bradykinin generation or by decreasing the propofol concentration.[12] As the solvent propylene glycol in amidate and the increase in propofol concentration were mainly responsible for the pain on injection, we tried to evaluate the effect of etomidate, propofol and its admixture on induction and intubation in this study.

These two drugs were analysed in the pharmacology department at Hacettepe University, for availability of its admixture. They announced that these drugs can be mixed and are physically stable too.[8]

Hypotension with propofol induction is mainly due to reduction of sympathetic activity causing vasodilation or its direct effect on vascular smooth muscles.[13,14] This sudden hypotension may have deleterious effects in maintaining the circulation to vital organs in patients with coronary artery disease, valvular stenosis, uncontrolled hypertension and shock.

Although hypotension after induction of anaesthesia with propofol has been well documented, the degree of hypotension noticed differed between studies. In our study, a slight fall of MAP was noticeable among all the study groups. However, it was clinically significant in propofol group. These results were similar with study conducted by F.de Wit et al.[15]

In a study, the effects of propofol upon myocardial function was assessed by measuring the changes in left ventricle function using transthoracic tissue Doppler echocardiography (TDE) and it was concluded that the decrease in MAP following propofol administration is secondary to reduction in cardiac filling or a consequence of a direct negative inotropic action of propofol.[16]

Hypotension following propofol induction was due to reduction of preload and afterload, which was not synchronized with compensatory responses such as increased cardiac output and increased HR. This hemodynamic drop would be intensified by high doses of the drug and high speed of injection of the drug.[17] In parallel to their study, we got similar results in propofol group. There was significant hypotension following induction and it was not synchronized with increased heart rate.

A major drawback of propofol was pain on injection. In our study, only 2 patients had pain on injection during induction in 1:1 mixture group. In etomidate and propofol group, pain was reported among 8 and 12 patients respectively. Incidence of pain was relatively lower in the 1:1 mixture group when compared to propofol or etomidate alone.

The hemodynamic stability seen with etomidate may be due to its unique lack of effect on both the sympathetic nervous system and baroreceptor function[18,19] and capacity to bind and stimulate peripheral alpha 2βadrenergic receptors with its subsequent vasoconstriction.[20] Etomidate suppresses corticosteroid synthesis in the adrenal cortex by reversibly inhibiting 11-beta-hydroxylase, an enzyme important in adrenal steroid production leading to adrenal suppression.[21]

In a study involving patients admitted for elective orthopaedic surgeries, etomidate (0.3 mg/kg) was the induction drug in group A and propofol (2-2.5 mg/kg) was the induction drug in group B. Cardiovascular responses like systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), and O2 saturation were measured before the laryngoscopy, during induction and at 1, 3, 5, 10 min after the induction. They concluded that patients receiving Etomidate had more stable hemodynamic condition.[22]

Haemodynamic effects of etomidate induction studied among 36 patients showed that SV and MAP were significantly reduced with an increasing trend in heart rate. They concluded that although etomidate has a negative inotropic effect, the variables remained within acceptable limits.[23] In our study, following induction with etomidate, there was reduction in MAP but it was not associated with reflex tachycardia as contradictory to their study.

One case of adrenal insufficiency was reported following administration of a single dose of etomidate for induction.[24] Another study showed that after administration of a single bolus dose of etomidate in patients undergoing gynaecological surgery, the cortisol response to surgery was absent for 48 hours; whereas, in the thiopental group, circulating cortisol increased significantly after the operation.[25]

In accordance with the concept of co-induction, combination of propofol with etomidate for induction had not only decreased the required dose of both the drugs but also had reduced the incidence of post-operative nausea and vomiting that is commonly seen with etomidate as propofol has antiemetic properties.[26]

In a study, patients were randomly divided into three groups of thirty each, with group P (propofol 2.5 mg/kg), group E (etomidate 0.3mg/kg) and group PE (propofol 1.25 mg/kg + etomidate 0.15 mg/kg). They found that etomidate-propofol combination was a valuable alternative to propofol or etomidate in extremes of hypotensive or hypertensive scenarios.[27] In accordance with their study, we got similar results that a 1:1 mixture of Propofol and Etomidate had a better hemodynamic stability compared to propofol and etomidate alone.

In agreement with previous literatures, the use of etomidate was found to be associated with higher incidence of myoclonic activity than propofol.[28] We observed myoclonus in three patients in the etomidate group. There were no cases of myoclonus in other two groups.

Previous studies[29] have also shown that the incidence of myoclonic movements can be reduced either by premedication with fentanyl or by pre induction priming with

sub anesthetic dose of etomidate. In our study, we used fentanyl for IV premedication for all cases as it is known to blunt the pharyngolaryngeal reflex on endotracheal intubation and decrease the incidence of myoclonus associated with etomidate.

Our study also had certain limitations. We did not measure plasma cortisol and adrenocorticotropic hormone levels following induction of etomidate. Patients were not observed for adrenocortical suppression post operatively.

Conclusion

The 1:1 mixture of etomidate and propofol combination provides a better haemodynamic stability compared to either propofol or etomidate alone. In addition, single dose of etomidate injection was associated with reported incidences of myoclonus in our study. Thus etomidate-propofol admixture can be preferred as an ideal cost effective induction agent of choice.

Conflict of Interest: None.

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