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ORIGINAL ARTICLE

Comparative study of propofol vs etomidate as an induction agent to evaluate hemodynamic changes during induction of anesthesia in controlled hypertensive patients

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ABSTRACT

Background and Aim: An ideal inducing agent for general anesthesia should have hemodynamic stability, minimal respiratory side effects and rapid clearance. Presently there are a number of induction agents available. Present study was done with an aim to compare propofol with etomidate as an induction agent to evaluate hemodynamic changes during induction of anesthesia in controlled hypertensive patients.

Methodology: A prospective randomized double blind study was conducted at our hospital. Sixty patients undergoing surgery under general anesthesia during April 2015 to April 2016 were randomly divided into two equal groups. Patients of Group-P were given inj fentanyl 2 µg/kg, followed by inj propofol 1-2 mg/kg; and patients of Group-E were given inj fentanyl 2 µg/kg, followed by inj etomidate 0.2- 0.4 mg/kg. Patients' hemodynamic parameters like systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure and heart rate (HR) were recorded at regular intervals. Any adverse event like pain during injection, myoclonus etc. were noted.

Results: Post-induction, heart rate did not change significantly in etomidate group, but in propofol group it decreased significantly compared to the pre-induction value (3.8% vs. 6.5%). The mean fall in SBP at T2 (3 min post induction) in Group-E was 4.7% which was less than that seen in Group-P (7.6%). Three min after induction the fall in DBP was observed to be 16.24% vs. 4.8% in Group-P vs. Group-E respectively. In etomidate group, post-induction SBP did not change significantly as compared to pre-induction. But in propofol group, SBP decreased significantly in post-induction. Post-induction, DBP did not change significantly in etomidate group, but the fall was significant in propofol group.

Conclusion: Etomidate is better in maintaining the heart rate and blood pressure and hence preferable to propofol in controlled hypertensive patients during induction of general anesthesia.

Key words: Diastolic blood pressure; Hemodynamic changes; Systolic blood pressure; Etomidate; Propofol; Hypertension

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INTRODUCTION

An ideal inducing agent for general anesthesia should have hemodynamic stability, minimal respiratory side effects and rapid clearance. Presently there are a number of induction agents available. Thiopental among the oldest induction agents to be discovered in 1934 by Lundy, known for rapid action and rapid

awakening,[1] has an additional property of decreasing ICP in refractory cases. Studies have showed that it causes peripheral vasodilatation, decrease in blood pressure, increase in heart rate and direct negative inotropic effect on heart.

Propofol decreases blood pressure[2-6] by decreasing preload and afterload,[7,8] ,cardiac output and systemic vascular resistance[9,10] due to inhibition of sympathetic vasoconstriction[11] and impairment of baroreceptor reflex regulatory system. Etomidate is characterized by hemodynamic stability,[12-20] minimal respiratory depression[21] with no bronchoconstriction[22] and cerebral protective effects. Its lack of effect on sympathetic nervous system,[23-25] baroreceptor function[26] and its effect of increased coronary perfusion even in patients with moderate cardiac dysfunction makes it an inducing agent of choice.[27-35] Besides Etomidate is used widely for RSI of anesthesia in the emergency department (ED) as a result of its relative cardiovascular stability.[36-39]

Etomidate suppresses corticosteroid synthesis[40-42] by reversibly inhibiting 11-beta-hydroxylase, an enzyme important in adrenal steroid production leading to primary adrenal suppression. However, due to lack of studies43 showing demonstrable negative effect of temporary adrenocortical suppression associated with induction doses of etomidate, as well as the finding that the mean cortisol levels usually remain in the low normal range after etomidate induction, suggests that the adrenocortical suppression following etomidate induction may not be clinically significant.[44]

However, the adverse effects such as nausea, pain on injection, thrombophlebitis and myoclonus for both the agents have been corrected by using reformulated Lipofundin (Lipuro®) solution,[45-48] and pretreating with the fentanyl - an opioid.[49]

This study is an attempt to compare the hemodynamic changes of etomidate and propofol as an induction agent in controlled hypertensive patients. There was also a need to assess and compare any side effect of either drug perioperatively in this group pf patients.

We aimed to evaluate and compare hemodynamic changes in controlled hypertensive patients during induction of anesthesia using propofol or etomidate as an induction agent and to study the incidence of adverse effects such as myoclonus, nausea, pain during injection and thrombophlebitis.

METHODOLOGY

A prospective randomized double blind study was conducted at GMERS Medical College and Hospital, Sola, Ahmedabad, in 60 patients undergoing surgeries under general anesthesia during April 2015 to April 2016.

Inclusion criteria were; age group 35 to 60 years, controlled blood pressure with anti-hypertensive drugs except beta blockers, BP ≤ 140/90 mmHg, a history of hypertension ≤ 5 years, American Society of Anesthesiologist grade I – II, undergoing surgery under general anesthesia. Written consent was obtained from all patients to take part in the study.

Exclusion criteria were; patients' refusal, patients with end organ damage, patients undergoing emergency surgeries, patients having co-morbid conditions including any heart disease, (congenital or valvular), epilepsy, COPD, obese patients, known primary or secondary adrenal insufficiency, on prolonged steroid medication, allergic to any study drug, obstetric (PIH) and pediatric patients, and patients with shock.

The approval to carry out the study was obtained from institutional ethics committee. Routine preanesthetic check-up and detailed history was taken. The airway was assessed pre-operatively a day before surgery and in the pre-induction room on the day of surgery. All necessary investigations were done as per institutional protocol. An informed written consent was taken from each patient. Patients was kept nil per orus for at least 6 to 8 hours. Premedication was given with inj glycopyrrolate 0.005 mg/kg, inj ranitidine 1 mg/kg, inj ondansetron 0.06 mg/kg and inj midazolam 0.03 mg/kg.

On arrival to the operation theatre, a 20 G intravenous cannula was inserted, all patients received infusion of 500 ml of dextrose saline solution. Standard monitors like electrocardiography (ECG), non-invasive blood pressure (NIBP) monitoring and pulse oximetry was attached and the baseline parameters were recorded. All patients were preoxygenated with 5-7 L/min of oxygen for 3-5 min.

Patients of Group-P were given inj fentanyl 2 μg/kg followed by inj propofol 1-2 mg/kg, and patients of Group-E was given inj fentanyl 2 μg/kg followed by inj etomidate 0.2- 0.4 mg/kg. After checking for ventilation, succinylcholine 2 mg/kg was given to facilitate insertion of endotracheal tube. Laryngoscopy was performed about 3 min after the induction agent and endotracheal tube was inserted. Patient's hemodynamic parameters, including systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MBP) and heart rate (HR) were recorded at following intervals in a data collection form; before induction (baseline) (T 0), and then at 1, 3, 5, 10, 15 and 30 min (T 1, T 2, T 3, T

4, T 5, T 6 respectively).

Any adverse event, e.g. pain during injection, myoclonus were noted. At the end of surgery, neuromuscular blockade was reversed by using neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg .The extubation was performed after the patient was fully awake. The patient was monitored 24 hours for postoperative nausea and thrombophlebitis. Nonsteroidal anti-inflammatory drug were used besides fentanyl.

The occurrence of pain on injection was recorded as no pain; verbal complaint of pain, or withdrawal of the arm or both.

Myoclonus was assessed for about 1-2 min after infusing the induction agent and then after checking for ventilation, patient was given succinylcholine to avoid confusion between etomidate induced myoclonus and succinylcholine induced fasciculation. The incidence of myoclonic movements after loss of consciousness was noted. The degree of such muscular activity was scored as follows:

0-no myoclonic movements

1-minor; slight movement of a body segment (face, a finger or a shoulder)

2-moderate; slight movement of two different muscles or muscle groups of the body (face and leg)

3-major; intense movement in two or more muscle groups (e.g. fast abduction of a limb)

The incidence and intensity of nausea was recorded by use of a visual analogue scale (VAS = 0-100 mm), where 0 = least severe, 100 = most severe) at 2, 6, 12, and 24 h postoperatively.

Thrombophlebitis with presence of inflammation around the used vein was noted for 24 hours postoperatively. An anesthesiologist recorded all the hemodynamic parameters at preset time intervals for 30 min after giving the induction agent.

All collected data were summed up. Blinding was ensured by keeping anesthesiologist unaware of the drugs being used. Both etomidate and propofol were filled in identical syringes by a second anesthesiologist.

The patients were assigned to either Group-E or Group-P based on a computer generated randomization table and only the moderator knew the number allocation to the drug. Moderator gave a code to the anesthesiologist doing study and gave the induction agent to the patient.

After observing and collecting intraoperative and postoperative data of all 60 patients, decoding of the drug was done.

Statistical Analysis:

Qualitative data were expressed as percentages and proportions and quantitative data expressed as mean ± standard deviation. The differences between two groups with respect to continuous variables were analyzed using t-test while categorical variables were analyzed using chi-square test. All the statistical tests were performed in SPSS version 15 software. $p < 0.05$ was considered as statistically significant, while $p < 0.01$ was considered as highly significant.

RESULTS

A total of 60 patients of ASA physical status I & II, between ages 35-60 years, were randomly assigned into two groups. Demographic data of the patients are shown in Table 1.

Table 1: Comparison of demographic data

Demographic variables	Group-P (Propofol) Mean ± SD	Group-E (Etomidate) Mean ± SD	*p-value*
Age (in years)	44.5 ± 9.01	48.8 ± 8	0.05*
Weight (kg)	56.6 ± 9.8	61.2 ± 8.88	0.059
Height (cm)	156.7 ± 9.9	162.11 ± 8.88	0.02*
BMI (kg/m2)	22.6 ± 1.59	23.7 ± 1.61	0.01*
Gender (Male : Female)	11 : 19	10 : 20	

*statistically significant at $p \leq 0.05$

Table 2: Comparative changes in heart rates (beats/min) at different time intervals

Observation Time	Propofol (Mean ± SD)	p value	Etomidate (Mean ± SD)	p value
T 0	81.11 ± 7.12		85.5 ± 7.24	
T 1	76.67 ± 9.88	0.05*	81.6 ± 9.1	0.07
T 2	75.78 ± 7.77	0.007*	82.24 ± 7.2	0.08
T 3	79.66 ± 6.8	0.42	83.3 ± 6.3	0.21
T 4	76.9 ± 6.56	0.02*	80.99 ± 6.01	0.01*
T 5	74.54 ± 5.67	0.0002*	78.01 ± 5.12	0.0001*
T 6	82.28 ± 7.22	0.52	86.01 ± 6.76	0.77

**indicates statistically significance at $p \leq 0.05$*

Table 3: Comparative changes in SBP (mmHg) at different time intervals

Observation Time	Propofol (Mean ± SD)	p value	Etomidate (Mean ± SD)	p value
T 0	130.07 ± 7.44		134.43 ± 7.01	
T 1	118 ± 7.9	0.0001*	131.11 ± 6.67	0.06
T 2	120.44 ± 6.84	0.0001*	132 ± 6.04	0.15
T 3	121 ± 7.5	0.0001*	129 ± 8.85	0.01*
T 4	116.03 ± 7.36	0.0001*	130.44 ± 8.85	0.02*
T 5	122.1 ± 8.01	0.0002*	129.56 ± 12.34	0.06
T 6	124.48 ± 7.83	0.006*	130 ± 11.23	0.07

**indicates statistically significance at p ≤ 0.05*

Table 4: Comparative changes in DBP (mmHg) at different time intervals

	Propofol (Mean ± SD)	p value	Etomidate (Mean ± SD)	p value
T 0	78.84 ± 8.31		83.32 ± 7.99	
T 1	70.22 ± 8.61	0.0002*	80.02 ± 8.22	0.12
T 2	66.03 ± 8.01	0.0001*	79.32 ± 8.76	0.06
T 3	68.85 ± 8.43	0.0001*	80.12 ± 7.66	0.12
T 4	71.2 ± 8.46	0.0008*	82.12 ± 7.87	0.56
T 5	80.08 ± 8.1	0.56	85.2 ± 7.01	0.33
T 6	78.8 ± 8.41	0.98	83.01 ± 7.75	0.87

**indicates statistically significance at p ≤ 0.05*

Table 5: Comparative changes in MBP (mmHg) at different time intervals

	Propofol (Mean ± SD)	p value	Etomidate (Mean ± SD)	p value
T 0	95.91± 7.31		100.3± 6.97	
T 1	86.14± 7.42	0.0001*	97.05± 7.03	0.198
T 2	84.16± 7.67	0.0001*	96.88 ± 6.99	0.06
T 3	86.23 ± 7.43	0.0001*	96.41 ± 7.1	0.03*
T 4	86.14 ± 7.5	0.0001*	98.22 ± 7.05	0.25
T 5	94.08± 7.66	0.34	99.9 ± 7.03	0.82
T 6	94.02 ± 7.5	0.32	98.67 ± 7.1	0.37

**indicates statistically significance at p ≤ 0.05*

Demographically both the groups were comparable with respect to mean weight, but mean age, mean height and mean BMI were significantly higher in Group-E ($p \leq 0.05$)

Comparative changes in heart rates (beats/min) at different time intervals are shown in Table 2.

Heart rate did not significantly change in etomidate group after induction compared to pre-induction rate, but in propofol group, the heart rate significantly decreased after induction compared to the pre-induction.

Table 3 shows the changes in mean SBP in the two study groups at different time intervals. Pre-induction was taken as baseline value. There was no significant change in etomidate group during post-induction period, but in propofol group, mean SBP decreased significantly after induction.

Table 4 shows changes in mean DBP in the two study groups after induction and comparison of them with pre-induction (baseline) value. There was a significant decrease in propofol group, but mean DBP did not decrease significantly in etomidate group.

Table 5 shows the changes in mean of the MAP in the two study groups after induction. In etomidate group, post-induction MAP did not decrease, but in propofol post-induction MAP decreased significantly.

DISCUSSION

Etomidate is a short acting intravenous anesthetic agent used for the induction of general anesthesia. It has a very stable cardiovascular profile.[27,28]

In our study with propofol mean pre-induction HR was 81.11 and 3 min post induction 75.78 while with etomidate, the mean HR pre-induction value was 85.5 and 3 min post induction was 82.24 which was insignificant. This corroborated with the study conducted by M Das et al.[13] Moller et al[2] however, showed that decrease in both the groups was significant (p value < 0.05) for propofol and etomidate. There was not much difference among the two groups regarding change in HR. Ram Kaushal et al[39] reported a decrease in both the groups as insignificant. However study conducted by Shah[12] showed the same result 1 min post induction but later i.e. after 3 min there was mild increase in HR for propofol group there was a significant rise in HR (p value 0.001) while in etomidate group HR was insignificant. This may be perhaps due to the anxiolytic effect of midazolam and fentanyl used as premedication by them.

Coming to the blood pressure trends, in our study

change in mean SBP with propofol was very significant and with etomidate it was insignificant. This corroborated with the study conducted by M Das et al.[13] Anil Pandey[16] observed a significant decrease in SBP 5 min post induction from 150.2 to 99.66 (p value 0.0001) in propofol group while in etomidate group also the change was significant. Moller et al[2] too showed that decrease in both the groups was significant. There was not much difference among the two groups regarding change in SBP.

Our study showed a change in mean DBP with propofol as significant, while with etomidate the change was insignificant. This was similar to the observations of other researchers.[12,13,15,39]

The fall in pre-induction MAP with propofol and etomidate in our study was also similar to the observations by Ram Kaushal et al.,[39] M Das et al.[13] and G Karki.[15]

The magnitude of variations in SBP, DBP and MAP from baseline was greater when propofol was used as sole induction agent versus etomidate in comparable doses. The mechanisms of arterial hypotension following IV anesthetic induction are multifactorial. The hemodynamic stability seen with etomidate may be due to its unique lack of effect on both the sympathetic nervous system,[23-25] and baroreceptor function and capacity to bind and stimulate peripheral alpha-2B adrenergic receptors with a subsequent vasoconstriction. Decrease in systemic blood pressure after bolus injection of propofol, is dependent on both vasodilation with reduced preload and afterload and myocardial depression (negative inotropic action).[2-6,30]

In our study, 9 out of 30 patients complained of pain with propofol (6 had a pain score of 2 i.e. withdrawal of limb and 3 had a score of 1 i.e. verbal complaint) while 1 out of 30 patients verbally complained of pain with etomidate. This was in accordance to the study conducted by Nyman Y45 in pediatric age group (2-16 years). Pain was due to the addition of propylene glycol diluent to etomidate, which can be minimized by administering etomidate with prior use of lignocaine or opioid through a large vein with a rapid intravenous infusion rate as that shown by Mayer et al[47] in 1996. The rate of injection also influences the likelihood of pain on injection. In a study conducted by Kosarek L et al,[48] reducing the injection time from 30 sec to 15 sec decreased the pain on injection from 27% to 14%, respectively. This may be due to the fact that we had given injection fentanyl and midazolam intravenously prior to induction and succinylcholine after induction. In 2014, a study by Isitemiz et al[49] in adults has shown that the incidence of myoclonic movements can be reduced either by premedication with fentanyl or midazolam or by pre-induction priming with a subanesthetic dose of etomidate.

None of the patients in either of the two groups had thrombophlebitis after 24 hours of giving injection. The dose of etomidate may also play a role in pain on injection, as larger doses are associated with a higher incidence of venous sequelae. Also the lipid emulsion formula was associated with significantly less pain on injection and significantly less phlebitis and thrombosis compared with etomidate in propylene glycol. None of the patients in either of the two groups complained of nausea. Mayer et al47 in 1996 reported that etomidate formulated in a medium chain lipid emulsion causes significant less discomfort for the patients than propofol, which is solved in a long chain formulation.

LIMITATIONS

Our findings may not be applicable to other age groups of the general population. Patients with serious comorbidities, hemodynamically compromised patients or those with low cardiac reserve were not selected for our study. But from the drug profile of etomidate, it is expected to show similar hemodynamic stability in such patients too. Thus, it would be interesting to evaluate the effects of etomidate induction on hemodynamic parameters in these patients. Pretreatment with midazolam and fentanyl modifies the induction of anesthesia with etomidate by reducing the frequency of myoclonic movements and therefore, episodes of etomidate induced myoclonus could not be seen in our study population. Also we looked for such myoclonic activity for only 1-2 min after injecting. We recommend larger randomized controlled trials on prevention of etomidate induced myoclonus in our population.

CONCLUSION

Our study shows that etomidate provides a greater hemodynamic stability than propofol when used as induction agent in patients with controlled hypertension. Propofol causes more pain at injection site than with etomidate.

Conflict of interest: None declared by the authors
Authors' contribution:
JS: Study Design, Manuscript Editing
IP: Drafting of the manuscript, Statistical analysis
AG: data collection

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