

Comparative Study of the Effects of Intravenous Etomidate and Propofol Used for Induction of General Anesthesia

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Abstract

Aims and objectives: To compare hemodynamic responses and side effects while induction and intubation with intravenous etomidate and propofol. **Material and Methods:** We conducted a prospective, randomized, double-blind study, in which 100 patients undergoing elective surgery under general anesthesia were enrolled for the study. Patients were randomly distributed in two groups (50 in each group). Group P received propofol at 2 mg/kg and Group E received etomidate at 0.2 mg/kg. **Results:** When both the groups were compared it was found out there was statistically significant difference in Group P as compared to Group E in terms of decrease in HR, SBP, DBP, MAP, incidence of myoclonic movements and incidence of pain on injection. There was no overall complication in both groups. **Conclusion:** Induction of anesthesia with etomidate had more stable hemodynamic conditions as compared to propofol. There was significant reduction in heart rate and blood pressure leading to hypotension in propofol group while etomidate group had stable hemodynamics. Incidence and severity of pain on injection was more with propofol while incidence of myoclonus was more with etomidate. Overall, it was concluded that etomidate was a better choice for induction of anesthesia, only drawback being higher incidence of myoclonus.

Keywords: Hemodynamic responses; Etomidate; Propofol.

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Introduction

For general anesthesia, an idyllic inducing agent must have hemodynamic stability, negligible respiratory side effects and rapid clearance. Currently etomidate and propofol are most common rapid acting inducing agents.¹⁻³ Propofol is one of the regularly used drugs for induction of general anesthesia. Due to its satisfactory recovery, short half-life and quick elimination from the blood circulation causing less sedative effects and vomiting, this agent is used more commonly.⁴ The

most significant side effects of this drug are unstable hemodynamics and cardiovascular complications. Propofol can lead to profound reduction in heart rate.⁵⁻⁷ In an analysis done on 25000 patients, 4.2% of patients had fall in heart rate after administration of propofol.⁸ Induction of anesthesia with propofol could drop arterial pressures as much as 25 to 40% in all patients irrespective of any underlying conditions.^{9,10} Reduction of preload and after load of heart is the cause behind propofol induced hypotension. This is not harmonized with heart's compensatory mechanism and were intensified

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when high dose is given or when the drug is infused fastly.^{11,12} Etomidate is also a short-acting drug, used for induction and maintenance of anesthesia.¹³ Nausea and vomiting, myoclonic movements and hiccups are common side effects of etomidate.¹⁴⁻¹⁶ One of the most important side effects of this drug is the adrenocortical suppression by reversible inhibition of 11 beta hydroxylase enzyme but this effect is not so common. Administration of etomidate leads to a stable hemodynamic status.¹⁴⁻¹⁹ This study was performed to explore the cardiovascular response during the induction of anesthesia with etomidate and propofol and to assess pain on injection and myoclonic movements after injecting respective drugs in elective surgeries under general anesthesia due to varied range of consequences and controversies in other studies.

Aims and Objectives

1. To compare hemodynamic responses while induction and intubation with intravenous etomidate and propofol.
2. To compare the myoclonus, pain on injection or any other side effects during induction with both the drugs.

Materials and Methods

After having approval from the institutional scientific and ethics committee, a prospective randomized comparative study on 100 patients was undertaken in the Department of Anesthesiology, M.G.M. Medical College, Kamothe, Navi Mumbai. This included history of any systemic diseases like hypertension, bronchial asthma, cardiac and/or pulmonary disorder, psychiatric disorder, substance abuse and allergy to any drugs. Additionally a thorough general and systemic examination was carried out for each patient enrolled. The study was conducted as a double-blind trial from May, 2016 to May, 2017 at Mahatma Gandhi Mission Institute of Medical Sciences, Kamothe, Navi Mumbai. Sixty patients scheduled for elective surgery under general anesthesia were randomized into two groups.

Sample size: Sixty patients were enrolled for the study (randomly distributed in two Groups D and C [n = 30 in each group]. Group D dexmedetomidine group and Group C control group).

Patients age 18 to 50 years of both sexes with ASA grade I and II and hemodynamically stable were included in the study.

Patients with vascular diseases, habituation to analgesics (cardiac, pulmonary, neurological disease), allergy to the drug to be used were excluded.

In this study a total of 100 patients undergoing elective surgery under general anesthesia were randomized in two groups comprising 50 patients each. In order to randomize computer generated randomization table was used. Among the two groups, the first group (Group P) underwent general anesthesia by Propofol and the second group (Group E) by Etomidate. All the patients underwent a thorough pre-anesthetic check up and were investigated for all the routine and special investigations. Study was carried out after taking the written informed consent from the patient.

Methodology: A detailed pre-anesthetic check-up of all patients were done including airway assessment, clinical history, general and systemic examination, routine biochemical investigations, chest X-ray and electrocardiography. All patients were kept fasting overnight. Patients were given Tablet Pantoprazole 40 mg and Tablet Alprazolam 0.5 mg on the day before surgery during pre-anesthetic evaluation. On entering the operation theater, IV line were secured. Monitors like Electrocardiogram (ECG), Non-invasive blood pressure monitor (NIBP) and pulse oximeter was connected and baseline parameters were recorded.

Patients were randomly assigned to propofol (P) group and etomidate (E) group. Baseline hemodynamic parameters were measured. Fentanyl 2 microgm/kg and Midazolam 0.02 mg/kg were given IV. Patients were preoxygenated with 100% oxygen for 3 minutes. Two minutes after fentanyl administration; anesthetic agents were injected. Propofol group was receive propofol at 2 mg/kg and etomidate group was receive etomidate at 0.2 mg/kg. Pain on injection and myoclonic movements were recorded, if any at induction. As soon as the onset of unconsciousness occurs consumed dose of anesthetic were recorded individually.

Endotracheal intubation was done using vecuronium 0.1 mg/kg and anesthesia were maintained as per institutional protocol. The cases in which tracheal intubation could be performed successfully within 30 seconds in a single attempt were included in the study. Reversal of residual neuromuscular blockade was done with neostigmine 0.05 mg/kg and glycopyrolate 0.008 mg/kg. Trachea was extubated after adequate recovery of muscle power and patients were

monitored postoperatively.

The patient’s hemodynamic and cardiovascular indicators such as systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR) and oxygen saturation (O₂ sat) were recorded before induction (T1), before intubation (T2) and at 1 (T3), 3 (T4), 5 (T5), and 10 (T6) minutes afterward. The hemodynamic parameters before induction, i.e. T1 were taken as baseline. Hypertension was defined as increase in baseline SBP > 20% while hypotension as <20% of baseline, Tachycardia as HR > 20% of baseline and bradycardia were defined as <60 heart rate. Patient whose oxygen saturation was fall below 90% were considered to be desaturating.

Adverse effects such as pain on injection and myoclonus if any were recorded. Pain on injection was measured using four graded scale (0: no pain, 1: verbal complaint of pain, 2: withdrawal of the arm, 3: both verbal complaint and withdrawal of arm. Patients were observed visually for myoclonus and when present, myoclonus severity were graded. Degree of such muscular activity were scored as follows - 0: no myoclonus, 1: minor myoclonus, 2: moderate myoclonus, 3: severe myoclonus. The rescue drugs - IV Mephentramine 6 mg bolus was given if the mean arterial pressure (MAP) was drop by > 20% from baseline, IV Diltiazem 2.5 mg were used if MAP was increase by > 20% from the baseline and IV Esmolol 20 mg were employed in case the heart rate was rise above 100 beat per minute.

Results

The mean age among group P and E was 32.06 + 9.69 and 32.51 + respectively. Statistically, there was no noteworthy difference between the two groups (p = 0.82). The male : female ratio in Group P was 19 : 29 and in Group E was 29 : 18 which was comparable.

The mean weight of patients in Group P was 57.98 + 5.76 and 56.77 + 6.29 which was statistically insignificant (p = 0.37).

The baseline SBP was comparable in both groups and had no statistically significant difference (p = 0.42). There was significant difference in SBP in both groups measured before intubation and after intubation at 1, 3, 5 and 10 minutes with p < 0.001 at all stages (Fig 1).

The baseline DBP was comparable and had no statistically noteworthy difference in both groups (p = 0.072). There was significant difference before intubation (p=0.032) and after intubation at 1 minute (p < 0.001), 3 minutes (p < 0.001), 5 minutes (p = 0.001) and 10 minutes (p = 0.003) in Group P and E (Fig 2).

The baseline MAP showed no statistically significant difference (p = 0.18) in baseline values amongst both groups. There was statistically substantial difference before intubation (p < 0.001) and after intubation at 1 minute (p < 0.001), 3 minutes (p < 0.001), 5 minutes (p = 0.017) and 10 minutes (p < 0.001) in Group P and E (Fig. 3).

Heart rate was comparable in both the groups and had no statistically significant difference in baseline values (p = 0.72). There was difference before intubation and after intubation but the difference was not statistically significant (p = 0.11 and p = 0.29 respectively). Heart rate at 3, 5 and 10 minutes showed significant difference amongst two groups (p = 0.008, p = 0.04 and p = 0.03 respectively) (Fig. 4).

Mean saturation for Group P was 98.9 + 0.7 and for Group E was 98.6 + 0.6 and showed no statistically noteworthy difference (p = 0.13). Mean time for laryngoscopy for Group P was 17.13 + 2.92 and for Group E was 17.40 + 3.2 and was comparable. It showed no statistically significant difference (p = 0.66).

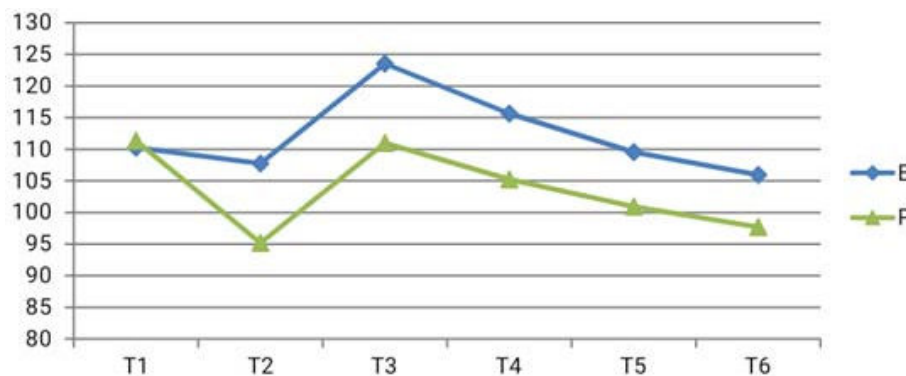


Fig. 1: Systolic Blood Pressure (SBP)

Incidence of myoclonic movements in Group P and E showed statistically substantial difference ($p < 0.05$). Incidence of pain on injection after

administering the drug in Group P and E showed statistically significant difference ($p < 0.05$).

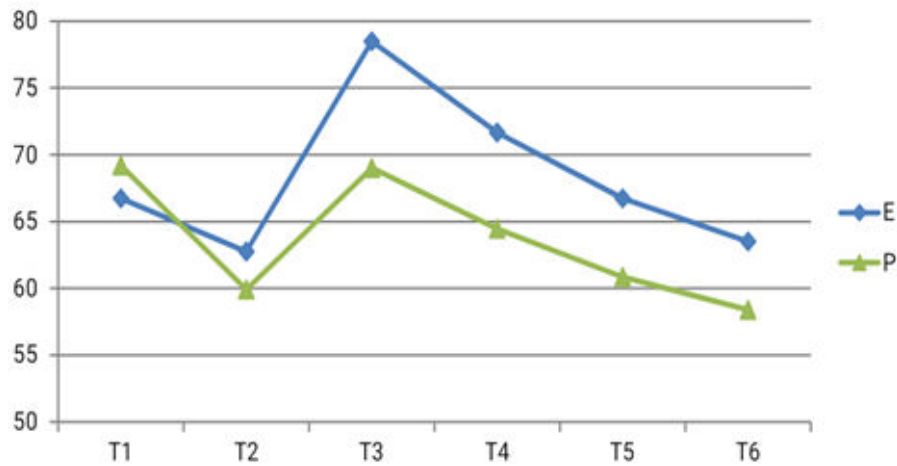


Fig. 2: Diastolic Blood Pressur (DBP)

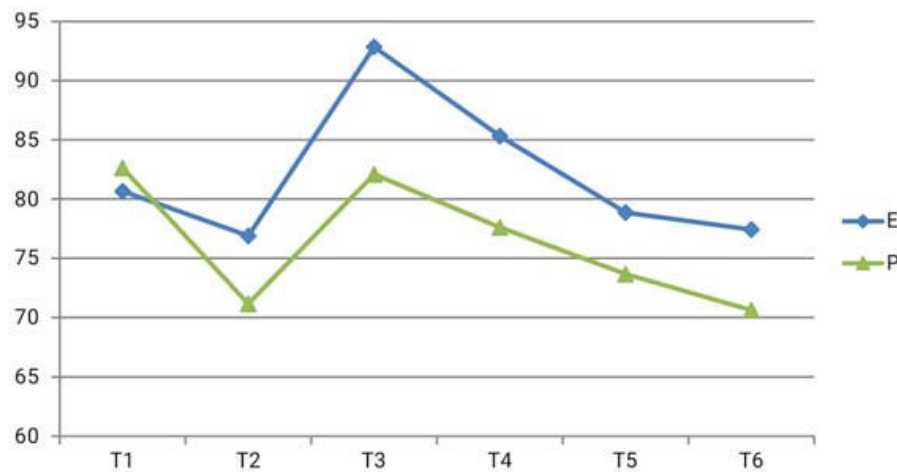


Fig. 3: Mean Arterial Pressure (MAP)

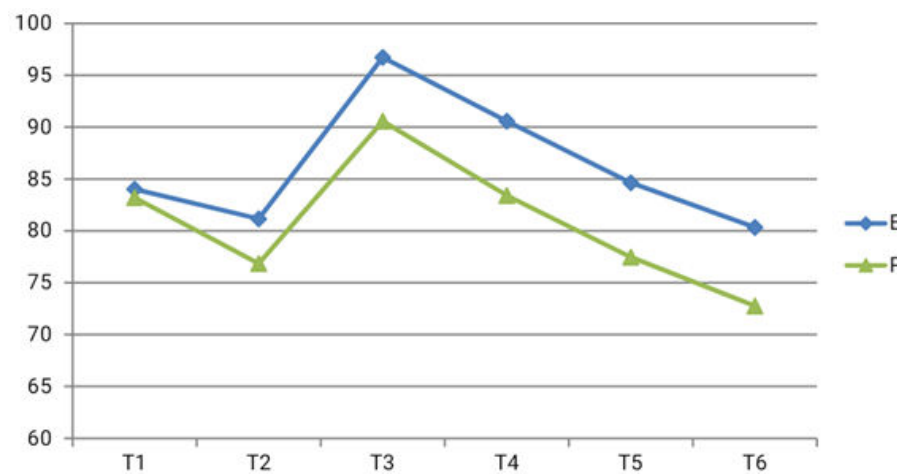


Fig. 4: Heart rate

Discussion

Demographic Profile

The mean age of patients in Groups P and E was 32.06 ± 9.69 years and 32.51 ± 9.13 years respectively. Statistically, there was no significant difference between the groups ($p = 0.82$). The mean weight of patients in Group 1 and Group 2 was 59.17 ± 9 and 60.43 ± 9.4 kilograms respectively. Statistically, there was no significant difference between the groups ($p = 0.599$). The mean weight of patients in Groups P and E was 57.98 ± 5.76 kg and 56.77 ± 6.29 kg respectively. Statistically, there was no significant difference between the groups ($p = 0.37$). The gender ratio (Male : Female) in patients of Group P was 29 : 19 and in patients of Group E was 18:29 and were comparable.

This was in settlement with study done by Ebert TJ, Muzi M where both groups were demographically similar and had no significant difference in age, height and weight.²⁰ A. Pandey (70) in his study also showed that demographic characteristics namely age, weight and sex distribution were similar in etomidate and propofol group.²¹

Arterial Blood Pressure:

In our study, arterial blood pressure was recorded before induction (T1), before intubation (T2) and at 1 (T3), 3 (T4), 5 (T5), and 10 (T6) minutes after intubation. Baseline systolic, diastolic blood pressures and mean arterial pressures in both the groups were comparable and variations were statistically insignificant. We observed that both systolic and diastolic BP reduced from the baseline values, mean SBP being $107.4 + 11.6$ and $95.1 + 7.8$ while mean DBP being $62.7 + 6.9$ and $59.9 + 5.6$ respectively after induction with etomidate and propofol. MAP also dropped from baseline values with mean value being $76.8 + 7.8$ and $71 + 5.8$ respectively with etomidate and propofol. We observed that there was marked reduction in all 3 parameters after induction with propofol as compared to that of etomidate which was statistically significantly (p values being <0.001 , 0.032 and <0.001 for SBP, DBP and MAP respectively).

This is in agreement with study done by Ebert TJ, Muzi M, Berens R *et al.* in which both systolic and diastolic blood pressures were well maintained with etomidate but were decreased after induction with propofol.²⁰

After intubation, blood pressure recordings were done at 1, 3, 5 and 10 minutes'. There was significant

increase in all 3 parameters namely SBP, DBP and MAP (p values being < 0.001 at 1 and 3 minutes for all three parameters, < 0.001 , 0.001 and 0.017 at 5 minutes and < 0.001 , 0.003 and < 0.001 at 10 minutes of SBP, DBP and MAP respectively), as compared to before intubation values but in case of propofol, the arterial pressures did not increase more than the baseline values.

This is in settlement with the study done by Harris CE, Murray AM *et al.* on 303 patients in which it was observed that there was significant decrease in arterial pressures after induction with propofol and just prior to intubation was highly significantly lower than the baseline values as compared to etomidate.²² Aggarwal Supriya *et al.* also concluded in their study on 100 patients that etomidate is better for its hemodynamic stability as compared to propofol.²³

Pandey, N. Makhija *et al.* studied hemodynamic response on 100 patients and stated that SBP and DBP were significantly lower post induction in propofol group as compared to etomidate group suggesting that etomidate was associated with more hemodynamic stability on induction of anesthesia than propofol.²¹ Study done by Fatma S, Sennur U *et al.* also recorded that etomidate is associated with hemodynamic stability of very high degree as compared to propofol.²⁴ Our result is also in agreement with the results stated by Miner J.R. *et al.* which concluded that there was a larger percentage of decrease in SBP in patients who received propofol than who received etomidate.²⁵

In our study and in agreement with previous literatures, in spite of stimulus provided by intubation, arterial pressures remained lower than baseline values in propofol group as compared to etomidate. Hypotension occurring due to propofol is mainly because of decrease in sympathetic activity which leads to vasodilatation or direct effect of propofol on vascular smooth muscle while hemodynamic stability observed with etomidate can be because of its unique lack of effect on sympathetic nervous system and baroreceptor function.²²

Heart Rate

In present study baseline heart rate was comparable between the two groups. We observed that heart rate decreased after induction in both the groups from the baseline values but the changes were not statistically significant ($p = 0.11$). After intubation there was rise in heart rate in both the groups at 1 and 3 minutes, significantly more rise in etomidate group than propofol group at 3 minutes ($p = 0.008$).

After 5 and 10 minutes of intubation heart rate fell back near the baseline values with etomidate group but showed statistically significant decrease in patients induced with propofol ($p = 0.04$ and $p = 0.03$ respectively at 5 and 10 minutes).

Gooding JM, Corsen G *et al.* in their study showed there was 10% rise in heart rate after induction with etomidate.²⁶ This is also in settlement with randomized controlled trial done on 60 adults by Shah SB, Chowdhury I *et al.* where post induction there was rise in patients allocated in etomidate group.²⁷ Harris CE, Murray AM observed that there were significant increases in heart rate in both groups ($p < 0.01$) but there was greater increase in those who received etomidate.²² Ko YK *et al.* in his study on 46 patients observed that patients induced with propofol had significant decrease in heart rate and concluded that propofol precipitates vascular dilatation, decreases preload and afterload, and impairs myocardial contractility.²⁸

Kaushal RP *et al.* also stated that there was significant decrease in cardiac output and cardiac index in patients induced with propofol than in those induced with etomidate.²⁹ Tachycardia and increase in arterial blood pressure are the two commonest cardiovascular response to intubation because of increased sympathetic activity.²² Cardiovascular hemostasis is mediated by sympathetic nervous system which helps in modulating heart rate, myocardial contractility, arterial resistance and venous capacitance. Propofol seems to attenuate greatly the baroreflex changes in sympathetic activity that occurs in response to BP perturbations while during administration of etomidate there is preservation of both tonic and baroreflex regulation of sympathetic activity.

Oxygen Saturation

In current study the saturation was recorded before induction (T1), before intubation (T2) and at 1(T3), 3(T4), 5(T5), and 10 (T6) minutes post intubation. The mean saturation for Group P was 98.8 ± 0.7 and for Group E it was 98.6 ± 0.6 which showed statistically insignificant difference ($p = 0.13$).

Time for Laryngoscopy

The mean time taken for laryngoscopy for group E was 17.4 ± 3.23 seconds and for group P it was 17.13 ± 2.92 seconds showing no statistically significant difference ($p = 0.66$). Laryngoscopy is part and parcel of anesthesia. To secure and protect the airway is of prime importance while inducing anesthesia. Prolonged laryngoscopy can lead to

sympathetic stimulation leading to increase in heart rate and blood pressure. Hence, in our study only those patients were included in whom time for laryngoscopy was < 30 seconds. 5 patients were excluded since the time for laryngoscopy exceeded 30 seconds.

Myoclonus

In present study incidence of myoclonic movements observed among two groups and severity of myoclonus was graded as follows: 0: no myoclonus, 1: minor myoclonus, 2: moderate myoclonus, 3: severe myoclonus. Out of all the patients induced with etomidate 31.2% showed myoclonic movements of grade 1 (20.8%) 2 and 3 (10.4%) while none of the patients in propofol group showed myoclonic movements. This difference was statistically significant ($p < 0.05$).

In study done by Miner J.R., Danahy M *et al.* they found that out of 110 patients randomized in etomidate group 20% had myoclonic movements depicting that myoclonus was observed much more frequently in patients receiving etomidate.²⁵ Our results are also in correlation with study done by Fatma S, Sennur U *et al.* which suggested that a higher incidence of myoclonic activity was seen in etomidate group (93.4%) as compared with propofol group.²⁴ Study done by Aggarwal Supriya *et al.* also showed that myoclonic movements were only seen in etomidate group and patients induced with propofol did not show any sign of myoclonus.²³

The neurologic mechanism of myoclonus is unclear. There are few theories suggesting that it represents some kind of seizure activity while other theories suggest that it's a disinhibition phenomenon, apparently because large doses of etomidate depresses cortical activity before the depression of subcortical activity.³⁰

Pain on Injection

In our study we measured pain on injection using four graded scale (0: no pain, 1: verbal complaint of pain, 2: withdrawal of the arm, 3: both verbal complaint and withdrawal of arm). We observed that out of all the patients receiving propofol 48% experienced pain on injection while administration of drug of Grade 1 (31.3%) and 2 (16.7%) while only 6.3% patients in etomidate group experienced pain of Grade 1 on injection.

In the study done by Fatma S, Sennur U *et al.*, they observed that there was a very high incidence of pain on injection after administering propofol and was statistically significant as compared to

etomidate group.²⁴ Aggarwal Supriya *et al.* observed that 50% of patients receiving propofol complained of pain while only 4% of patients experienced pain in etomidate group concluding that patients receiving propofol had higher incidence as well as severity of pain on injection.²³

Pain on injection post-administration of propofol is common and can be a bad experience to the patients. Many factors appear to affect the incidence of pain on administration of propofol, few being size of vein, site of injection, speed of injecting drug, propofol concentration in aqueous phase and the buffering effect of blood. Degree of pain also depends upon the volume injected and the flow of blood through the vein.³¹

Conclusion

Etomidate was having more stable hemodynamic conditions as compared to propofol induced anesthesia. There was significant reduction in heart rate and blood pressure leading to hypotension in propofol group while etomidate group had stable hemodynamics. Incidence and severity of pain on injection was more with propofol while incidence of myoclonus was more with etomidate. Thus, we can conclude that etomidate can be a better choice of induction for general anesthesia as compared to propofol, only drawback being higher incidence of myoclonic movements.

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