Original article:

A Randomised Controlled Trial to Compare Etomidate and Propofol for Induction of General Anesthesia in Adults

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Abstract :

Introduction: Anaesthetic induction techniques are based on haemodynamic stability, rapid clearance, minimal intubation stress response respiratory side effects and ease of administration. Etomidate and Propofol are rapid acting and safe induction agents however both drugs have different induction characteristics.Aim of this study was to compare haemodynamic parameters, myoclonus, pain on injection and other side effects during induction of anaesthesia with Propofol and Etomidate.

Method: Single centered, double blinded, prospective randomised study done on 100 ASA grade I and II patients of age group 18-60 years scheduled for elective surgeries requiring general anesthesia. Patients were randomly divided into two groups of 50 each, group P and group E, receiving Propofol (2 mg/kg,) and Etomidate (0.3 mg/kg) respectively as an induction agent. Haemodynamic parameters, myoclonus and pain on injection at induction were recorded for comparison. Quantitative data were analysed using student's t test with help of INDOSTAT software. p and t values were obtained. P values less than 0.05 were considered significant.

Results: Both groups were comparable in terms of demographic and baseline haemodynamic characteristics. The fall in MAP at times T2 (one min post induction) and T3 (three min post induction) was much sharper and significant for Propofol group (12.50 and 18.57 mm of Hg respectively) as compared to Etomidate group (3.82 and 6.26 mm of Hg respectively), p values 0.004 and 0.001 respectively.

The stimulus of laryngoscopy and intubation (time T4) failed to bring the MAP above baseline levels in Propofol group (8.33 mm of Hg below baseline) while in Etomidate group there was 3.62 mm of Hg rise in MAP above baseline after laryngoscopy(p value 0.001).

Myoclonus was graded as mild in 22%, moderate in 10% and severe in 2% patients in Etomidate group. Myoclonus was not observed with Propofol. Incidence of pain on injection was 4% in Etomidate group and 34% in Propofol group.

Conclusion – Etomidate is a better alternative to Propofol as an induction agent because of haemodynamic stability and less pain on injection. However, use of appropriate premedications is required for decreasing incidence and severity of myoclonus with Etomidate.

Key words- Anesthesia, Anesthesiology, Anesthetics, Intravenous, Etomidate.

Hemodynamics, Humans, Intubation, Myoclonus, Pain, Propofol, Prospective Studies.

Introduction:

An ideal induction agent for general anaesthesia should have haemodynamic stability[1], minimal respiratory side effects, minimal intubation stress response and rapid clearance.

Over years there has been a continuous search for better and safer intravenous agent. Presently Etomidate and Propofol are popular, rapid acting and safe induction agent however these two drugs have different induction characteristics.

Propofol is one of the most commonly used drug, has rapid onset, satisfactory recovery, short half-life and rapid elimination from the blood circulation.

The most important side-effect of this drug is haemodynamic instability. Propofol causes reduction of heart's preload and after load, which are not synchronized with compensatory responses and would be intensified by high doses and high speed injection of the drug. Propofol decreases blood pressure, cardiac output and systemic vascular resistance due to inhibition of sympathetic vasoconstriction and impairment of baroreceptor reflex.[2] These effects may be exaggerated in hypovolemic and elderly patients with compromised left ventricular function.

Induction of anaesthesia with Propofol is frequently associated with apnoea in both adult and paediatric patients.

A major problem with the use of Propofol is high incidence of pain on injection, though reduced by adding lignocaine to Propofol solution, still the incidence remain unacceptably high.[3]

Haemodynamic stability of Etomidate is unique among the rapid onset induction agents. Stability of cardiovascular function suggests lack of effect on sympathetic nervous system and baroreceptor reflex regulatory system. It also does not have significant effect either on the peripheral and pulmonary vascular bed or on myocardium itself. Therefore Etomidate is most appropriate in patients with cardiovascular compromise particularly with poor left ventricular function as it does not cause hypotension. Etomidate is also preferred in patients with respiratory airway disease,[4] intracranial hypertension and in patients with shock. Common side effects of Etomidate are nausea and vomiting that may lead to aspiration in patients. Etomidate also induces spontaneous movement or myoclonic activity and can increase focal epileptogenic activity in patients with epilepsy. The incidence of myoclonus can be reduced by various agents including Benzodiazepines, Magnesium Sulphate, Rocuronium and Opioids.[5-8]

Pain on injection is another side effect of the drug. [9] Pain on injection, venous irritation and haemolysis have been abolished by new fat emulsion of Etomidate, but the new solvent has not reduced the incidence of myoclonus after Etomidate injection.

One of the most important, but rare side effect of this drug is the reversible inhibition of 11-beta-hydroxylase enzyme, causing reduction in serum cortisol level even after a single dose for upto twenty four hours [10].

Considering the common use of Propofol and Etomidate for induction of anaesthesia and the importance of patient's haemodynamic stability during the surgery, this study was conducted with primary objective to compare the effects of these drugs for the induction of general anaesthesia with reference to haemodynamic parameters, myoclonus and pain at the site of injection while safety, recovery time and complications were the secondary objectives.

Method:

After approval by the Institute Ethical Committee., this study was carried out as a double–blind randomized prospective study on patients between the age group of 18 and 60 years belonging to

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American Society of Anaesthesiology Grade I and II undergoing surgery under general anaesthesia.

Patients were randomized into 2 groups of 50 patients each and randomization was based on computer generated random numbers.

Group E (n=50): recieved inj. Etomidate 0.3 mg/kg intravenous.

Group P (n=50): recieved inj. Propofol 2.0 mg/kg intravenous.

Patient with known allergy to the drugs used in the study, with significant cardiac, respiratory, hepatic or renal dysfunction, an anticipated difficult airway, hypotension, history of seizure disorder, presence of primary and secondary steroid deficiency or on steroid medication were excluded from study.

After complete pre-anaesthetic assessment, the procedure was explained to the patients and written informed consent was taken one day before surgery.

The patients were shifted to the operating room with all aseptic precautions. Patients were examined to confirm the finding of pre anaesthetic check- up and were enquired about the fasting status. An intravenous line was secured. Then standard monitoring and recording of non invasive B.P., pulse rate, oxygen saturation, ECG and respiratory rate before induction of anaesthesia. Premedication with Inj. Glycopyrrolate 0.2mg intravenous + Inj. Fentanyl 1µg/kg intravenous was given 15 minute before induction of anaesthesia.

All patients were pre-oxygenated for 3 minutes with 100% oxygen. Patients were induced either with Inj. Etomidate (group E) or Inj. Propofol (group P) according to randomization. Propofol and Etomidate are both opaque white liquids which allowed the study to be conducted under double blind conditions.

Appropriate sized endotracheal tube was inserted after giving Inj. Succinylcholine 1-1.5mg/kg.

In both the groups, pain, myoclonus and haemodynamic parameters (heart rate, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure , oxygen saturation) were recorded at baseline and then T1 to T6 till up to 5 min post intubation where-

- T0= baseline(before pre- medication)
- T1= at the time of induction
- T2= 1 min post-induction
- T3= 3 min post- induction
- T4= after 1 min laryngoscopy
- T5= 3 min post - intubation
- T6= 5 min post- intubation.

Maintenance of anaesthesia was achieved with oxygen (O_2), nitrous oxide (N_2O) in 1:1 ratio, Isoflurane and Vecuronium 0.06mg/kg bolus followed by 0.02 mg/kg as per need with controlled ventilation.

Intraoperative haemodynamic parameters (heart rate, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, oxygen saturation) were recorded every 10 minute for first hour of surgery then every 15 min till the end of surgery.

After completion of surgical procedure, reversal of neuromuscular blockage was achieved with Inj. Neostigmine (40µg/kg) and Inj. Glycopyrrolate (6µg/kg) and extubation done when adequate muscle power, regular spontaneous respiration and cough reflex was present.

Patients were observed for 2 hours in PACU (post anaesthesia care unit) for any post operative complications like nausea, vomiting, hypotension, bradycardia, respiratory depression, agitation, arrhythmias. The complications were treated with appropriate measures.

subjective assessment of pain was done with VAS scoring which is a 10 cm horizontal line labelled as "No pain" at one end (0) and "Worst pain"

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imaginable on the other end (10). Patients were asked to mark on the line where the pain lies.

Patients were observed visually for myoclonus and intensity of myoclonic movements were graded according to the following score-

Grade 0= no myoclonus

Grade 1= mild myoclonus- movements at the finger or wrist only

Grade 2= moderate myoclonus - movements involving the face and leg

Grade 3= severe myoclonus - generalized response or movement in >one extremity.

All the data was filled up in the proforma attached and statistical analysis were performed using SPSS software version 17.0 to draw conclusions.

Results:

Both groups were comparable in terms of demographic and baseline haemodynamic characteristics. The fall in MAP at times T2 (one min post induction) and T3 (three min post induction) was much sharper and significant for Propofol group (12.50 and 18.57 mm of Hg respectively) as compared to Etomidate group (3.82 and 6.26 mm of Hg respectively), p values 0.004 and 0.001 respectively.

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Myoclonus was graded as mild in 22%, moderate in 10% and severe in 2% patients in Etomidate group. Myoclonus was not observed with Propofol. Incidence of pain on injection was 4% in Etomidate group and 34% in Propofol group.

Table 1: Demographic Charactristics

	Etomidate Group	Propofol Group
Age (yrs±SD)	43.54±4.2	43.12±5.6
Sex (male:female)	16:84	30:70
Weight (yrs±SD)	60.26±10.19	62.74±10.08
ASA Grade(I:II)	32:18	29:21

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Table 2: Comparision Between Heart Rate in Groups Etomidate and Propofol.

Heart rate	Etomidate group (Mean ± SD)	Propofol group (Mean ± SD)	t/p value
Base line (T0)	89.21±7.52	88.13±10.64	0.54/0.58
At the time of induction (T1)	86.17±11.54	85.05±11.82	1.33/0.86
1 min post-induction (T2)	85.52±12.26	84.32±14.03	0.45/0.64
3 min post- induction(T3)	82.30±9.33	80.58±11.26	0.83/0.40
After laryngoscopy(T4)	98.60±10.38	95.40±9.67	1.57/0.11
3 min post- intubation(T5)	93.3±8.76	92.10±10.10	0.63/0.52
5 min post- intubation(T6)	88.72±13.20	86.30±14.92	0.85/0.39

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Table 3: Comparision Between Mean Arterial Pressure in Groups Etomidate and Propofol.

Mean Arterial Pressure at	Etomidate (E) group (Mean ± SD)	Propofol (P) group (Mean ± SD)	t/p value
Base line (T0)	96.78±9.78	98.12±8.88	0.71/0.47
At the time of induction (T1)	96.26±9.00	96.83±10.82	0.28/0.77
1 min post-induction (T2)	92.96±10.48	85.62±9.61	3.65/0.0004
3 min post- induction(T3)	90.52±8.76	79.55±7.89	7.77/0.0001
After laryngoscopy(T4)	100.39±7.73	89.79±8.11	6.69/0.0001
3 min post- intubation(T5)	97.18±8.52	88.47±9.28	4.88/0.0001
5 min post- intubation(T6)	94.56±7.52	86.76±8.15	4.97/0.0001

Table 4: Incidence of Myoclonus Between Groups Etomidate and Propofol.

	Mild		Moderate		Severe	
Group	Number of Patients	%	Number of Patients	%	Number of Patients	%
Etomidate (E) Group	9	18	3	6	1	2
Propofol (P) group	0		0		0	

Table 5: Incidence of Pain in Groups Etomidate and Propofol.

	Mild (<3)		Moderate (3-6)		Severe (>6)	
Group	Number of Patients	%	Number of Patients	%	Number of Patients	%
Etomidate (E) Group	6	12	nil	0	Nil	0
Propofol(P) group	14	28	4	8	1	2

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Discussion:

Rapid induction and haemodynamic stability in the absence of any serious side effects are important characteristics desired from an ideal induction agent therefore appropriate drug is chosen to maintain haemodynamic stability during induction of anaesthesia. Unfortunately, none of the drug is an ideal induction agent due to its own side effects. The main aim of this study was to compare the effects of Etomidate and Propofol for the induction of general anaesthesia with reference to haemodynamic parameters, myoclonus and pain at the site of injection. Results showed that patients had no significant differences regarding their underlying variables such as sex, age, weight and ASA gread hence, the confounding effect of these variables has probably been neutralized and the results are all about the drugs. Results showed that there was a significant difference between two groups regarding SBP, DBP, and the mean of arterial blood pressure this study was conducted with primary objective to while safety, recovery time and complications were the secondary objectives.

The influence of Propofol and Etomidate on heart rate is controversial. Heart rate may increase, decrease or change minimally following administration of these drugs. The reason for these differences is not clear.

According to studies of Siedy J et al, [11] Ghafoor et al[12] and Kaur et al[13], mean heart rate was comparable in two groups.

In the studies of Ulsamer et al[14] , Moffat et al[15] Etomidate was associated with unacceptably high increase in heart rate while Shah et al[1] reported sustained increase in HR with Propofol

Propofol induced hypotension is due to reduction of sympathetic activity causing vasodilatation, direct effect on intracellular calcium mobilization, inhibition of prostaglandin synthesis in endothelial cells etc. The haemodynamic stability seen with Etomidate may be due to its lack of effect on sympathetic nervous system, baroreceptor function and capacity to bind and stimulate peripheral alpha 2-B adrenergic receptors with a subsequent vasoconstriction.

Decrease in SBP, DBP and MAP was more significant in Propofol group as compared to Etomidate group and p value at various time intervals i.e. from 1 min after induction (T2) till 5 min post intubation (T6) remained highly significant. These results depict that Etomidate provided better haemodynamic stability.

Shah et al[1] , Masoudifar and Beheshtian[16], Aggarwal et al[17] , Kaur et al[13], Kaushal et al[18] and various other studies[2,11,19,20] also concluded that Etomidate provides better haemodynamic stability than Propofol during induction and intubation.

In agreement with previous literature [13,17,21,22] the use of Etomidate was found to be associated with higher incidence of myoclonus activity than Propofol.

Myoclonus was observed to occur in 26% of the patients in Etomidate group while no equivalent signs were noted in Propofol group in our study.

The incidence of myoclonus in our study was lower than other studies, which may be due to fentanyl pretreatment in all patients before induction. Slow Etomidate administration may also explain this lower incidence. Previous studies have also shown that the incidence of myoclonus movement can be reduced either by pre-medication with opioids [6-8] and midazolam or by pre-induction priming with sub-anaesthetic dose of Etomidate.

Pain on injection is most commonly reported adverse event associated with Propofol administration to awake patients. As a result several interventions have been investigated to alleviate the pain associated with Propofol injection. Changing the composition of

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carrier fat emulsion for Propofol to long and medium chain triglycerides decrease the incidence of pain on injection however pretreatment using lignocaine in conjunction with venous occlusion has been reported to be the most efficacious intervention.

Pain on injection after Etomidate has been attributed to the vehicle (propylene glycol) in which drug is dissolved. Pain is eliminated when Etomidate is dissolved in lipofundin[21] (medium chain triglycerides) and this preparation has now been approved and is available in numerous countries. However, aqueous solutions of Propofol and Etomidate are reported to cause less pain on injection.

Table 9 shows significant number of patients had pain on injection in Propofol group (38%) as compared to Etomidate group (12%).

Sowinski et al[23] and Kaur et al[13] also observed lower incidence of pain with Etomidate.

However due to continuous oxygen supply, no significant difference in Spo_2 was detected between the two groups.

In our study we did not find any significant nausea and vomiting in both groups. However previous studies found that incidence of nausea and vomiting was more in Etomidate group compared to Propofol group.

No other complications were noted in both Etomidate and Propofol groups.

Recovery time was comparable and statistically insignificant in both groups.

Limitation of study:

Our study design had some limitation. The first is that we did not measure plama cortisol and adrenocorticotropic hormone levels. It has been well known that adrenocortical suppression is one of the most important adverse effects of Etomidate. Although Etomidate causes adrenocortical suppression, a single injection to induce anaesthesia will only produce a transient and clinically insignificant interference with adrenocortical function. Other limitation is that the study was conducted on a single centre with small group of patients with normal LV function which will truly not reflect for very old age patient with relatively unstable haemodynamics.

Large multi-centric trials, on varied patient categoies, undergoing different surgical therapies may be needed to further validate the obtained results.

Conclusion:

According to our study, patients induced with Propofol had significant decrease in systolic, diastolic and mean arterial pressures at 1 to 3 minute after induction as compared to Etomidate. Heart rate changes were not significant between the two groups. Incidence of pain on injection was more with Propofol group while incidence of myoclonus was significantly high in Etomidate group however myoclonus was not reported in Propofol group. So these characteristics indicate that Etomidate is better as an induction agent in terms of haemodynamic stability.

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