INDUCTION OF ANAESTHESIA WITH ETOMIDATE IN LIPID EMULSION: A RANDOMIZED COMPARISON WITH THIOPENTONE AND PROPOFOL

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ABSTRACT

Intravenous induction is smooth, fast and pleasant. In search for alternative to thiopentone, various agents such as propofol, etomidate are introduced.

AIM OF STUDY

Present study is undertaken to evaluate induction characteristics and haemodynamic responses and side effects of etomidate as an intravenous induction agent in comparison with thiopentone and propofol.

MATERIAL AND METHODS

Seventy five ASA I and II patients between 18 -50 years undergoing elective surgical procedures were randomly divided in to 3 groups of 25 patients each. Each group received either etomidate or propofol or thiopentone as an induction agent. Time taken for induction, heart rate, blood pressure, pain on injection of drug and severity of myoclonus were recorded. BP and HR recorded at pre-induction, after induction at one minute intervals till 5 minutes, thereafter at 5-minute intervals.

RESULTS

Time taken for induction was almost same in all groups. Heart rate was increased in thiopentone and etomidate groups. Blood pressure was decreased significantly in propofol group whereas blood pressure was well maintained in etomidate group. Pain on injection with etomidate lipuro was much less than propofol. Myoclonic movements were much higher in etomidate group.

CONCLUSION

Etomidate is more cardio stable agent.

KEYWORDS

Etomidate Lipuro, Propofol, Haemodynamics, Myoclonus, Induction Agent.

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INTRODUCTION

Intravenous mode of induction of anaesthesia was found to be smooth, fast and pleasant and enable to control the dosage administrated. The recovery was much quicker and pleasant due to lack of the unpleasant side effects of vomiting, nausea and headache. Thiopentone was first administered by water and Lundy in 1934 has proved very useful as an IV anaesthetic, it remained the standard drug against which all the recently introduced drugs compared.

But the thiopentone has a long half-life, which makes it less ideal use in ambulatory patients and can result in accumulation on repeated doses or as a continuous infusion. Thus there is a need for short acting and effective intravenous anaesthetic agent. It should maintain haemodynamic stability. These can be used safely in outpatient or day care surgery and patients can be discharged free from the side effects.

So the above limitations provided the incentive for continuous search for an ideal IV anesthetic agent that is chemically different from barbiturates which is potent and also has wide margin of safety.

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Such non-barbiturate group of drugs are etomidate and 2-6 di-isopropyl phenol (Propofol) being given a trial in the recent times.

The present study undertaken to evaluate induction characteristics, haemodynamic responses and side effects with etomidate as an intravenous induction agent in comparison with thiopentone and propofol.

MATERIAL AND METHODS

Seventy five patients, ASA grade I and II patients of both sexes between 18 to 50 years undergoing elective general, gynaecological or orthopedic surgical procedures were selected for this study.

Complete pre-anaesthetic check-up done for all the patients, a detailed history was taken and complete physical examination performed and presence of any organic medical disorder was excluded. Patients with history of allergy to lipid emulsion or primary or secondary dysfunction of the adrenal cortex (eg. secondary to steroid medication) were excluded from the study.

Institutional committee approval obtained for the study. On the day of surgery informed consent obtained from each patient.

Patients were divided in to 3 groups of 25 patients each by sealed envelope method. Group E received etomidate 0.3 mg/kg, group P received propofol 2mg/kg and group T received thiopentone 5mg/kg as IV induction agent.

Venous access was secured with 18G intravenous cannulae over right and left forearm veins. Right cannula was utilized solely for the injection of IV induction agent.

Left intravenous access utilized for injection of all other drugs and IV fluids. All the patients were pre-medicated with 2µg/fentanyl, Inj. Glycopyrrolate 0.2mg and inj. midazolam 1mg intravenously.

After pre-oxygenation each group received appropriate induction agent through right venous access followed by clearing volume of 10ml ringer lactate was given. Inj. vecuronium bromide 0.1mg/kg was injected through left venous access and patient was ventilated with 50:50 percent N_2O and O_2. After 3 minutes endotracheal intubation was performed. Anaesthesia was maintained with oxygen and nitrous oxide, vecuronium bromide and inhalational agent isoflurane 1% and patient's respiration was controlled. At the end of surgery patient neuromuscular blockade was reversed with mixture of glycopyrrolate and neostigmine. After full recovery patients were shifted to post-operative ward for further observation.

Patients were intraoperatively monitored with non-invasive blood pressure, ECG, heart rate, O_2 saturation and $ETCO_2$.

The following parameters were observed:

1. Time taken for induction: It is the time interval between starting of injection of induction agent to loss of eyelash reflex measured in seconds.
2. Heart rate.
3. Blood pressure.
   Heart rate and blood pressure were recorded preoperatively and after premedication, after injection of induction agent then after every 1 minute till 5 minutes, then after every 5 minutes.
4. Pain on injection: was graded as follows.[1]
   1. No pain.
   2. Verbal complaint of pain.
   3. Withdrawal of arm.
   4. Both verbal complain and withdrawal of hand.

Severity of myoclonus was graded as follows.[2]

1. No myoclonus.
2. Minor myoclonus.
3. Moderate myoclonus.
4. Severe myoclonus.
5. Post-operative nausea and vomiting if any noted.
6. Post-operative venous redness, swelling, induration and pain will be noted by examination the site of injection daily for 3 days postoperatively.

STATISTICAL ANALYSIS

In our study data was expressed as mean + standard deviation where appropriate, statistical analysis. Probability values <0.05 were considered as statistically significant.

OBSERVATION AND RESULTS

GROUPS	DRUG	NO. OF PATIENTS
E	Etomidate	25
P	Propofol	25
T	Thiopentone	25

Table 1: Division of patients in groups

	Group E	Group P	Group T
Age (Yrs) Mean±SD (Range)	31.3± 11.7 (18 – 50)	29.64± 10.14 (19 – 50)	27.45 ± 10.14 (18 – 50)
Weight (Kgs) Mean±SD (Range)	56.9 ± 4.84 (50 – 65)	56.4 ± 4.91 (48 – 65)	55.6 ± 4.91 (48 – 66)
Sex ratio Male/Female	12/13	16/9	13/12

Table 2: Anthropometric Data

The groups were compared for physical characteristics (Age, weight), which were comparable and difference is not significant (p>0.001) in three groups.

Group	Induction Time in Seconds Mean±SD
E	23.44±2.9
P	23.4±3.08
T	21.96±3.42

Table 3: Time taken for Induction

There was statistically insignificant difference in the induction time with all the three groups (P >0.001, the induction time was almost same in the three groups).

Heart Rate	Group E	Group P	Group T	P value
Baseline	91±15	86±7	85±9.1	NS
1min.after induction	92±14	82±8.7	100±13	NS
2min.after induction	91±14	82±8.7	104±16	P<0.001*
3min.after induction	92±13.2	82±8.7	104±15.2	P<0.001*
4min.after induction	102±12.8	89±7.6	113±13	P<0.001*
5min.after induction	99±13	89±7.6	104±14	NS
10min.after induction	91.4±13.3	80±8.2	95±15	NS

Table 4: Heart Rate variables three groups at different time points

NS – not significant * statistically significant

Systolic BP	Group E	Group P	Group T	P value
Baseline	114±12	121±10.5	112±5.75	NS
1min.after induction	107±9.5	104±7.52	100±5.6	NS
2min.after induction	104±9.9	97.8±6.73	98.4±6.3	P<0.001*
3min.after induction	106±14	93.8±6.98	101.±10.4	P<0.001*
4min.after induction	121±9.82	110±7.55	122±8.77	NS
5min.after induction	116±11	113±9.66	116±10.5	NS
10min.after induction	111±11.2	113±8.34	112±10.5	NS

Table 5: Systolic Blood pressure variables three groups at different time points

NS – not significant * statistically significant

Diastolic BP	Group E	Group P	Group T	P value
Baseline	72±7.6	77.4±5.78	70.6±6.4	NS
1min.after induction	70±7.7	65.9±6.09	65.6±4.51	NS
2min.after induction	68±8.8	61.1±5.85	63.6±4.68	P<0.001*
3min.after induction	69.7±9.88	59.7±5.85	64.8±9.7	P<0.001*
4min.after induction	79.1±10	70±6.33	79.4±9.87	NS
5min.after induction	75±9.4	72.2±8.44	73.3±10.2	NS
10min.after induction	74.8±9.57	72±6.51	69.5±10.1	NS

Table 6: Diastolic Blood pressure variables three groups at different time points

Mean Arterial Pressure	Group E	Group P	Group T	P value
Baseline	85±9	91.8±7.01	84.1±5.83	NS
1min.after induction	82.2±7.59	78.3±6.46	76.8±4.29	NS
2min.after induction	80±9.4	73.7±5.44	74.4±4.66	P<0.001*
3min.after induction	81±11	71.7±5.35	76±9.49	P<0.001*
4min.after induction	90±9.7	83.2±6.3	93.2±9.91	NS
5min.after induction	88.2±9.41	85.4±7.0	93.2±9.91	NS
10min.after induction	86.8±9.5	85.4±7.07	82.3±7.66	NS

Table 7: Mean Arterial pressure variables three groups at different time points

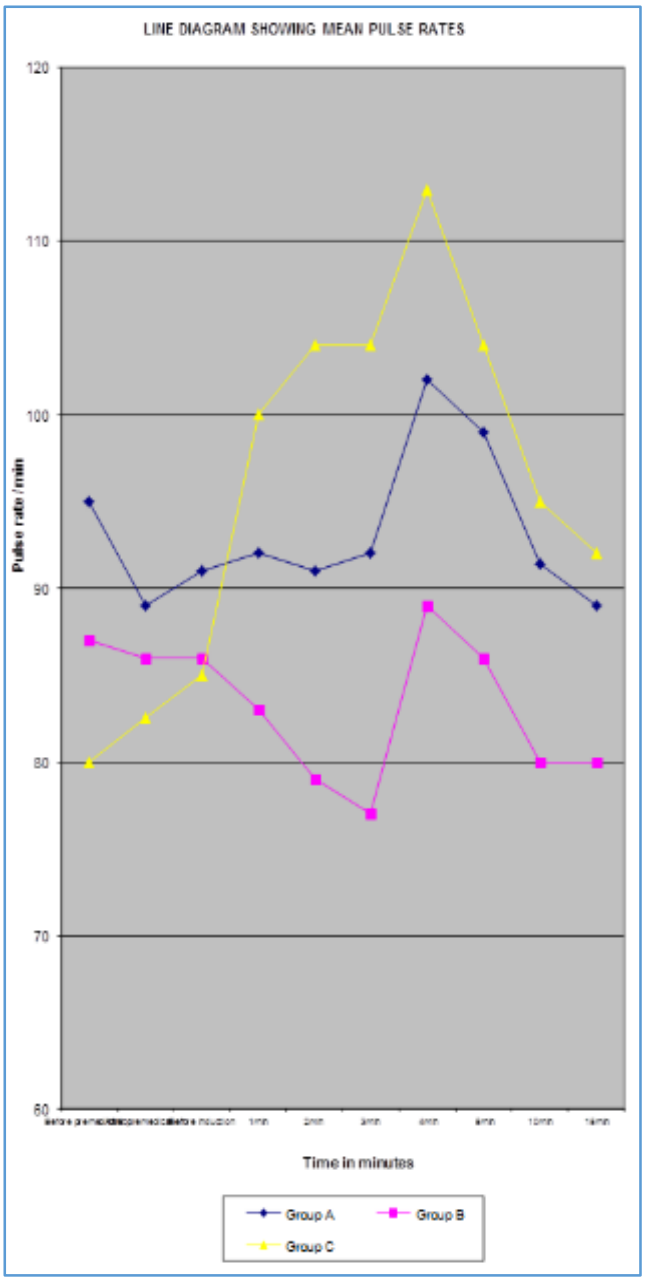
NS – not significant * statistically significant

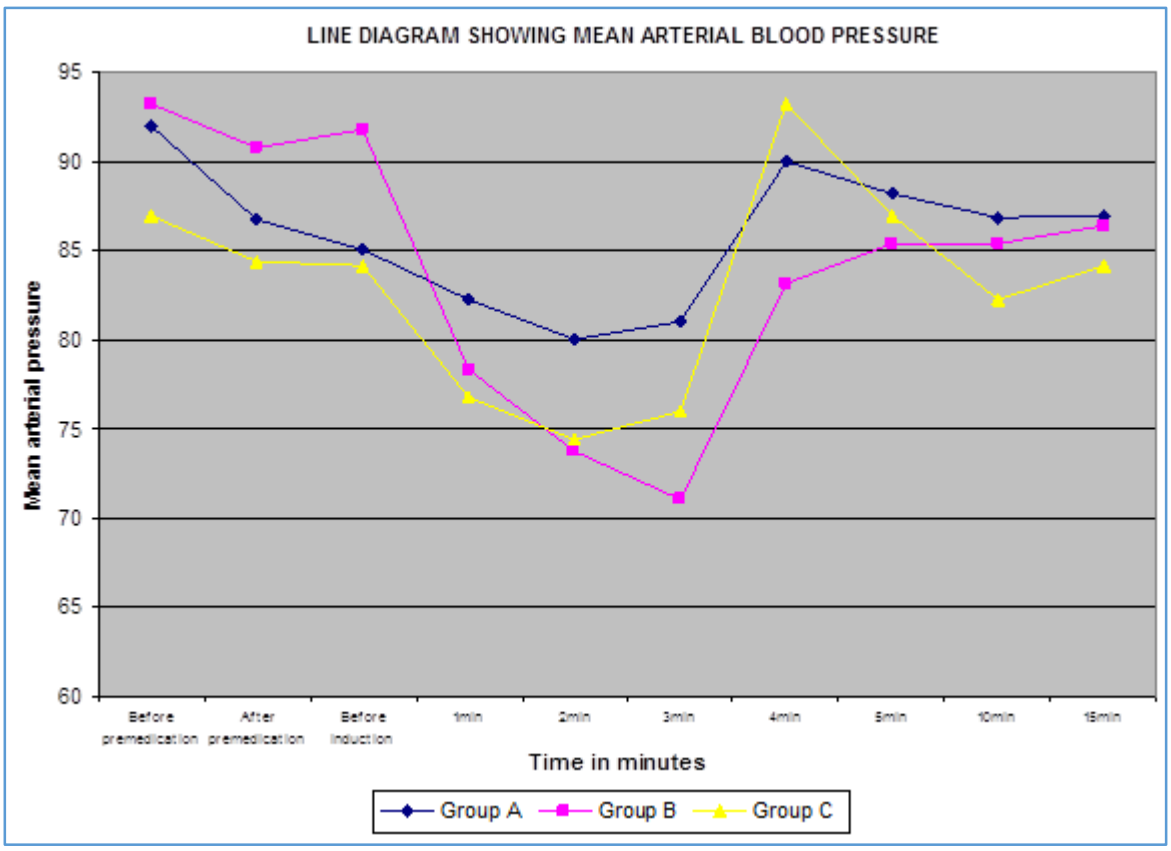
Baseline haemodynamic values before induction in three groups were similar and there is no statistical significant difference. (p>0.001).

In etomidate group, there was an insignificant increase in pulse rate after induction, in the thiopentone group; there was increase in pulse rate in the range of 5-20 beats/minute. In propofol group there was significant fall in pulse rate, systolic diastolic and mean arterial blood pressure compared with etomidate and thiopentone group. In thiopentone group there was raised in pulse rate but there is statistically significant fall in systolic, diastolic and mean arterial blood pressure compared with etomidate group. (p<0.001).

The mean arterial blood pressure is insignificant fall with etomidate compared with thiopentone and propofol.

The haemodynamic values are raised in three groups at 4th minute, but the rise is statistically insignificant. (p>0.001). Haemodynamic values coming to pre-induction values in three groups after 5 minutes after induction. (P >0.001).





	Group E	Group P	Group T
Pain on injection	3	5	0
Myoclonus	7	2	0
Nausea & vomiting	9	2	3
Venous sequelae	3	8	3

Table 8: Other Complications

In our study, pain on injection with etomidate in lipid emulsion was much less (12%) than propofol group (20%) and no one complained pain with thiopentone induction. Spontaneous movements during induction with etomidate (28%) were much higher than the propofol group (8%). Postoperative nausea and vomiting was least with propofol group (3%), highest in etomidate group (36%). Postoperative venous redness highest in propofol group (32%) compared to etomidate and thiopentone groups (12%).

DISCUSSION

Ideally an intravenous anaesthetic agent should induce sleep in one arm brain circulation time. The recovery should be quicker, with minimal cardiovascular upset and pleasant induction with minimal side effects (Vomiting, nausea and headache).

Etomidate is a hypnotic agent causing minimal histamine release and stable haemodynamic profile. In the present prospective randomized study effect of intravenous etomidate was evaluated and compared with intravenous propofol and thiopentone.

In present study the induction time was almost same in the three groups and equivalent to the one arm brain circulation. There was statistically insignificant and comparable in the induction time with all the three groups in present study. Doenicke A (1974) reported that the onset of anaesthesia after a routine induction dose etomidate is rapid onset of action and equivalent to that obtained with an induction dose of thiopentone or methohexital.[3] Saricaoglu F et al. (2015) reported statistically significant prolongation of induction time with etomidate compared to propofol, using time to reach BIS to 40 as end point of induction whereas in present study we have taken loss of eyelash reflex as criteria for induction time.[4]

Gooding JM, et al. (1977) studied effect of etomidate on the cardiovascular system and reported that an induction dose of etomidate given to cardiac patients for non-cardiac surgery results in almost no change in heart rate, mean arterial pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, central venous pressure and cardiac index.[5]

Coates DP, et al. (1987) studied haemodynamic effect of infusion of emulsion formulation of propofol. They reported that propofol decrease systolic blood pressure, diastolic and mean arterial pressure associated with decrease in cardiac index.[6]

Eckstein JW, et al. (1961) reported that the primary cardiovascular effect of thiopentone induction is peripheral vasodilatation resulting peripheral pooling of blood in the venous system, decease in cardiac contractility, which causes the decrease in arterial pressure and increase in heart rate.[7]

Saricaoglu F, et al. (2015) reported significant decrease in mean and systolic blood pressure in propofol group compared to etomidate.[4] Similar findings also reported by Stephan et al. (1986), Kaushal et al. (2015), Singh R, et al. (2015).[8,9,10]

Our study is correlated with above studies. In present study haemodynamic values are maintained near to the base line values in the etomidate group. In the propofol group there was statistically significant fall in the pulse rate, systolic blood pressure, diastolic blood pressure and mean arterial pressures. In the thiopentone group, there was statistically significant fall in the systolic blood pressure, diastolic blood pressure and mean arterial pressure compared with the pre induction values. The haemodynamic values were touched to the base line values after 5th minute in all three groups.

Pain on injection is a problem with the use of propofol. Addition of lidocaine to the propofol solution is commonly practiced, but despite this the incidence of pain on injection remains unacceptably high (20-39%).[1,4] Solvent used in etomidate causes pain on injection. The side effects of etomidate dissolved in PG can be eliminated while retaining the profile of actions when it is dissolved in lipofundin (medium chain triglycerides).[1] The new lipuro emulsion preparation of etomidate has decreased the incidence of adverse effects such as pain on injection, phlebitis and myoclonus. In our study, pain on injection with etomidate in lipid emulsion was much less (12%) than propofol group (20%) and no one complained pain with thiopentone induction. Our results correlated with other studies.[1]

Reddy RV, et al. (1993) reported that spontaneous movements occur in 50% to 80% of patients, receiving etomidate in the absence of pre medication. Prior administration of an opioid or benzodiazepine may decrease the incidence of spontaneous movements associated with etomidate administration.[11]

Doenicke AW, et al. (1999) reported in there study that the incidence and intensity of myoclonus following the administration of etomidate is dose related and suppressed by pre-treatment with small dose of etomidate (0.03 to 0.075 mg/kg) before administration of an induction dose.[12]

In our study spontaneous movement's incidence was much higher in etomidate group than propofol group. The incidence and severity of postoperative nausea and vomiting was least with propofol.

Wagner RL, et al. (1984) reported that intravenous anesthetic etomidate for prolonged sedation has been associated with low levels of plasma cortisol and increased mortality.[13] They measured the cortisol and aldosterone responses to ACTH stimulation in five patients receiving etomidate and they also studied the direct effects of etomidate on enzymes in the rat steroidogenic pathway. One patient who was receiving a 20-hour infusion of etomidate (1.3 to 1.5mg per kilogram of body weight per hour) had marked adrenocortical suppression that was still evident four days after etomidate was discontinued.

Four surgical patients receiving etomidate during their operations were all found to have adrenal suppression four hours after the operation. In rat adrenal cells, etomidate produced a concentration-dependent blockade of the two mitochondrial cytochrome P-450-dependent enzymes, cholesterol-side-chain cleavage enzyme, and 11 beta-hydroxylase without evident inhibition of the microsomal enzymes in the glucocorticoid pathway. Physicians should be aware that etomidate inhibits adrenal steroidogenesis, and they should consider treating selected patients with corticosteroids if etomidate is used. In the present study, the cortisol levels were not measured.

SUMMARY AND CONCLUSION

The present study was carried out on 75 patients, divided randomly into three groups, 25 patients for each group. Time taken for induction, haemodynamic changes after induction and side effects were studied in three groups and results were statistically analyzed.

The following conclusions were drawn from our present study:

1. Time taken for induction in three groups was comparable and it is statistically insignificant.
2. Pulse rate remained more stable with etomidate during induction than propofol and thiopentone. There was fall and rise of pulse rate with propofol and thiopentone respectively.
3. Blood pressure was more stable with etomidate induction whereas decrease of blood pressure was observed with propofol and thiopentone.
4. Pain on injection is more with propofol compared to etomidate.
5. Spontaneous movements were more with etomidate compared to propofol.

Hence, it is concluded that etomidate is more cardiac stable.

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