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Original Article

Anaesthesia Section

# A Randomised Clinical Study on Haemodynamic Effects of Thiopentone and Etomidate as Induction Agents in General Anaesthesia

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## ABSTRACT

**Introduction:** Thiopentone and Etomidate like anaesthetic agents are often used for induction during anaesthesia. Induction is the preliminary step in general anaesthesia and the search for a perfect agent is a persistent quest for the anaesthetist.

**Aim:** To compare the haemodynamics status and safety profile of thiopentone and etomidate as induction agent.

**Materials and Methods:** The present randomised clinical trial was conducted on 120 patients, of either sex between 18-45 years of age belonging to American Society of Anesthesiology (ASA) grade I and II. They were divided into two groups with 60 patients in each. Group T patients were induced with injection (inj.) thiopentone 5 mg/kg and group E patients were induced with inj. etomidate 0.3 mg/kg as an induction agent. Vital parameters like heart rate, non invasive blood pressure of all patients were recorded at baseline (before induction), after induction and post intubation at an interval of 1, 3 and 5 minutes. Adverse effects during intraoperative period were noted and later analysed. Quantitative data were analysed using Unpaired t-test to assess the changes within group.

**Results:** Out of 120 study participants, 70 were males and 50 females with the mean age of 35.63±12.20 and 34.50±7.46 in group T and group E respectively. The induction time in the Group E (27.5±3.31 seconds) was significantly less ($p<0.05$) as compared to group T (31.71±4.8 seconds). Change in heart rate was lesser ($p<0.05$). There were no significant changes in the respiratory rate in either at any stage of anaesthesia. Adverse effects like apnoea were evident more in the group T patients whereas pain at injection site and myoclonus was more evident in the group E patients. But, the overall safety profile of etomidate was better than thiopentone.

**Conclusion:** Etomidate found to be more effective, rapid acting induction anaesthetic agent with good cardiovascular stability and respiratory stability with least incidences of apnoea as compared to thiopentone.


**Keywords:** Cardiovascular changes, Efficacy, Inducing anaesthetic agents, Safety

## INTRODUCTION

An ideal inducing agent should have a rapid and smooth onset of action, haemodynamic stability, minimal respiratory effects, rapid clearance and no adverse effects in postoperative period. Induction being an initial step during general anaesthesia often brings haemodynamic changes in the system with different induction agents at variable magnitude.

Thiopentone introduced in 1934 was one of the most significant advances in the general anaesthesia. It is a derivative of barbituric acid, sulphur analogue of pentobarbitone. It was considered the gold standard inducing agent because of its rapid onset of action and short duration of action without excitatory effects as seen during induction with inhalation gases [1,2]. But, there are some side-effects like increased incidence of laryngospasm, bronchospasm and allergic reaction. It also causes peripheral vasodilatation, decrease in blood pressure, increase in heart rate and direct negative inotropic effect on heart [1]. Due to its cardiorespiratory depressive effects, thiopentone is not regarded as the drug of choice in haemodynamically unstable patients [2,3].

Etomidate is an imidazole derivative, non opioid intravenous anaesthetic agent. It is short acting drug, used for induction and maintenance of anaesthesia [4,5]. The onset of action is in one arm brain circulation. It provides faster onset and rapid recovery with haemodynamic stability and minimal respiratory depression. The cardiovascular stability and rapid recovery are the features that commend its use as an induction agent in sick and shocked patients [3]. The most important side-effects of etomidate are nausea and vomiting that may lead to aspiration in patients [6-8]. Intravenous injection of etomidate would cause a burning sensation. But, its use declined due to reports of adrenocortical suppression [9]. Later, it was found that adrenal suppression by etomidate induction is not so significant [10]. Lack of new reports of adrenocortical suppression against many benefits led to a renewed interest and its reintroduction to therapeutics. Many previous studies had concluded that the induction of anaesthesia by etomidate would lead to a stable haemodynamic condition for performing laryngoscopy and endotracheal intubation [7,8,11].

Thus, inconclusive remarks on the merits as well as demerits of both these two inducing agents as evident from the above-mentioned studies create a void space in the knowledge on these two fairly promising agents. Since, most of the studies currently in the public domain are done abroad and no recent Indian study was conducted. Hence, this study made a humble attempt with the primary objective to compare the haemodynamic status of the patients and the secondary objective was to estimate the safety profile of thiopentone and etomidate in a tertiary care hospital of Eastern India.

## MATERIALS AND METHODS

A randomised clinical (single-blinded) study was conducted in the General Surgery operation theatres of Bankura Sammilani Medical College, Bankura, West Bengal, India under the supervision of the Department of Anaesthesiology during January 2017 to June 2018 (total 18 months). A prior approval from the Institutional Ethics Committee (Memo No. BSMC/Aca/3868 dated 24.11.2016) was obtained. A written informed consent was obtained from all patients who were included in the study.

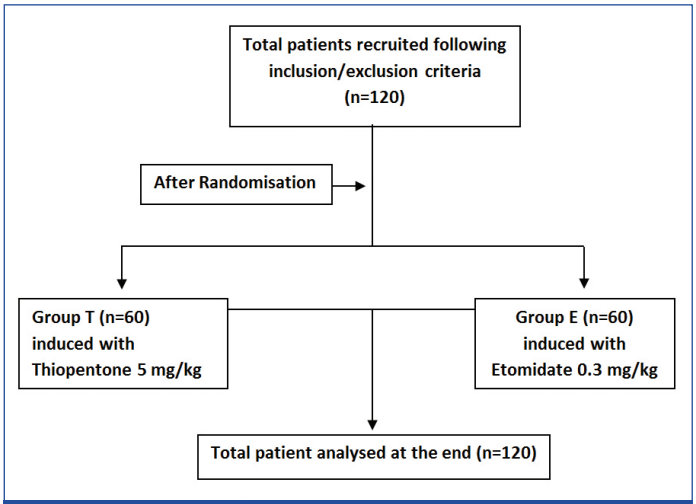
**Sample size calculation:** With 5% margin of error and a 95% confidence interval considering a sample proportion of 50% and expecting a 10% dropout, the sample size was calculated around n=110 which was rounded-up to 120 patients.

Patients were selected after thorough preanaesthetic assessment and investigations. All patients were visited and evaluated thoroughly on the previous day of surgery. Thorough history and complete physical examination were undertaken. Routine relevant laboratory investigations were done.

**Inclusion criteria:** Patients aged 18-45 years of either sex with ASA grade I and grade II and Mallampati score (MP) grade 1 and 2 were selected for the study.

**Exclusion criteria:** Patients refusing general anaesthesia/preferring regional anaesthesia, ASA grade III & IV patients, emergency surgeries and patient with history of hypersensitivity to any of above drugs were excluded from the present study.

The selected patients were randomised with online software Random© into two groups (n=60) each; group T patients were induced with thiopentone 5 mg/kg and group E patients received etomidate 0.3 mg/kg. The patients were blinded during group allocation and were unaware of the type of study drugs administered to them. Only the study investigators knew their group allocation [Table/Fig-1].




**[Table/Fig-1]:** Flow chart of the study.

In the operating room, vital parameters like pulse rate, non invasive blood pressure, oxygen saturation of all patients was monitored by using pulse oximeter, Electrocardiography (ECG), sphygmomanometers at an interval of 1, 3 and 5 minutes. Prior to the induction of anaesthesia, all patients were premedicated with injection fentanyl 2 microgram per kg and inj. glycopyrrolate 0.2 mg intravenously 10 minutes before induction. Patients were pre-oxygenated with 100% $O_2$ for 3 minutes. Inducing agents either inj. etomidate 0.3 mg/kg (group E patients) or inj. thiopentone 5 mg/kg (group T patients) administered i.v. within 30 to 60 seconds. Patients were asked to take deep breaths.

The induction time was calculated from the start of injection of either drug to the loss of eyelash reflex. Cessation of the respiration for more than 10 seconds was considered apnoea. Apnoea (if any) was treated by ventilation with 100% of oxygen. After the 3 minutes of induction, the patients were intubated with appropriate size endotracheal tube following administration of relaxant i.e., injection succinylcholine 2 mg/kg. Anaesthesia was maintained with 33% oxygen and 66% nitrous oxide plus non depolarising muscular relaxants (vecuronium 0.05 mg/kg). At the end of surgery, when the patient had respiratory efforts, patients were reversed with injection Neostigmine 0.05 mg/kg plus injection glycopyrrolate 0.01 mg/kg and extubated. The patients of both the group were later shifted to the recovery room and followed-up. Adverse effects (if any) during intraoperative period were noted and later analysed.

## STATISTICAL ANALYSIS

All data were presented as mean and standard deviation. Quantitative data were analysed using Unpaired t-test to assess the changes within group. The statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 20.0. A p-value of less than 0.05 was considered statistically significant.

## RESULTS

The age and weight of both groups (presented as mean±SD) shows no statistically significant difference as p-value remains ≥0.05 [Table/Fig-2]. The baseline haemodynamic parameters of the study groups showed no significant statistical difference [Table/Fig-3]. Preoxygenation done with 100% moist oxygen for 3 to 5 minutes to all the participants of both the study groups and their oxygen saturation were maintained around 98%-99% during the entire observation.

| Variables | Group T (n=60) | Group E (n=60) | p-value (Chi-square test) |
|---|---|---|---|
| Sex (Male:Female) | 37:23 | 33:27 | 0.459 |
| Age (years) | 35.63±12.20 | 34.50±7.46 | 0.541 |
| Weight (kg) | 49.98±3.33 | 50.10±39 | 0.843 |

**[Table/Fig-2]:** Demographic pattern of the study population.
Group T: Thiopentone ; Group E: Etomidate

| Variables (Baseline) | Group T (n=60) | Group E (n=60) | p-value (Mann-Whitney U test) |
|---|---|---|---|
| Heart rate (beats/minute) | 82.25±2.10 | 82.46±5.41 | 0.77 |
| Systolic BP (mm of Hg) | 124.37±5.94 | 124.23±69 | 0.90 |
| Diastolic BP (mm of Hg) | 77.56±4.47 | 76.33±4.8 | 0.7 |
| Mean arterial BP (mm of Hg) | 92.55±2.93 | 91.93±3.37 | 0.287 |
| Respiratory rate (beats/minute) | 13.83±1.16 | 13.96±1.19 | 0.53 |

**[Table/Fig-3]:** Comparison of haemodynamic parameters at baseline in both the study group.
Group T: Thiopentone; Group E: Etomidate; BP: Blood pressure; All parameters expressed in (mean±standard deviation)

Time for induction in etomidate was significantly shorter as compared to thiopentone group [Table/Fig-4]. The heart rate showed no significant change in both the study group after premedicated but, there was slight increase in heart rate in group T which was not statistically significant. Following induction, heart rate decreased in group E. There was initially an increase in heart rate in group T from the baseline values to that at 1 minute and then a decrease at 3 minutes.

| Patients (n=60) | Induction time (seconds) | p-value (Chi-square test) |
|---|---|---|
| Group T | 31.71±4.8 | <0.05 |
| Group E | 27.5±3.31 | |

**[Table/Fig-4]:** Comparison of induction time between the two study groups.
A p-value of less than 0.05 was considered statistically significant.

There was a significant increase in heart rate after intubation in group T compared to the group E [Table/Fig-5].

| Heart rate* at different time interval | Group T (n=60) | Group E (n=60) | p-value (Fisher's exact test) |
|---|---|---|---|
| Baseline | 82.25±2.10 | 82.46±5.4 | 0.78 |
| **Induction time** | | | |
| 1 minute | 83.61±5.2 | 81±2.46 | 0.17 |
| 3 minutes | 82.28±5.36 | 82.21±5.40 | 0.14 |
| **Post intubation** | | | |
| 1 minute | 103.87±4.9 | 102.17±5.24 | **<0.05** |
| 3 minutes | 91.75±8.19 | 84.95±5.25 | **<0.05** |
| 5 minutes | 84.58±5.31 | 81.78±4.3 | **<0.05** |

**[Table/Fig-5]:** Comparison of heart rate at different time interval.
*Beats/minute (bpm), A p-value of less than 0.05 was considered statistically significant.

During induction, there was decrease in respiratory rate in both the groups [Table/Fig-6]. There was initially an increase in etomidate group, preinduction rate was 13.95±1.16 beats/minute. After induction, rate

increase to 14.6±1.21 beats/minute and 13.40±1.83 beats/minute at 3 minutes, respectively. The respiratory rate was fixed to 12 rates/min after 1 minute of intubation in both the groups and later, it was changed according to patient profile. The mean arterial pressure in thiopentone group were found to be significantly greater ($p<0.05$) as compared to etomidate group in the post intubation period [Table/Fig-7]. Incidences of apnoea occurred more frequently in thiopentone group (18%) compared to the etomidate group (5%), whereas pain on injection and myoclonus was observed more in the etomidate group [Table/Fig-8].

| Respiratory rate at different time interval (breaths per minute) | Group T (n=60) | Group E (n=60) | p-value (Fisher's exact test) |
|---|---|---|---|
| Baseline | 13.83±1.19 | 13.96±1.16 | 0.53 |
| **Induction time** | | | |
| 1 minute | 13.63±1.5 | 12.81±1.9 | 0.8 |
| 3 minutes | 14.6±1.21 | 13.40±1.83 | 0.9 |
| **Post intubation** | | | |
| 1 minute | 12 | 12 | -- |

**[Table/Fig-6]:** Comparison of respiratory rate in the two study groups.
Group T: Thiopentone ; Group E: Etomidate

| Mean arterial pressure at different time interval | Group T (n=60) | Group E (n=60) | p-value (Fisher's exact test) |
|---|---|---|---|
| Baseline | 92.55±2.93 | 91.93±3.37 | 0.287 |
| **Induction time** | | | |
| 1 minute | 90.66±5.6 | 91.60±5.46 | 0.89 |
| 3 minutes | 90.75±2.6 | 92.25±4.33 | 0.38 |
| **Postintubation** | | | |
| 1 minute | 101.4±4.96 | 98.5±4.6 | **<0.05** |
| 3 minutes | 97.78±5.8 | 92.46±4.19 | **<0.05** |
| 5 minutes | 98±4.52 | 93.11±43 | **<0.05** |

**[Table/Fig-7]:** Comparison of mean arterial pressure (mm of Hg) between the two study groups.
A p-value of less than 0.05 was considered statistically significant.

| Adverse drug effect | Group T (n=60) | Group E (n=60) |
|---|---|---|
| Apnoea | 11 (18%) | 3 (5%) |
| Pain on injection | 5 (8%) | 15 (25%) |
| Myoclonus | 0 (0%) | 15 (25%) |

**[Table/Fig-8]:** Comparison of adverse drug effects recorded in the two study groups.

## DISCUSSION

An ideal intravenous induction agent should produce minimal disturbance of cardiovascular and respiratory functions, should induce sleep in one arm brain circulation time, should chemically be stable, non inflammable, non toxic, easy to administer. Induction is an important step, while administering general anaesthesia. Patients were susceptible to haemodynamic lability at the time of induction. Thus, an agent with least effect on haemodynamics would be the agent of choice.

In this study, the demographic profile of both study groups was comparable. The time of induction in the etomidate group was significantly shorter when compared with inj. thiopentone. The mean induction time in thiopentone group was 31±4.8 seconds and with etomidate group was 27±3.3 seconds ($p<0.05$) which is statistically significant. Similar findings were evident in the studies conducted by Shah SC et al., Batra RK, et al., where etomidate achieved a fast and smooth induction of anaesthesia [12,13]. These results were consistent with the present study i.e., the mean induction time with etomidate was shorter than the mean induction time with thiopentone.

The current study revealed that apnoea occurred more frequently in the thiopentone group (18%) than in etomidate group (5%). In etomidate group, there was a phase of hyperventilation followed by apnoea. This was statistically significant, and correlates with other studies by Batra RK et al., and Ghonem MM and Yamada T, also where they observed a high incidence of apnoea in thiopentone group (88%) compared to (12%) in etomidate group [13,14]. In this study, the incidence of pain during injection in patients was higher in the etomidate group (25%) and just 5% in the thiopentone group, which correlates with reports by Batra RK et al., and Jeffrey GL et al., [13,15].

Regarding heart rate, there was an increase in the thiopentone group compared to the etomidate group. During the 1st minute tachycardia was seen in thiopentone group. From 3 minutes onwards there was a tendency for decline in heart rate towards preanaesthetic value. The heart rate showed marginal increase when compared to the preinduction value in etomidate group which is not statistically significant. Harris CE et al., found that thiopentone increases the heart rate and returns to the preinduction level just prior to the intubation [16].

The respiratory rate tends to decrease in the thiopentone group at 1 and 3 minutes. The etomidate group showed increase in respiratory rate at 1 and 3, minutes after the induction. The present study correlates with the study conducted by Korgaonkar SV and Shetti RN [17]. Etomidate increases the respiratory rate slightly after induction. The incidence of myoclonus occurred in etomidate group is 25% and there was no myoclonus observed in thiopentone group in the present study. These findings are almost similar to reports published by Batra RK et al., [13]. There the incidence of myoclonus was 28% in etomidate group and none in thiopentone group. Gisele JL et al., also found that patients in whom anaesthesia was induced with etomidate had myoclonus more than thiopentone [15].

### Limitation(s)

The study was conducted in a single institute on a limited number of selected patient's undergone elective surgery. Also, the serum catecholamines which are the most important markers to assess the sympathoadrenal stress response to any stimulus and its level were not measured due to scarcity of the resources.

## CONCLUSION(S)

Induction with etomidate, demonstrated no significant change in heart rate, respiratory rate and mean arterial pressure. On top of that, the induction time was lesser with etomidate and the incidence of apnoea was also much less. Etomidate as compared to thiopentone found to be an effective, safe and rapid acting induction anaesthetic agent with good cardiovascular stability and respiratory stability.

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