Original Research Article

Comparative study of etomidate and fentanyl citrate with propofol (1%) and fentanyl citrate for total intravenous anaesthesia in short surgical procedures

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A B S T R A C T

Total intravenous anaesthesia (TIVA) is a combination of Induction agents, analgesic drugs and muscle relaxants, excluding simultaneous administration of any inhaled drugs. This study has major objective, to determine the efficacy of Etomidate and Propofol (1%) as anaesthetic induction agents in terms of Induction time, maintenance doses requirements and Recovery parameters. This study suggests that both Etomidate–Fentanyl citrate and propofol (1%)–Fentanyl citrate produced smooth induction, easy maintenance and quick recovery with only minor hemodynamic fluctuations makes them excellent combinations as TIVA technique. Etomidate is preferred over Propofol (1%) especially for hemodynamically unstable patients because of minimal effects on cardiovascular and respiratory system. hypotension and pain on injection was observed more frequently with Propofol (1%) while myoclonus with Etomidate. With these observations in mind and careful selection of patients, both agents appear similarly safe for use in elective and short surgical procedures.

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1. Introduction

Total intravenous anaesthesia (TIVA) is a combination of Induction agents, analgesic drugs and muscle relaxants, excluding simultaneous administration of any inhaled drugs.¹ Therefore it can be an effective alternative to inhalational anaesthesia² and for ambulatory surgery when the speed and completeness of recovery are important.³ Drugs used for TIVA should have quick onset, smooth induction, easy maintenance, quick recovery and minimal side effects. Various drugs have been tried singly or in different combinations from time to time in TIVA to provide balanced anesthesia, since no single drug can provide all the characteristics of an ideal intravenous agent. Over the past years, Propofol (1%) has been one of the commonly used drugs for induction of GA. Satisfactory rapid recovery, short half-life, rapid elimination from the blood circulation, causing less sedative affect and preventing nausea, vomiting are the reasons for using this drug more commonly.⁴ The most important side-effect of this drug is cardiovascular suppression leading to hypotension. Inducing anesthesia with Propofol (1%) (2–2.5 mg/kg) could lower blood pressure as much as 25–40% in all the patients regardless of any underlying conditions.⁵,⁶ Pain on injection and hypersensitivity reaction are other principle disadvantage of this drug. Etomidate is a carboxylated imidazole-derived non barbiturate; non-narcotic, hypnotic agent mainly used for induction of general anaesthesia. It has rapid onset of anaesthesia, short duration of action due to rapid distribution profile and rapid recovery without hangover effect due to fast metabolism by ester hydrolysis. The drug was reformulated using lipid emulsion and reintroduced in 2007 in India. In view of its pharmacologic properties, it has beneficial use in emergency and cardiovascular surgery; in 1-day surgery and short surgical procedures i.e. dilatation and curettage, Endoscopic procedures; in high cardiac risk patients; in patients with anticipated airway problems and
in anaesthesia for diagnostic and elective procedures, such as cardioversion.\(^7\) The major adverse effect associated with etomidate is the reversible adrenocortical suppression, although cortisol levels do not fall below the normal physiologic range.\(^8,9\) Transient myoclonus, incidence of nausea and vomiting, hiccups are another principal disadvantage observed. Fentanyl citrate is used extensively in TIVA now-a-days. It belongs to opioid group of drugs. It is hundred times more potent analgesic than morphine, and as a part of balanced anaesthesia it relieves pain, reduces somatic and autonomic response to airway manipulation, and provides hemodynamic stability and lesser respiratory depression.\(^10\) The combination of these drugs provides complete and balanced anaesthesia and has advantages such as high potency, lower dosages and fewer side effects. In the quest for complete anaesthesia, various combinations of these new drugs have been tried which include Etomidate–Fentanyl, Etomidate–Ketamine, midazolam–ketamine, propofol–ketamine, propofol–fentanyl and many more each with varying results.

2. Aims and Objectives

1. To compare the hemodynamic effects of Etomidate and Propofol (1%) as induction agents in short surgical procedures.
2. To compare the efficacy by evaluating induction time, maintenance and recovery duration of Etomidate and Propofol (1%) for total intravenous anaesthesia in short surgical procedures.
3. To compare the safety by means of recording any adverse events during and after the completion of surgical procedures.

Intravenous anaesthetic agents are commonly used to induce anaesthesia which is then maintained with an appropriate inhalational agent. Induction with TIVA approach is usually smoother and more rapid than that associated with most of the inhalational agents; so, the patient passes through excitatory stage of anaesthesia nearly instantaneously, with fewer risks.\(^11\) Intravenous anaesthetics may also be used for maintenance either alone or in combination with an analgesic and a muscle relaxant; they may be administered as repeated incremental dose or by continuous i.v. infusion particularly for short surgical procedures. Till recently, inhalational agents have remained the routine choice for maintenance of anaesthesia. One of the principle reasons is the availability of sophisticated delivery systems for volatile anaesthetics, which allows the anaesthetists to have a fine degree of control on the concentration administered to the patient.\(^12\) Despite all these advantages, inhalational agents have their own drawbacks and shortcomings that are as follows:

1. Cost factor.

2. Different specific vaporizers require repeated maintenance.
3. Scavenging system is necessary; otherwise pollution of operation room environment is a big hazard.

TIVA has many advantages over inhalational anaesthesia such as

1. No operating room pollutions
2. Minimal cardiac depression
3. Lesser neuro humoral response
4. Decreased oxygen consumption
5. Avoids distension of air-filled spaces within the patient’s body, thus producing optimum operating conditions for the surgeon.
6. Avoids postoperative diffusion hypoxemia and decreases the incidence of postoperative nausea and vomiting (PONV).

In day care surgery, etc. Moreover, TIVA can be used not only in well-equipped hospital setting but at remote location also with only oxygen and ventilation facilities.\(^12\)

3. Material and Methods

This randomized single blinded prospective trial was conducted from October 2014 to August 2016. After approval from Institute Research Committee (IRC) for guided research of hospital, 100 patients aged between 18 to 60 years of both sex and ASA physical status I and II scheduled for short surgical procedure of less than 30 minutes like ICR therapy, Colonoscopy, Dilatation & curettage under Total Intra Venous Anaesthesia were taken for study. Written informed consent was taken from all patients.

3.1. Inclusion criteria

1. Age: 18-60 years,
2. ASA status: I and II,
3. Short surgical procedures less than 30 minutes

3.2. Exclusion criteria

1. ASA score greater than II
2. Surgical procedure lasted more than 30 minutes
3. Pregnant women
4. H/o of epilepsy/convulsion
5. H/o of drug/Alcohol abuse
6. Presence of steroid deficiency or on steroid medication
7. Patient refusal
8. Emergency surgery
9. Patient with history of hypersensitivity to Propofol /Etomidate
10. Mouth opening <2.5 cm
11. Patients with cardiovascular diseases like ischemic heart disease or hypertension
12. Bronchial asthma
13. Mallampati grade 3 and 4
14. Existence of considerable pathology in pharynx / larynx
15. Patient with GERD

Group allocation: 100 patients were randomly allocated in 2 Groups (n=50).

Group E (Etomidate) Induction with Inj. Etomidate (0.3 mg/kg) IV.

Group P (Propofol 1%) Induction with Inj. Propofol (1%) (2 mg/kg) IV.

Airway assessment like mouth opening, Mallampati grading, dentition, neck flexion and extension of all patients was done. Preoperative heart rate (HR), mean arterial blood pressure (MAP) and oxygen saturation (SPO2) were noted. All patients were kept nil per orally for 10 hours prior to surgery.

Inj. Glycopyrrolate 40-60 mcg/kg IV, Inj. Ranitidine 1 mg/kg IV, Inj. Ondansetron 0.1mg/kg IV and Inj. Fentanyl citrate 1 µg/kg IV was given 3 minutes before induction. For induction Group E received inj. Etomidate 0.3 mg/kg IV bolus over 10 seconds and Group P received inj. Propofol (1%) 2 mg/kg IV bolus over 10 seconds. After induction of anaesthesia, hemodynamic variables were recorded later 1 minute after loss of consciousness; this was confirmed by inability to respond to verbal commands and loss of eyelash and corneal reflex. Anaesthesia was maintained by intermittent boluses of Inj. Etomidate 0.1 mg/kg as needed or tolerated in Group E or by Propofol (1%) 0.5 mg/kg as needed or tolerated in Group P. Incremental doses of induction agents were given when the patient became light as evidenced by change in HR, B.P. and Respiratory rate and limb movements. Total numbers of incremental doses and Total dose were noted in both groups. When oxygen saturation was below 92% for more than 10 seconds or when apnea for more than 20 seconds, jaw thrust manoeuvre and ventilation with bag and mask were started with 100% O2. Heart rate, mean arterial blood Pressure, Respiratory rate and oxygen saturation were continuously monitored and recorded at 1, 5, 10, 15, 30 and 45 minutes after induction. Any incidence of pain on injection was noted after induction in both groups. Severity of pain was recorded as Grade 0-no pain, Grade 1-verbal complain of pain, Grade 2- withdrawal of arm, Grade 3- both verbal complain and withdrawal of arm. Any incidence Myoclonus was noted after induction in both groups. Severity of myoclonus was recorded as, Grade 0-no myoclonus, Grade 1- Short movement of body segment (eg: finger or shoulder), Grade 2- Slight movement of different muscle or muscle group of body (eg: face and leg), Grade 3- Intense clonic movement in two or more groups of muscle (fast abduction of limb).

3.3. Statistical analysis

The parameters recorded were entered on a computer and compared between the two groups using unpaired t test for continuous variables and chi-square test for contingency data. And statistical software from below mentioned site was used. Statistical software: www.Graph pad/instate3 software Significant Figure 1. SS- Statistically Significant (P: ≤ 0.05) 2. HS- Highly significant (P: ≤ 0.01)
3. NS- Not significant (P: > 0.05).

4. Observation & Results

100 patients, ages between 18-60 years of both sexes belonging to ASA Class I and II posted for short surgical procedures under Total Intravenous Anesthesia were selected for the study. Following observations were done.

Fig. 1: Peri operative changes in the heart rate

1. Showing HR at different time intervals. Baseline Heart rate were comparable among both groups with no statistical significant differences (p>0.05).
2. But Heart rate of both groups after 1 minute of induction were different both clinically and statistically (p<0.05).
3. But after that Heart rate among both groups are again not significant (p>0.05).

Fig. 2: Peri operative changes in the mean arterial blood pressure
Table 1: Demographic data: age, weight and duration of procedures (Values are mean ± SD).

<table>
<thead>
<tr>
<th></th>
<th>Group E</th>
<th>Group P</th>
<th>P-value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>45.78±9.38</td>
<td>41.92±11.50</td>
<td>0.069</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>50.74±7.70</td>
<td>50.7±8.07</td>
<td>0.979</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of procedure (min)</td>
<td>15.06±7.184</td>
<td>15.3±7.346</td>
<td>0.87</td>
<td>NS</td>
</tr>
</tbody>
</table>

1. Showing MAP at different time intervals. Baseline MAP were comparable among both groups with no statistical significant differences (p>0.05).
2. But MAP of both groups after 1, 5, 10, 15, 20, min of induction was different both clinically and statistically (p<0.05).
3. After 20 min MAP among both groups were again not significant (p>0.05).

1. Showing SPO2 at different time intervals. Baseline SPO2 were comparable among both groups with no statistically significant differences (p>0.05).
2. But after 1 min of induction there was transient fall of SPO2 in group P which was highly significant (p<0.05).
3. After 5,10,15,20, 30 & 45 min of induction SPO2 of both groups were not significant statistically (p>0.05).

1. Showing incidence of myoclonus among both groups. Which were only seen in group E (p<0.05). Severity of myoclonus was noted as grade 1 (12%), grade 2 (8%) in group E.
2. The recovery time was prolonged in group E than group P was highly statistically significant (p value <0.01).

1. Showing incidence of pain on injection site among both groups. Which was significantly higher in group P (30%) compared to only (6%) in group E, with p value <0.05.
5. Discussion

TIVA has been a subject of interest for all anesthesiologists. TIVA was initially attempted with a single drug (e.g., Sodium thiopentone, propofol, Ketamine) but was associated with side effects and no drug was found to give complete anesthesia. Therefore, various drugs have been used individually or in combination with the other drugs to produce rapid induction, good plane of surgical stage of anesthesia and at the end of surgery, smooth emergence and early recovery. This study has major objective, to determine the efficacy of Etomidate and Propofol (1%) as anesthetic induction agents in termed of Induction time, maintenance doses requirements and Recovery parameters. Perioperative adverse events that presented as the hemodynamic and respiratory changes and to compare the safety of induction agents in termed of incidence of adverse effects during and after completion of surgical procedures. Sagun Bhatia et al compared hemodynamic effects of intravenous etomidate versus propofol during induction and intubation showed sustained increase in HR throughout induction and intubation in Propofol group while it remained stable throughout in Etomidate group. Nadia et al compared etomidate- fentanyl versus propofol-fentanyl for sedation in colonoscopies showed heart rate remained stable throughout procedures in both groups. Results are also concordant with the study conducted by Ghafoor et al., Mehdad et al., Siidy J et al., The Mean Arterial Blood Pressure was comparable in both groups before induction, which was statistically not significant (p > 0.05). There was a fall in MAP in Group P with the maximum decrease at 1-minute post induction from the baseline. However, it gradually returned towards pre induction value during recovery period. While in Group E mean arterial pressure remained stable throughout surgical procedure. MAP was statistically significant till 20 minutes’ post induction among both groups (p < 0.05). Results showed that Propofol (1%) group showed more hypotension and the Etomidate group had a more stable blood pressure. No patients in our study required treatment for hypotension or had any negative sequelae. But all patients in the study were already receiving intravenous fluids as a standard part of the departmental clinical protocol, and we did not measure for changes in the rate of fluid administration for any patients in our study. The study of Hug et al. that was conducted on 25000 patients showed that Propofol would lead to bradycardia in 4.2% of patients and hypotension in 15.7% of patients. The hemodynamic stability seen with etomidate may be due to its unique lack of effect on both the sympathetic nervous system and baroreceptor function and capacity to bind and stimulate peripheral alpha-2B adrenergic receptors with a subsequent vasoconstriction. Mayer et al. and Wu et al. also concluded that etomidate preserves hemodynamic stability during anesthesia. Hypotension occurs with propofol (1%) is mainly due to reduction of sympathetic activity causing vasodilation or its direct effect on vascular smooth muscles. Severity of decrease in MAP after bolus injection of propofol (1%) is dependent on both vasodilation with reduced preload and afterload and myocardial depression (negative inotropic action). Sudden hypotension and tachycardia have deleterious effects on maintaining the circulation to vital organs in patients of coronary artery disease, valvular stenosis, uncontrollable hypertension and shock. Oxygen saturation (SPO2) remained stable throughout surgical procedure in all patients in Group E. There was a significant fall in the oxygen saturation (SPO2) in Group P as compared to Group E with maximum fall at 1-minute post induction because of hypoxia and apnea, which was statistically significant among both groups (p < 0.05). In our study induction with Propofol (1%) plus Fentanyl citrate caused fall in SPO2 below 90% in 20% (10 out of 50) patients. On which 6 patients required jaw thrust maneuver and 4 patient required bag and mask ventilation with 100% O2. Saturation returned to the baseline in all patients within 2-3 minutes of management and no patients suffered from significant respiratory depression and comparable among both groups. The severity of pain was more with Group P. In previous conventional etomidate formulation, propylene glycol (pH 6.9) was used as a solvent which produces high incidence of adverse effects like pain on injection and hemolysis compared to propofol (1%). Study conducted by Mehdad et al. also found no significant difference in blood oxygen saturation between both drugs in elective orthopedic surgery. Babita et al. showed significant fall in respiratory rate in propofol-fentanyl group as compared to propofol-ketamine group and the maximum fall was at 1-minute post induction but postoperatively it returned to the baseline. Pain during injection of anesthetic agent is a bad experience for patient while it quite embarrassing situation for an anesthesiologist. In our study 30% (15 out of 50) patients in Group P complained pain on injection while only 6% (3 out of 50) patients in Group E, which was statistically significant (p > 0.05). Also, the severity of pain was more with Group P. In previous conventional etomidate formulation, propylene glycol (pH 6.9) was used as a solvent which produces high incidence of adverse effects like pain on injection and nausea/vomiting. We used etomidate available as emulsion for injection 10ml containing etomidate BP 2 mg along with lipid excipients like soybean oil USP, glycerol BP and egg lecithin. This formulation into medium chain-length lipids appears to have low incidence of injection pain and hemolysis compared to propofol (1%) or conventional etomidate formulation. Etomidate shown a favorable outcome and it was very well supported by Saricaoglu et al. and Wu et al. and Mayer et al. in their studies. Pain on injection with propofol is attenuated by various methods like injection of propofol (1%) slowly in carrier fluid, large vein, and use of xylocard (2%) before injection, analgesics and anesthetic drugs. The rapid induction without
side effect is a valuable characteristic that is wanted from an ideal induction agent. In our study we observed that Induction time was prolonged in Group P (1.12±0.26 min) compared to Group E (0.864±0.23 min), which was statistically highly significant (p < 0.01). As far as numbers of incremental doses are concerned Etomidate required fewer doses (1.46±1.11) compared to Propofol (1%) (2.14±1.32) (p < 0.05). However, amount of drug requirement was reduced in subsequent doses in Propofol (1%) group due to longer half-life of drug, while Etomidate has little cumulation when repeated doses are given. Results are concordant with the study conducted by Miner et al\textsuperscript{31} observed that Etomidate required less incremental doses compared to Propofol (1%) in procedural sedation in emergency department. Both etomidate and propofol (1%) are known to have rapid induction time with short duration of action. A bolus dose of 0.3 mg/kg Etomidate produce sleep in one arm-brain circulation time approximately 30-50 seconds and sleep lasting from 5 to 10 min. while Propofol (1%) has an onset of action of approximately 45-90 seconds and begins to redistribute from the blood to fat and muscle in 3 to 5 minutes, with a rapidly resolving clinical effect. Thus, incremental dose of 0.1 mg/kg Etomidate required less often (every 5-8 minute) compared to 0.5 mg/kg Propofol (1%) (every 3-5 min). In term of Adverse effects post operatively incidence of nausea and vomiting was significantly higher in Group E (16% (8 out of 50 patients) compared to 4% (2 out of 50 patients). Pre-treatment with H2 blockers and inj. ondansetron significantly reduced incidence in both groups. In our study we used Etomidate in lipid emulsion which has low incidence vomiting compared to etomidate conventional form. Propofol (1%) modulates subcortical pathway to inhibit nausea and vomiting or produce direct depressant effect on vomiting center, this makes it suitable over other induction agent like Thiopentone and etomidate. Incidence of hiccups are also seen in Group E (8% (4 out of 50 patients) while Group P didn’t show any incidence. Hypersensitivity reactions were more in propofol group compared to Etomidate group. As far as recovery time is concerned, it was prolonged in Group E (6.56±1.39 min) compared to Group P (5.52±1.39 min), which was statistically significant (p < 0.05). Miner et al\textsuperscript{31} also showed higher recovery time in Etomidate group (8.8 min±2.0 min) compared to Propofol (1%) (6.8±2.0 min) group. Our study findings showed that the time to return of protective airway reflexes like coughing and respond to follow verbal commands for patients receiving propofol (1%) was more than for those receiving etomidate, with a mean 1.5-minute difference. Both drugs provide smooth and quicker recovery without any prolonged sedation.

6. Summary & Conclusion

The present study entitled “Comparative study of Etomidate and Fentanyl citrate with Propofol (1%) and Fentanyl citrate for Total intravenous anaesthesia in short surgical procedures” was carried out in our department after getting institutional ethics committee approval.

1. Baseline vital parameters like heart rate, mean arterial blood pressure, SPO2, respiratory rate were comparable between two groups.
2. There was significant Tachycardia and Hypotension occurred after induction with Propofol (1%) and Fentanyl citrate; while induction with Etomidate and Fentanyl citrate showed stable cardiovascular effect throughout procedure and during recovery period.
3. Etomidate showed minimal effect on respiratory system; while propofol (1%) caused falling oxygen saturation and transient apnoea within 2-3 minute of induction without marked respiratory depression.
4. Incidence of pain on injection was more after induction with propofol (1%); while incidence of myoclonic activity was only seen after induction with Etomidate.
5. Induction time, numbers of incremental doses required less in induction with Etomidate; while there was quicker recovery occurred with Propofol (1%).
6. Regarding adverse effects, incidence of nausea and vomiting, hiccups was more in Etomidate group; while Propofol (1%) showed more hypersensitivity reaction. This study suggests that both Etomidate–Fentanyl citrate and propofol (1%)–Fentanyl citrate produced smooth induction, easy maintenance and quick recovery with only minor hemodynamic fluctuations makes them excellent combinations as TIVA technique. Etomidate is preferred over Propofol (1%) especially for hemodynamically unstable patients because of minimal effects on cardiovascular and respiratory system. Hypotension and pain on injection was observed more frequently with Propofol (1%) while myoclonus with Etomidate. With these observations in mind and careful selection of patients, both agents appear similarly safe for use in elective and short surgical procedures.

7. Source of Funding

None.

8. Conflict of Interest

None.

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