Comparison of effect of etomidate with propofol on hemodynamics during modified electroconvulsive therapy

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Abstract

Background and Aims: Studies comparing the effect of propofol and etomidate on hemodynamic parameters during electroconvulsive therapy (ECT) have shown ambiguous results. Although some studies observed a larger increase in blood pressure and heart rate during the use of etomidate than propofol in ECT, whereas some studies have shown no difference in hemodynamic parameters with the use of etomidate or propofol. Most of the studies done to compare the hemodynamic effects of etomidate and propofol were limited by small sample size or retrospective in nature. Therefore, we conducted a prospective randomized trial to compare the effects of etomidate and propofol on hemodynamics during ECT.

Material and Methods: A prospective randomized crossover study was conducted on 30 patients with American Society of Anaesthesiologist physical status I and II, between age 18 and 65 years, suffering from a mental disorder as per International Classification of Diseases-10 and requiring bilateral ECT as per clinical decision of consultant psychiatrist. They were randomized to receive both the drugs for their successive ECT sessions and were subjected to evaluation after clubbing together the ECT sessions of propofol or etomidate as anesthetic agent.

Results: Duration of motor seizures was significantly more in patients receiving etomidate, whereas patients receiving propofol had more stable hemodynamics.

Conclusion: Though propofol maintains stable hemodynamics during MECT, yet clinical applicability of etomidate outstrips it by a reasonable margin due to its better effect on seizure parameters.

Keywords: Etomidate, modified electroconvulsive therapy, propofol

Introduction

Electroconvulsive therapy (ECT) is widely recognized and an effective mode of treatment for various neuropsychiatric disorders which do not respond to psycho-pharmacological methods.[1] ECT has come a very long way since its introduction in 1937 owing to the discovery of wide range of anesthetic agents and muscle relaxants that have been utilized to prevent psychological and physiological side effects subsequent to ECT-induced generalized tonic–clonic seizure.[2,3] The mechanism of clinical improvement secondary to induced seizure remains elusive till date. However, the optimal seizure duration of 20–25 s has been shown to improve therapeutic efficacy of ECT.[4]

Thiopental and propofol are the most commonly used induction agents in the conduct of ECT with inherent advantage of blunting the autonomic response to induced seizure as well as no awareness or recall of the same.[5] However, the use of these agents is fraught with their anticonvulsant activity resulting in the need for supplementation to prevent postictal hypotension.

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in decreased seizure duration and increased threshold for subsequent ECT. Therefore, an ideal anesthetic agent for ECT requires an optimum balance between its anticonvulsant and hypnotic activity.

Etomidate is an intravenous induction agent with a propensity to prolong the seizure duration as well as provide hemodynamic stability. In spite of various advantages, etomidate has not gained popularity as an induction agent due to its perceived effects on adrenocortical axis which were feared to be sustained than transient. Literature has shown conflicting results on the use of etomidate and propofol and no drug can be deemed superior to the other regarding effect on hemodynamic responses or seizure duration. Therefore, the present study with a cross-over design was planned to compare the effects of etomidate and propofol on hemodynamic responses during and immediately after ECT and on the motor seizure duration.

### Material and Methods

The present study was conducted after obtaining approval from Institutional Ethics Committee and registration with Clinical Trial Registry of India (CTRI No: CTRI/2016/01/006530). ECT is performed bi-weekly in the institute as per clinical decision and consequent referral by the consultant psychiatrist; most of the patients require, on an average, five to six ECT treatments for achieving the therapeutic benefits. Thiopentone and propofol are two most commonly used intravenous induction agents in our institute.

Sample size was estimated based on the results of the study done by Gazdag et al. with mean blood pressure (MBP) as the primary outcome. Sample size was estimated to be 18 subjects for a cross-over study at a power of 80% and confidence interval of 95%. It was decided to include a total of 30 patients in the study to compensate for potential dropouts.

After obtaining written informed consent from either the patient or relatives, a prospective randomized crossover study was conducted on 30 patients. Patients with ASA physical status I and II, between age 18 and 65 years, suffering from a mental disorder as per ICD-10 and requiring bilateral ECT were included in the study. Patients with history of relevant drug allergy, pregnancy, prior treatment with ECT, substance abuse, and anticipated difficult airway were excluded from the study.

A total of 30 patients were randomized for the initial ECT to receive either etomidate or propofol using computer random number generator to create random permuted blocks. The block length was 2, 4, and 6 which also varied randomly. Blinding was done by sequentially numbered opaque sealed envelopes. After randomization, the patients were divided into two groups as follows:

Group E1 (n = 15) received etomidate as inducing agent during in their first ECT and Group P1 (n = 15) received propofol in their first ECT. For their subsequent ECT, patients in group E1 received propofol and patients in Group P1 received etomidate as induction agent. They were labeled as Group P2 (n = 15) and E2 (n = 15), respectively. All the observations in group E1 and group E2 were clubbed together to form a group E (n = 30) and group P1 and P2 were clubbed together to form a group P (n = 30). A total of 60 ECT sessions were evaluated in the present study.

**ECT procedure:** No premedication was administered and all patients were kept nil per oral for at least 6 h prior to procedure. Written informed consent was procured either from the patient or from their relatives, in case the patient was unable to give the same because of the underlying disorder or being uncooperative.

A pre-ECT counseling session was held on the evening prior to the ECT with the basic purpose of explaining about the anesthetic and ECT stimulus procedure in detail and the procedure was undertaken early in the morning in the ECT treatment room of the psychiatry ward which is equipped with an anesthesia workstation and all the resuscitative equipments and drugs. Intravenous cannulation (20G/18G cannula) was performed in all patients to provide access for medications and fluids and blood pressure cuff was tied on the ipsilateral arm. Patients were connected to standard ASA monitor (S/5™ Datex Ohmeda USA) and baseline parameters like heart rate (HR), systolic and diastolic blood pressure (SBP and DBP), electrocardiogram, and arterial oxygen saturation (SpO2) were recorded before the start of procedure. A tourniquet was applied on the contralateral arm to measure motor seizure duration during ECT. Preoxygenation was carried out using 100% oxygen and intravenous (IV) glycopyrrolate (5 mcg kg⁻¹) was administered in all the patients prior to the procedure. The patients received equihypnotic dose of either intravenous (IV) etomidate (0.2 mgkg⁻¹) or propofol (1 mgkg⁻¹) as previously established by Avramov et al. On loss of responsiveness to verbal commands, tourniquet was inflated to a value above the systolic blood pressure on upper arm. After ensuring adequate mask ventilation, neuromuscular blockade was achieved with depolarizing muscle relaxant succinylcholine (1 mgkg⁻¹). Mask ventilation was continued with 100% oxygen till adequate muscle relaxation was achieved along with maintenance of eucapnia (end-tidal CO₂ {etCO₂} 30–35 mmHg) and SpO₂ between 98 and 99%. Subsequent to achievement of
conducive conditions, a mouth gag was inserted inside the oral cavity to prevent damage to oral cavity, tongue, and teeth during the procedure.

Postinduction, a suprathreshold electrical stimulus (frequency 70 Hz, pulse width 1 msec 220 V) with bifrontal temporal electrodes was given to patients by a psychiatrist from the primary treating team using Brief pulse constant current ECT machine (Medic Aid, BPE791) Brief pulse stimulation of 0.6–3 s was used in all the treatments. Seizure duration was recorded by another psychiatrist in the treatment room. Motor seizure duration was measured using isolated forearm technique.

Following the electrical stimulus and seizure subsidence, bite block was removed and ventilation via facemask was continued until recovery of spontaneous and sustained respiratory efforts.

After 15 min the patients were transferred to postoperative anesthesia unit for observation and subsequently back to the ward if they met the discharge criteria, i.e., stable hemodynamic and respiratory status, response to verbal commands and ability to move from bed. Oral intake was not allowed for 4 h after recovery from anesthesia.

HR, SBP, DBP, and MBP were recorded before induction, after administration of study drug, during the seizure activity and after 1, 3, 5, and 10 min of seizure activity. Any side effects like pain on injection site, nausea, vomiting, postictal agitation, and memory deficits were also recorded.

The statistical analysis was carried out using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 17.0 for Windows). All nominal or categorical variables were described as frequencies and proportions. For all ordinal variables; mean, median, and standard deviation were calculated. Mean values across the two groups were compared using Student’s (independent) t-test. For repeat measurements within the group, Dunnett’s test was applied. Statistical tests were two-sided and performed at a significance level of α = 0.05.

Results

The present study was carried out over a span of 14 months. A total of 36 patients were assessed for eligibility, of which 30 patients met the inclusion criteria and were enrolled in the study. All 30 patients received both the induction agents, etomidate and propofol, either for their first or second ECT. There were no dropouts in the study.

The overall mean age of the sample 32.97 ± 9.34 years with predominantly (60%) male patients having mean body weight of 58.87 ± 18.55 kg; 29/30 patients belonged to ASA I physical status. Hence, it was a relatively physically healthy sample reflective of the intake criteria used in the study. Of the 30 patients, 23 (77%) were suffering with either unipolar or bipolar affective disorder and rest 7/30 (23%) had schizophrenia, thus being the predominant indications for ECT.

The baseline parameters, i.e., HR, SBP, DBP, and MBP were recorded before induction (T0), after administration of the study drug (T1), during the seizure activity (T2), and after 1, 3, 5 and 10 min (T3, T4, T5, T6, respectively) of the seizure activity.

On evaluation of longitudinal responses over time for etomidate, it was observed that mean HR significantly increased from the baseline ranging from 13 to 17 beats at all-time intervals from T2 to T6, i.e., from the time of occurrence of seizure activity till 10 min after the seizure. For propofol this significant change occurred only at one time point T6 i.e., 10 min after the seizure. [Table 1] On evaluation of longitudinal responses in etomidate group, significant increase from baseline was observed in MBP at time intervals T2 and T3 only. However, for propofol, no such significant changes were made through the course of monitoring and observations [Table 2].

When etomidate was compared to propofol, the mean values of HR were found to be significantly higher in etomidate group only at one time interval T3, i.e., 1 min after the seizure activity [Figure 1], whereas the mean values of MBP were observed to be significantly higher at three time intervals, i.e., T1, T2, and T3 [Figure 2].

Motor seizure duration was significantly longer in etomidate group (37.60 ± 23.67 s) as compared to propofol group. (22.83 ± 18.52 s) [Table 3]. Three patients in the etomidate group and seven patients in propofol group did not manifest with a seizure. However, this observation had no statistical significance (X² = 1.92; df = 1, P value = 0.165) Incidence of postoperative side effects (pain at the site of injection, nausea, vomiting, headache, and postictal confusion) was similar in both the groups from immediate post-ECT up till 24 h.

Discussion

ECT is the mainstay of treatment in psychiatric disorders not amenable to standard pharmacological treatment. Usually performed under general anesthesia, choice of an ideal anesthetic agent has always been debatable in view of varying pharmacodynamics of the commonly employed intravenous agents. Although a number of studies have
been conducted to compare the effects of thiopentone and propofol on the hemodynamic parameters and seizure duration during modified ECT, etomidate has been sparingly used for the same. However, the availability and resurgence in the use of etomidate in the field of anesthesia prompted us to compare and evaluate its effect on hemodynamic variables and motor seizure duration in comparison to propofol during anesthesia for ECT. Review of literature has revealed that most of the studies in ECT have measured the HR and blood pressure before and after the seizure, thereby ignoring the peak cardiovascular changes that occur during the seizure. Moreover all the studies do not have similar conclusions with respect to hemodynamic profile and are limited by either a small sample size or retrospective nature of the studies. Hence, the present study was conducted as a prospective double blind trial to compare the cardiovascular effects of commonly used induction agents, etomidate and propofol, during and after the seizure activity. In addition, the present study also measured the seizure duration with respect to both these induction agents.

The study design was of crossover design in which 30 patients were randomized to receive both the drugs for their successive ECT sessions and were subjected to evaluation after clubbing together the ECT sessions of propofol or etomidate as the anesthetic agent. The present study design practically eliminated the selection bias with comparable demographic distribution in both the groups. In 30 patients subjected to ECT, 13 patients (44%) were diagnosed to have depression, 10 patients (33%) had bipolar disorder, and 7 patients (23%) had schizophrenia.

The results of the present study in terms of higher HR and MBP during the seizure activity and up to 3 min after the seizure only in etomidate group than propofol group (Tables 1 and 2) can be explained by cardiovascular depressant effect of propofol which dominates over the sympathetic stimulation caused by seizure induced during ECT.[13] Though absolute values of MBP were lower in propofol group post induction at all-time intervals; however, this change from the respective baseline values was not significant which suggests that though propofol-induced fall in hemodynamics was more as compared to etomidate, still it was not significant to cause any potential deleterious effects. Similar hemodynamic profile after administration of etomidate at 3 and 6 min has been observed in other studies.[14,15] However, previous studies did not observe a higher HR or greater rise from baseline at 1 min after the seizure. This discrepancy with respect to our study can be explained by time delay between administration of induction agents and time at which seizure activity (ECT) was initiated. This delay might be less in the previous studies than ours.[14,15]

The results of the present study are in contradiction to study by Rosa et al.,[16] who demonstrated no significant difference

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### Table 1: Comparison of heart rate across varying time intervals with respect to baseline (T0) in both groups (Etomidate and Propofol) using Dunnett’s test

| Time | Mean HR±SD (beats/min) | HR at baseline (T0) | Variation from baseline | Level of significance | Mean HR±SD (beats/min) | HR at baseline (T0) | Variation from baseline | Level of significance |
|------|------------------------|---------------------|------------------------|----------------------|------------------------|---------------------|------------------------|----------------------|
| T1   | 100.07±17.33           | 94.90               | 5.17                   | 0.665                | 96.00±14.70            | 96.50               | 0.50                   | 1.000                |
| T2   | 110.13±17.58           | 94.90               | 15.23                  | 0.002**              | 103.33±17.47           | 96.50               | 6.83                   | 0.364 NS             |
| T3   | 112.77±15.77           | 94.90               | 17.87                  | <0.001***            | 102.63±16.53           | 96.50               | 6.13                   | 0.475 NS             |
| T4   | 109.33±17.19           | 94.90               | 14.43                  | 0.004**              | 106.93±15.58           | 96.50               | 10.43                  | 0.058 NS             |
| T5   | 110.77±17.33           | 94.90               | 15.87                  | 0.001**              | 106.73±14.92           | 96.50               | 10.23                  | 0.065 NS             |
| T6   | 108.13±14.91           | 94.90               | 13.23                  | 0.010*               | 107.27±15.70           | 96.50               | 10.77                  | 0.047*               |

P<0.05*; P<0.01**; P<0.001***; NS=Not Significant

### Table 2: Comparison of mean blood pressure (MBP) across varying time intervals with respect to baseline (T0) in both groups (Etomidate and Propofol) using Dunnett’s Test

| Time | Mean MBP±SD (±SD) (in mmHg) | MBP at baseline (in mm Hg) | Variation from baseline | Level of significance | Mean MBP±SD (±SD) (in mmHg) | MBP at baseline (in mm Hg) | Variation from baseline | Level of significance |
|------|-----------------------------|-----------------------------|------------------------|----------------------|-----------------------------|-----------------------------|------------------------|----------------------|
| T1   | 101.30±15.61               | 96.25                       | 5.04                   | 0.506                | 91.09±12.33                | 95.66                       | -4.58                  | 0.731NS              |
| T2   | 112.10±14.60               | 96.25                       | 15.84                  | <0.001***            | 98.01±17.04                | 95.66                       | 2.34                   | 0.982 NS              |
| T3   | 114.28±16.40               | 96.25                       | 18.02                  | <0.001***            | 102.38±17.32               | 95.66                       | 6.71                   | 0.362 NS              |
| T4   | 107.70±15.95               | 96.25                       | 11.44                  | 0.007**              | 101.83±19.12               | 95.66                       | 6.17                   | 0.448 NS              |
| T5   | 100.79±10.40               | 96.25                       | 4.53                   | 0.612                | 97.92±15.57                | 95.66                       | 2.25                   | 0.985 NS              |
| T6   | 97.10±9.15                 | 96.25                       | 0.84                   | 1.000                | 95.28±15.27                | 95.66                       | -0.39                  | 1.000 NS              |

P<0.01**; P<0.001***; NS=Not Significant
in HR from baseline in both the etomidate and propofol group just after the seizure.\cite{16} This can be explained by use of comparatively higher dose of etomidate (0.15–0.30 mg/kg) and propofol (1–1.5 mg/kg) in their study as compared to relatively lower dose of 0.2 and 1 mg/kg of etomidate and propofol in present study.

MBP increased in both etomidate and propofol groups during and after the seizure. Absolute values of MBP and change in these values from baseline were significantly greater in etomidate group during the seizure and 1 min after the seizure [Table 2]. Similar trends were observed for SBP and DBP. However, it may be pertinent to add here that we have taken into account only MBP values as it has greater relevance with respect to hemodynamic stability and for monitoring purposes during any procedures requiring anesthesia. Although etomidate is perceived to be a cardiostable agent in routine anesthetic practice because of absence of hypotension during induction, still the increase may be explained by the fact that no premedication or inhalational agent was administered to patients that could presumably blunt the sympathetic responses; additionally, the increased apnea time secondary to increased motor duration of the seizure could have contributed to the same.

The increase in MBP and HR from the baseline in etomidate as compared to propofol group observed in our study [Figures 1 and 2] is in keeping with previous studies.\cite{11,12} Hence from these observations, it can be safely concluded that propofol is more effective in blunting the sympathetic response to seizure and provides more cardioprotection. The conclusion drawn with respect to the hemodynamic profile is however contrary to our initial hypothesis. In contrast there are studies which either demonstrate significant decrease with etomidate or no difference in HR or MBP with the use of both inducing agents. This difference may be due to the difference in methodology, small sample size or use of variables doses of propofol or etomidate.\cite{16-18}

Motor seizure duration was significantly longer in etomidate group (37.16 ± 23.67 s) than in propofol group (22.83 ± 18.52 s) in present study [Table 3] in keeping with the current literature related to the use of both etomidate and propofol. Most of the studies that have compared the EEG as well as EMG seizure duration with both these drugs have observed increased seizure duration with the use of etomidate. Additionally, decreased seizure duration with increasing dose of propofol has previously been reported by other researchers.\cite{11,12,15,19} The comparatively longer seizure duration in both the groups observed by Avramov et al. as compared to the present study could be a reflection of the monitoring methods used to measure seizure duration, i.e., EMG monitoring versus isolated forearm technique in the present study.\cite{12}

The seizure prolongation effect has also been shown in seizure resistant individuals undergoing ECT.\cite{17,18} As a clinical dictum, a seizure duration of at least 25 s is considered adequate for generation of good response to ECT.\cite{20} However, a cut off of 20 s is deemed to be sufficient with “cuff monitoring method.”\cite{21,22} Nevertheless, the mean value of 22.83 s can be a matter of concern in patients receiving propofol as the probability of experiencing inadequate/ineffective seizure will be higher than in patients receiving etomidate. The number of failed seizures was observed to be more in propofol induced group, although this difference was not statistically significant.

As far as the use of both the drugs is concerned during ECT, it can be stated that both the study drugs have contrasting beneficial effects in patients undergoing ECT. While propofol provides better hemodynamics, etomidate has an advantage of providing better therapeutic efficacy due to seizure prolongation. However, etomidate as the first-line induction agent in healthy patients undergoing ECT along with the use of certain drugs (e.g., beta blockers, calcium channel blockers, and opioids) can prevent seizure related sympathetic response and may hasten recovery; thereby potentially achieving early clinical remission.\cite{23,25}

Also, etomidate may be especially useful in patients at high risk of cardiac complications during and after MECT because such patients are highly dependent on their sympathetic tone
to maintain the hemodynamics; therefore, even a low dosage of propofol may lead to hypotension. Etomidate, on the contrary, may be even extremely helpful in patients with catatonia (that is a potentially a life-threatening situation where patients are usually dehydrated and hypotensive requiring MECT as the first line of treatment for therapeutic response) owing to its minimal effect on hemodynamics.

The study is not without limitations. The seizure duration was measured with isolated forearm technique which underestimates the seizure duration as compared to measurements done by EEG/EMG. Also, the effect of increasing the seizure duration on the remission and recovery of the patients was not studied and the effect of etomidate on subsequent MECTs could not be studied as it was a cross-over study. ASA III and IV patients were not included in the study and the role and the advantages of the etomidate in high-risk patients need to be evaluated.

Hence, it may be summarized and concluded that though propofol has better hemodynamics during MECT, yet the clinical applicability of etomidate outstrips it by a reasonable margin due to its better effect on seizure parameters and the clinical conditions that require MECT. We are of the opinion that etomidate can be a potential first line drug of choice in MECT due to its wide spectrum of applicability in healthy patients, seizure resistant patients, patients with significant cardiovascular diseases, and severe catatonia. However, the efficacy and role in these clinical situations need to be evaluated with further studies. Also the concomitant use of beta blockers, calcium channel blockers, and opioids with etomidate to prevent the seizure-related sympathetic response may have beneficial effect for achieving good clinical remission. Nevertheless, the place of propofol as an anesthetic agent in delivering MECT should not be frivolously and summarily dismissed as it can be used in healthy patients in view of its cardio-protective effect though at the expense of decreased seizure duration leading to decreased therapeutic effect of ECT.

Hence, overall both the drugs have contrasting beneficial effects and profiling for patients who need to undergo MECT. This is an area which needs further confirmation.

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**Conflicts of interest**

There are no conflicts of interest.

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| TABLE 3: Seizure duration across both groups | GROUP (N=30 each) | Mean | S.D. | t-test* (df) | Level of Significance |
|--------------------------------------------|-------------------|------|------|--------------|----------------------|
| Seizure Duration                           | Etomidate         | 37.60| 23.68| 2.691 (58)   | 0.009**              |
|                                            | Propofol          | 22.83| 18.52|              |                      |

*Independent (unpaired) t-test
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