A comparative Study of Hemodynamic Effects, Recovery Pattern and Seizure Activity of Propofol, Ketofol and Etomidate in Modified Electroconvulsive Therapy

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ABSTRACT

Introduction: Electroconvulsive therapy (ECT) is a widely used and safe evidence based intervention in modern psychiatry as a treatment for a variety of psychiatric disorders. The choice of anesthetic agent may influence recovery pattern, hemodynamic effects, seizure activity, cognitive functions and cost-effectiveness of the procedure. There is relative paucity of literature in this regard. Given this background, the present study was designed to compare the effects of propofol, etomidate and ketofol on recovery pattern, hemodynamic effects and seizure activity in patients undergoing modified electroconvulsive therapy.

Material and Methods: A total of 150 patients undergoing modified ECT in the age group of 18 to 65 years of either sex were consecutively selected and randomly divided into three groups of 50 each to receive propofol (group I), etomidate (group II) or ketofol (group III).

Results: Comparisons of the mean pulse rate, mean systolic blood pressure, mean diastolic blood pressure and mean arterial blood pressure in the study groups did not reveal statistically significant differences. Patients in the ketofol group had a longer mean seizure duration compared to patients who received propofol and etomidate. Patients in group I in comparison with groups II and III had a significantly shorter time to return of spontaneous respiration, time to eye opening and time to respond to verbal commands. The three groups do not differ significantly with regard to mean MMSE scores. The cost of the anesthetic drug for ECT was lowest in the propofol group as compared to etomidate group and ketofol group.

Conclusion: In patients undergoing modified ECT, propofol, etomidate and ketofol provide adequate hemodynamic stability and do not significantly impact cognitive functioning. Ketofol increased mean seizure duration compared to propofol and etomidate. Recovery time is shorter in patients who received propofol, in comparison with patients who received etomidate or ketofol. Propofol appears to be a cost effective option for patients undergoing ECT. Further research with ketofol in ECT is warranted.

Keywords: propofol, etomidate, ketofol, ECT, hemodynamic effects, recovery pattern, seizure duration

INTRODUCTION

Electroconvulsive therapy (ECT) is a widely used and safe evidence based intervention in modern psychiatry as a treatment for a variety of psychiatric disorders.[1] The choice of anesthetic agent for electroconvulsive therapy depends on seizure duration, hemodynamic and recovery parameters.[2] Propofol has been reported to be associated with favorable recovery pattern. Concerns that shorter seizures produced with propofol administration may compromise efficacy have not been supported.[3] Etomidate is known to increase seizure duration than propofol. Studies have reported increased confusion after ECT and longer recovery time with etomidate.[4] The combination of ketamine and propofol (Ketofol) is gaining reputation in ECT anesthesia and is reported to have better cognitive recovery and better antidepressant effects.[5] The main objective of general anaesthesia in ECT to produce an unconscious state with muscle paralysis. The choice of anesthetic agent may influence recovery pattern, hemodynamic effects, seizure activity, cognitive functions and cost-effectiveness of the procedure. There is relative paucity of literature in this regard. Given this background, the present study was designed to compare the effects of propofol, etomidate and ketofol on recovery pattern, hemodynamic effects and seizure activity in patients undergoing modified electroconvulsive therapy.

MATERIALS AND METHODS

The present single blinded randomized controlled study was conducted in the department of Psychiatry and department of Anesthesiology at Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India. The study was conducted after approval of the institutional ethics committee between December 2014 and August 2015. A total of 150 patients undergoing modified ECT in the age group of 18 to 65 years of either sex were consecutively selected and randomly divided into three groups of 50 each to receive propofol (group I), etomidate (group II) or ketofol (group III). The following exclusion criteria were applied:

1. Patients who decline consent
2. Age less <18 years and >65 years
3. Patients undergoing modified ECT for a subsequent time without seizure on the previous ECT session
4. Major medical disorders such as diabetes, hypertension, respiratory disorders, recent ischemic heart disease, recent cerebrovascular event
5. Raised intracranial pressure due to any cause

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6. ASA grade III and IV
7. Agitated patients requiring additional sedation

All patients underwent pre-anesthetic evaluation comprising of history taking, clinical examination in either anesthesia OPD or bed side in the psychiatry ward. Current medications were recorded and kept constant throughout the study. Informed written consent was obtained from the patient and his/her responsible relatives or guardians and the procedure fully explained to the patient and relatives in a clear, simple and vernacular language. The procedure was carried out in the morning with all patients fasted overnight for at least 6 hours, not using a dental prosthesis, contact lenses, or any ornaments, and were wearing proper clothing. The procedure room was fully equipped with drugs necessary for cardiopulmonary resuscitation, intubation and defibrillation.

The demographic data including age, body weight in kg, and their ASA physical status were noted. Investigations performed include haemogram, urine examination, chest x-ray, ECG, blood urea, serum creatinine, serum electrolytes. On arrival in the operation theatre, intravenous line was set up using 18G cannula. The multipara monitor was connected to the patients. Monitoring of systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), electrocardiogram (ECG) and hemoglobin oxygen saturation (SpO2) were recorded prior to induction and throughout the procedure. After starting intravenous line, all patients recieved pre-anesthetic medications with Inj. Glycopyrolate 0.2 mg IV just before the start of the procedure. All patients were pre-oxygenated with 100% oxygen for 5 minutes. Anesthesia was induced with either propofol(1%) at the dose of 1.5 mg/kg, etomidate at the dose of 1.5mg/kg, or ketofol (ketamine 0.8mg/kg and propofol 1.5mg/kg). The vital parameters were recorded again. The blood pressure cuff was applied to the arm needed to be isolated from the effect of muscle relaxation, for observing localized seizures, was inflated 100 mmHg above systolic blood pressure and then succinylcholine administered in the dose of 1 mg/kg body weight after isolating the arm by a blood pressure tourniquet. All the patients were ventilated with 100% oxygen with facemask using Magill's circuit (Mapleson A circuit) till fasciculation subsided and muscle relaxation was achieved. A mouth gag (Roberto's mouth gag) was inserted inside the oral cavity separating tongue, teeth and buccal mucosa, to prevent any damage to the soft tissue of the oral cavity, tongue and fracture of teeth during the procedure. The electroconvulsive therapy was applied to the head through two electrodes kept at both sides of the temporo-frontal regions (bi-temporal ECT) after applying ECT gel on to the electrodes. Modified electroconvulsive therapy was given to all patients in the study using a pulse of 60 Hz of 0.8 msec duration with total stimulus time not exceeding 1.25 seconds, by BPE-591 machine. The mouth gag was changed to Guedel airway after the seizure activity subsided and patients ventilated with 100% oxygen till regaining of spontaneous respiration.

The heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), SpO2 were recorded before induction of anesthesia (To), after administration of the study drug (Ti), after succinylcholine (Ts), after applying ECT (Te), at one minute (T1),three minute (T3), five minute (T5), ten minute (T10),15 minute (T15) and 20 minute (T_{20}). The duration of seizure activity was recorded in seconds by clinical method (tourniquet method) from the start of electrical impulse to the end of the clonic contraction using a hand held stopwatch.

The assessment of recovery was done on the following parameters:

- Time to return of spontaneous breathing
- Time to return of eye opening
- Time to respond to verbal commands

Probable side effects including nausea, vomiting, respiratory depression, hypoxemia were noted after the electrical stimulus until the patient was discharged from the post-anesthetic care to the psychiatry ward. Cognitive functioning was assessed using mini-mental state examination[6] score.

STATISTICAL ANALYSES

The data obtained was subjected to appropriate statistical methods using Statistical Package for the Social Sciences (SPSS) version 22.0.

RESULTS

The data is presented in the tables as mean, unless otherwise specified. Figures in brackets indicate standard deviation. The level of statistical significance used was $p<0.05$.

The three groups were statistically comparable in terms of socio-demographic profile and distribution of psychiatric diagnoses**.** Comparisons of the mean systolic blood pressure (Table 1) mean diastolic blood pressure and mean arterial blood pressure in the study groups did not reveal statistically significant differences. Statistically significant differences were observed in the study groups with regard to seizure duration (Table 2). The three groups do not differ significantly with regard to mean MMSE scores (Table 2). Patients in group I in comparison with groups II and III had a significantly shorter time to return of spontaneous respiration, time to eye opening and time to respond to verbal commands (Table 3). The cost of the anesthetic drug for ECT was lowest in the propofol group as compared to etomidate group and ketofol group in the present investigation (Table 4).

DISCUSSION

In the present study we have compared the hemodynamic effects, seizure duration and recovery in patients undergoing modified ECT induced with propofol, etomidate or ketofol. The convulsion produced as part of ECT is accompanied by significant increases in blood pressure, heart rate and cardiac output. Anesthesia cannot completely eliminate the cardiovascular and respiratory effects of ECT.

Hemodynamic effects

The maximum increase in pulse rate was observed at the 5th minute from the time of electrical stimulation. In a study comparing the hemodynamic effects of propofol and thiopentone, researchers[7] observed maximum increase in pulse rate at the 3rd minute from the time of electrical stimulation. Yalcin and colleagues[8] reported a significant increase in mean heart at the third minute from induction with ketofol in comparison with propofol. In the present study, the comparisons of mean pulse rates in the study groups were not

Time	Group I (n=50)	Group II (n=50)	Group III (n=50)	P value
T_0	114.21 (12.69)	114.37 (12.35)	113.12 (12.54)	0.079
T_i	108.42 (12.13)	107.88 (12.21)	107.26 (12.78)	0.092
T_s	108.27 (12.47)	107.66 (12.32)	108.34 (12.23)	0.069
T_e	110.32 (12.87)	111.32 (12.62)	111.43 (12.49)	0.21
T_1	114.21 (13.21)	115.21 (13.11)	114.78 (12.87)	0.081
T_3	114.26 (12.76)	116.76 (12.71)	115.43 (12.43)	0.071
T_5	114.37 (12.54)	114.68 (12.23)	114.21 (12.41)	0.095
T_{10}	112.44 (12.54)	111.32 (12.47)	112.65 (12.68)	0.082
T_{15}	110.57 (12.59)	110.43 (12.92)	111.21 (12.31)	0.084
T_{20}	114.69 (13.01)	114.87 (13.22)	114.12 (13.08)	0.62
T_0= time before induction, T_i= at induction, T_s= just after succinylcholine, T_e= just after the electrical stimulus was applied, T_1= at 1 minute, T_3= at 3 minute, T_5= at 5 minute, T_{10}= at 10 minute, T_{15}= at 15 minute, T_{20}= at 20 minute				
Table-1: Mean systolic blood pressure in the study groups				

	Group I (n=50)	Group II (n=50)	Group III (n=50)	P value
Seizure duration (in seconds)	22.31 (4.22)	24.87 (4.43)	25.21 (3.78)	0.08
MMSE score	27.28 (1.2)	28.01 (1.10)	27.21 (1.54)	0.06
Table-2: Mean seizure duration and MMSE score in the study groups				

Recovery parameter	Group I (n=50)	Group II (n=50)	Group III (n=50)	P value
Time to return of spontaneous respiration (in minutes)	3.57 (0.58)	3.89 (0.62)	3.77 (0.32)	0.045
Time to eye opening on command (in minutes)	5.42 (0.76)	5.78 (1.38)	5.88 1.25)	0.032
Time to respond to verbal commands (in minutes)	7.43 (1.51)	7.62 (2.04)	7.59 (1.89)	0.028
Table-3: Mean recovery time in the study groups				

Drug	Cost per unit (Rupees) / 10 ml
Propofol	199
Etomidate	425
Ketamine	120
Succinylcholine	67
Glycopyrolate	19
Table-4: Cost of the drugs used in the study	

statistically significant.

Comparisons of the mean systolic blood pressure (Table 1) mean diastolic blood pressure and mean arterial blood pressure in the study groups did not reveal statistically significant differences. The findings of the present study are consistent with previous reports.[9-11]The present study also confirms previous observations regarding the hemodynamic stability of ketofol.[12]

Seizure duration

Statistically significant differences were observed in the study groups with regard to seizure duration (Table 2). Patients in the ketofol group had a longer mean seizure duration compared to patients who received propofol and etomidate. The results of the present study confirm conclusions made by previous researchers that propofol is associated with shorter seizure duration.[3,13] Induction of high quality and longer seizures has been reported with etomidate.[14-15] Based on this finding which is consistent with observations made by Kayhan and co-researchers[16], it appears that ketofol can be an alternative to enhance seizure quality and clinical efficacy of modified ECT. Consequently, ketofol may be useful in patients in whom it is difficult to elicit a robust seizure.[17] This can be explained on the basis of the pro-convulsant effects of ketamine.[18]

Recovery parameters

Patients in group I in comparison with groups II and III had a significantly shorter time to return of spontaneous respiration, time to eye opening and time to respond to verbal commands (Table 3). Propofol is known to be associated with a shorter mean recovery period and stay in recovery room.[7,12,19] However, some randomized trials between propofol and either etomidate or thipentone have reported no difference in speed of recovery.[20-21] Based on the finding of the present study, it would be reasonable to conclude that the short recovery time seen with propofol is a desirable feature in outpatients undergoing ECT. This also translates into saving of valuable time of the anesthesiologist without compromising safety of the patients.

Side effects

No remarkable side effects or adverse events were observed in the three study groups.

Cognitive status

The three groups do not differ significantly with regard to mean MMSE scores (Table 2). Previous investigators have reported better cognitive functioning in patients who received propofol.[22-23] One study reported prolonged recovery of cognitive functions with etomidate due to longer seizure duration.[24] Studies focusing on whether the anesthetic agent selected may affect the cognitive impairment after ECT are limited, but some researchers suggest that agents such as ketamine may have particular benefit.[24] The effect of ECT on memory may be largely caused by effects mediated by glutamate at *N*-methyl-d-aspartate receptors and suggest that *N*-methyl-d-aspartate antagonists may offer protection from memory dysfunction during ECT.[25]

Cost of the drugs used in the study

The present investigators have tried to compare the cost effectiveness of the drugs in the study groups. The overhead and fixed cost of anesthesia was not taken into consideration as it remained constant in all the three groups. The cost of the anesthetic drug for ECT was lowest in the propofol group. However, a study from the United Kingdom concluded that patients who received propofol had longer acute courses of ECT and, consequently, longer and costlier inpatient stays and etomidate could be a better alternative induction agent in ECT.[27]

Limitations and merits of the study

The investigators acknowledge certain limitations of the present single blinded randomized trial. The sample size is sufficient to make reasonable statistical conclusions but a larger sample size is desirable. The investigators have excluded patients more than 65 years of age. The study drugs may have different effects in geriatric population undergoing modified ECT. The present researchers have not studied the maximum changes in the hemodynamic parameters, ECG and spO_2 changes during ECT due to the study drugs. Simple recovery parameters were used to assess the recovery profile instead of more sophisticated psychomotor tests. Assessment of cognitive status with MMSE can underestimate impairments resulting from right hemisphere dysfunction as well as milder forms of cognitive dysfunction irrespective of cortical origin.[28] Case studies that demonstrate its inaccuracy in identifying cognitive impairments in individuals with no formal education, average and low-average verbal intelligence quotients.[29]

Consecutive selection and randomization minimizes selection and sample bias. Specific inclusion/exclusion criteria, homogenous group of patients and an attempt at studying cost effectiveness are some of the merits of the study. According to the search carried out on PubMed/Ovid/Research Gate/Google Scholar, the present investigators failed to come across a published study comparing propofol, etomidate and ketofol. This may be considered a unique aspect of this study. Further research with these drugs in modified ECT, especially with ketofol is warranted.

CONCLUSION

In patients undergoing modified ECT, propofol, etomidate and ketofol provide adequate hemodynamic stability and do not significantly impact cognitive functioning. Patients who recieved ketofol had a longer mean seizure duration compared to patients who received propofol and etomidate. Patients who received propofol, in comparison with patients who received etomidate or ketofol had a significantly shorter time to recovery. Propofol appears to be a cost effective otion for patients undergoing ECT. Further research with ketofol in ECT is warranted.

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