PROPOFOL VERSUS WITH PROPOFOL-KETAMINE MIXTURE AS ANAESTHETIC AGENT FOR ELECTROCONVULSIVE THERAPY: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background: **Ketamine either alone or as an adjuvant is associated with an acute reduction in the severity of depression, while its effect on cognitive profile is is equivocal.**

Objectives: **This study compared the mood-elevating and cognitive outcomes of ketamine in combination with propofol versus propofol alone as anaesthetic agents in ECT.**

Methods: **In this randomised-controlled study, 70 patients, aged 18-65years, undergoing ECT for DSM-V major depressive disorder were randomised into two groups. The ketamine-propofol group received intravenous propofol 0.6mg/kg and ketamine 0.6mg/kg, while the second group received intravenous propofol 1.2mg/kg only. Hamilton Depression Rating Scale (HAM-D) was used to assess the severity of depression, the Mini-Mental State Examination (MMSE) was used to assess cognitive performance, pre-ECT (T1), post-1st ECT (T2) and post-3rd ECT course (T3).**

The Analysis of Covariance and the mixed model linear regression were used to analyse the effect of the intervention. Analyses were by SPSS at 95% CI, $p < 0.05$.

Results: **There was a significant reduction in HAM-D score post-3rd ECT in the ketamine-propofol group versus propofol group, $F(1,58) = 23.24$, $p = 0.000$, ¦ = 0.286. There was no significant group difference on post-ECT course HAM-D score, $F(1) = 0.004$, $p = 0.9$. There was no significant group difference on post-ECT course MMSE scores, $F(1) = 2.3$, $p = 0.1$.**

There was no significant group difference on post-3rd ECT MMSE score, $F(1,56) = 0.382$, $P = 0.5$, 5Øß2 = 0.007, no significant group difference on post-ECT course MMSE scores, $(F(1) = 2.3$, $p = 0.1$.

Conclusion: **Ketamine-propofol anaesthesia in ECT is associated with temporary improvement of depressive symptoms, without any superiority to propofol in cognitive outcome at any level of ECT treatment.**

Keywords: Ketamine-propofol combination, Propofol, ECT, Cognitive-impairment, Major depression.

INTRODUCTION

Treatment-resistant depression (TRD) remains a significant public health issue because up to 40% of individuals receiving treatment for either unipolar or bipolar depressive episodes fail to achieve significant clinical improvement with antidepressant medications.[1] Unfortunately, TRD is usually associated with high rates of medical comorbidity such as cardiovascular diseases, notably hypertension or heart failure and diabetes mellitus, contributing significantly to rates of hospital admissions, suicidality and mortality.[2]

Electroconvulsive therapy (ECT) remains the most effective treatment for severe depression and treatment resistant depression (TRD).[3-5] ECT is also the first-line treatment in severe suicidality, severe feed-refusal, severe psychosis and catatonia, and may have a safer profile than pharmacological agents in debilitated, elderly, pregnant[6] and breastfeeding patients.[7]

Despite the consistently demonstrated efficacy of ECT, the need for hospital care, stigma and cognitive side effects have greatly restricted its use.[8-10] ECT-associated cognitive impairment includes impaired attention and concentration, confusion, disorientation, anterograde and/ or retrograde amnesia. ECT-associated cognitive impairment may subside within 14 days, however, these problems persist for up to 1 year in certain high-risk sub-populations, leading to a high dropout rate.[9]

Strategies that have been employed in a bid to attenuate this ECT adverse effect include unilateral ECT electrode placement, use of low-dose stimulation energy, shorter pulse width, longer periods between sessions and administration of pharmacological agents. However, results have been inconsistent.[8] Thus, efforts aimed at amelioration of the cognitive side effects of ECT will be of tremendous importance and would ensure full utilisation of ECT, as well as prevent premature termination of the therapy.

There is growing evidence that ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist through its blockade of glutamate receptors prevents or attenuates ECT- associated cognitive impairment.[4, 11-13] Propofol is another intravenous anaesthetic agent commonly employed for modified ECT, as it is associated with rapid recovery and attenuates hemodynamic response to ECT and proffers good post-ECT cognitive profile.[14,15] Its antiemetic action is particularly useful in minimising post-ictal nausea and vomiting.[16] Consistent with the cognition-sparing hypothesis, the use of ketamine in combination with propofol may be an alternative in ameliorating the menace of ECT-associated cognitive impairment.[17] Beyond this, ketamine, either alone or in combination with propofol, has an antidepressant effect.[18]

In Nigeria, the use of modified ECT is greatly limited by the non-availability of the machine, poor knowledge of ECT, lack of anesthesiologists,[19] and lack of standard guidelines,[20] and cost of purchase, which has immensely contributed to the high, unmet need in the use of ECT, whenever indicated.[21]

Here, we examined the effects of propofol compared with ketamine-propofol combination (ketofol) as an anaesthetic agent during electroconvulsive therapy (ECT) for depression.

The first objective was to determine whether ketofol provides a superior antidepressant effect than propofol. The second objective was to determine if using ketofol resulted in less cognitive impairment compared with propofol following ECT.

We hypothesised that in the ketofol group there would be a better clinical response to depression and a better cognitive outcome compared with the propofol group.

METHODS

Study design

This was a double-blind, prospective, randomised controlled study, block-randomised into 2 groups.

The study setting

This study was carried out at 2 independent centres, the Psychiatric Department of the University College Hospital (UCH) Ibadan, and the New World Specialist Hospital (NWSH), Ibadan.[22] The UCH is an 800-bed hospital and the premier teaching hospital in Nigeria, with a 40-bed psychiatric department.[23] The NWSH is a 60-bed private psychiatric facility that offers mental health and addiction services in Ibadan. Ibadan is the capital city of Oyo state, Nigeria and has a population of about 3.5 million people.[24]

Study Population

Participants

Participants were aged 18-65 years and met the American Society of Anaesthesiologists (ASA) physical status scores 1 and 2 with the DSM-V diagnosis of treatment-resistant depression.

Inclusion criteria

Patients were eligible to participate if they were receiving ECT for major depressive disorder (MDD), were between age 18 to 65 years, met the met the American Society of Anaesthesiologists status 1 -2 and scored at least 24 on the Hamilton Depression Rating (HAM-D) Scale.[25] Participants were also expected to have at least 6 years of education.

Exclusion criteria

Participants with DSM-V bipolar disorder, schizophrenia, schizoaffective disorder, anxiety disorder substance use disorder, any other psychiatric diagnosis, and severe general medical conditions that were considered to be anaesthetic risk were excluded.

Sample size determination

The required sample size for the study was determined using the GPower software for calculating the difference in two independent means.[26]

In the computation, the input was an anticipated effect size of 0.7, α err prob = 0.05. power (1-β err prob) of 0.8, using 2 tail distribution, the minimum sample size was 64 in all.

The effect size of 0.7 input was based on a similar previous study,[27] and same effect was reported in a meta-analysis related to the study.[28]

The sample size software generated a minimum sample of 64, 32/group. Anticipating an attrition of 10%, the minimum sample was increased by 6, totalling 70.

Study groups

In this study, 70 participants were block randomised into 2 groups of 35/group, the ketofol group and the

propofol group. However, 3 withdrew consents in the ketofol group and 2 from the propofol group. Thus, assessments were conducted among 32 participants in the ketofol group and 33 participants in the propofol group pre-ECT, post-1st ECT and post-3rd ECT. The measures determined were the scores of the Hamilton Depression Rating Scale (HAM-D) and Mini Mental State Examination (MMSE) (Figure I).

Sample selection

Patients attending either of the two hospitals and who met the eligibility criteria were blindly consecutively allocated using a computer-generated block randomization sequence, and the two groups were comparable with respect to baseline characteristics, including age and duration of illness. Participants were aged 18 to 65 years, met DSM-V criteria for major depressive disorder and for whom ECT was indicated as adjudged by the attending psychiatrists, based on the severity of the disorders. Participants with major depressive disorder scored 24 or more on the Hamilton Depression Rating (HAM-D) Scale.[25] Participants met the American Society of Anaesthesiologists status 1 -2 and had at least 6 years of elementary education.

Randomization and allocation concealment

Eligible participants were randomly assigned to either the ketamine–propofol (ketofol) group propofol group or the in a 1:1 allocation ratio using a computer-generated randomization sequence. Block randomization was employed to ensure balanced allocation between the two groups throughout the recruitment period. Allocation concealment was maintained using sequentially numbered, sealed opaque envelopes, which were opened only after participant enrolment and completion of baseline assessment. Participants and the investigators responsible for outcome assessment were blinded to treatment allocation throughout the study.

Outcome variables

Primary outcome variable: Changes in HAM-D Score post ECT course between the propofol and ketofol groups.

Secondary outcome variable: Mini-Mental State Examination (MMSE) score post-ECT course in the ketofol group.

Potential confounders: Presence of medical comorbidities and recovery time.

Minimizing bias

Sources of bias were minimised by matching both groups by age and by the duration of illness.

Ethical considerations

Ethical approval for the study was obtained from the joint University of Ibadan and University College Hospital Ethical Committee UI/EC/17/0263, AD 13/479/573. Permission for the study was also obtained from the heads of the two hospitals.

Written informed consent was obtained from either the prospective participants or from their respective primary caregivers for those unable to give consent. The researchers adhered strictly to the principles of respect of autonomy, beneficence, non-maleficence and justice. Participants were not placed on any financial liability and confidentiality was maintained. Participants were instructed about the absolute willingness of the study and freedom to withdraw at any stage, without this affecting their treatment.

Adverse events

Participants were monitored for adverse events throughout the study. No serious adverse events or complications related to the study medications were observed in either treatment group.

Training and quality control

All interviewers were resident doctors in psychiatry and anaesthesiology who have had at least 2-year experience in clinical trials. The Project supervisors were two. One is an anaesthesiologist with about 10 years of experience, while the other is a psychiatrist with over 30 years of experience in ECT. All interviewers had two-week training sessions, followed by another session of debriefing when all conflicting areas were clarified.

Study procedure

Any prescribed benzodiazepines and mood stabilizers were discontinued 72 hours before the procedure. All the patients had intravenous glycopyrrolate 0.2mg as premedication prior to induction of anaesthesia. The control group was anaesthetised with intravenous propofol 1.2mg/kg, while the intervention group had intravenous propofol 0.6mg/kg and ketamine 0.6mg/kg. Also, intravenous suxamethonium 0.5mg/kg was administered for muscle relaxation after induction of anaesthesia. This was done by the attending anaesthetist who was blinded to the patient's grouping. Supplemental oxygen was provided to all the subjects using a bag and facemask and their airway was also supported with an oropharyngeal airway. A multi-parameter monitor (Mindray imec 10, Mindray (UK)

was used for continuous monitoring during the period of the procedure. Measured parameters included heart rate, blood pressure, mean arterial pressure, Oxygen Saturation, electrocardiography, and end-tidal Carbon dioxide.

Each of the participants had bilateral ECT with electric stimulation delivered with a brief-pulse ECT device. For the delivery, the pulse width was set between 0.5 and 1.0ms, pulse frequency at 100 to 200pulses/s and amplitude at 0.5 to 1.0A. Following the electrical shock, the patients were manually ventilated with 100% Oxygen until the return of spontaneous respiration.

Measurements and data sources

Socio-demographic questionnaire

This is a section comprising a set of questions about the socio-demographic characteristics of the respondents, such as age, gender, education, occupation, duration of illness, and diagnosis.

Hamilton depression rating (HAM-D) scale

The 17-item version of the Hamilton Depression Rating (HAM-D) Scale was used to assess the severity of depression.[25] The HAM-D scale is an interviewer-rated measure of the severity of depression that determines the mood is impacting an individual's work or leisure pursuits. Scoring is based on the 17-item scale and scores of 0–7 are considered normal, 8–16 suggest mild depression, 17–23 moderate depression and scores over 24 are indicative of severe depression; the maximum score is 52 on the 17-point scale. The HAM-D has been validated in Nigeria, with an inter-item correlation of 0.4.[29] The mean scores of the HAM-D were used in the analysis of the results.

Mini-mental state examination (MMSE)

The Folstein Mini Mental State Examination (MMSE), a 30 item assessment of cognitive function, was used to assess the cognitive functions of the patients.[30] The test includes simple questions, a test of orientation, attention and concentration, arithmetic, language use and basic motor skills. The maximum score is 30, with a traditional cut-off point of 23/24. The test was used in assessing the cognition of the patients before the commencement of ECT, after the third session and at the completion of ECT. The MMSE has been used in several studies in Nigeria,[31, 32] and validated with a sensitivity of 93.3% and specificity of 71.8%, AUC of 0.86.[33] The mean scores of the MMSE were used in the analysis of the results.

Assessments were carried out before the first ECT treatment (within 2 to 24 hours), post-3rd ECT (within 24 and 48 hours) and post-ECT course, also within 24 to 48 hours. Each assessment lasted between 34 and 38 minutes. Figure 1 shows the flow of the participants through each stage of the study.

Pilot study

A pilot study was carried out among 10% of the proposed sample size at the Psychiatric Unit of the Ring Road State Hospital, Ibadan, Oyo State. During this period, we assessed inter-rater reliability between the researchers, willingness to be a part of the study, dropout rate, and the entire study protocol. Participants scored over 90% in each of these constructs. The pilot study revealed the average time required for administration of all questionnaires and this was approximately 30 minutes. The inter-rater reliability was determined using kappa statistics and was 0.8 to 1.0.

Data collection and analysis

The sociodemographic characteristics of the two groups were compared using the Pearson Chi-square test. The differences in the mean heart rate, blood pressure, oxygen saturation, end-tidal Carbon dioxide, seizure duration, recovery time sessions and the primary and secondary outcome variables at the three stages of the study between the two groups were analysed using the independent t test.

In the immediate effect (post-3rd ECT) analysis, analysis of covariance (ANCOVA) was used to compare outcomes pre-ECT with post-3rd ECT measures, while controlling for the baseline scores and demographic variables associated with them at baseline, respectively. The effect size was estimated using the partial eta-squared (η^2_p).

For the analysis of the treatment effect, linear mixed models compared measures assessed pre-ECT with post-3rd ECT and post-ECT course. All data were analysed at 95% CI using Statistical Package for Social Sciences (SPSS) Version 23.

Missing Data

Participants with missing outcome data were excluded from the relevant analyses using listwise deletion. Listwise deletion was used because, the major outcome variable at any assessment stage in each of the two groups did not have more than 5% missing data and the listwise means versus means for all values are not statistically different.

RESULTS

Out of 70 prospective subjects recruited into the study, 5 participants withdrew consent after randomisation. Thus, data analysis was carried out on 65 participants. The mean age of the participants was 37.0 ± 14.7 and 38.1±13.6, p = 0.7 in the propofol group and ketofol group, respectively. The sociodemographic and clinical

Table 1: Sociodemographic and clinical characteristics of participants

	Ketofol		Propofol			
Variable	**N**	**%**	**N**	**%**	**X^2**	**P**
Age						
18-27	12	37.5	13	39.4	2.0	0.7
28-37	7	21.9	5	15.2		
38-47	4	12.5	8	24.2		
48-57	2	6.3	2	6.1		
>57	7	21.9	5	15.2		
Gender						
Male	19	59.4	14	42.4	1.9	0.2
Female	13	40.6	19	57.6		
Occupation						
Employed	17	53.1	13	39.4	0.7	0.3
Unemployed	15	46.9	20	60.6		
Duration of Illness						
0-5	25	83.3	24	82.8	1.1	0.8
6-10	4	13.3	3	10.3		
11-15	1	3.3	1	3.4		
>15	0	0.0	1	3.4		
Comorbidity						
Yes	30	93.8	23	69.7	FE	0.02
No	2	6.3	10	30.3		
No of ECT Sessions						
4	11	34.4	17	51.5	2.4	0.7
5	3	9.4	2	6.1		
6	16	50.0	14	42.4		
8	2	6.3	0	0.0		
Clinical Variables	**Mean**	**SD**	**Mean**	**SD**	**t**	**P**
Pre-ECT HAM-D	40.85	5.21	42.59	5.25	1.3	0.2
Post-3rd ECT HAM-D	20.85	5.21	22.47	5.23	-1.3	0.2
Post-ECT Course HAM-D	5.18	2.49	5.75	2.72	0.9	0.4
Pre-ECT MMSE (T1)	28.07	1.55	27.56	1.28	-.1.44	0.2
Post-3rd ECT MMSE (T2)	26.28	2.24	26.87	1.56	0.9	0.4
Post-ECT Course MMSE (T3)	27.10	3.21	26.36	2.06	0.8-	0.4
Number of ECT Sessions	5.13	0.13	4.93	1.11	0.6	0.6
Recovery Time	439.5	102.5	383.59	82.9	2.4	0.02

HAM-D: Hamilton Depression Scale; MMSE: Mini Mental State Examination; ECT: Electroconvulsive Therapy

profiles of the patients are presented in Table 1. A significantly higher proportion of respondents in the ketofol group reported any medical comorbidity, FE = 0.02. The mean time to recovery was significantly higher in the ketofol group than the propofol group t = -2.4, p = 0.02. (Table 1).

Acute effects (between pre-ECT and post-3rd ECT)
A significant main effect of type of anaesthetic agent on post-3rd ECT HAM-D scores was found compared with pre-ECT HAM-D scores, $F_{(1,58)}$=23.24, p = 0.000, ¦ = 0.286. The adjusted means (AdjM) score for propofol = 28.65, SE 0.08, AdjM for ketofol is 26.72, SE = 0.06. Pairwise comparisons show that the mean difference is significant.

A significant main effect of pre-ECT HAM-D score on post-3rd ECT HAM-D score, was found $F_{(1,58)}$=2521.49, p < 0.001, ¦2 = 0.978. There was no significant effect of recovery time, $F_{(1,58)}$= 1.42, p = 0.2, presence of medical comorbidity $F_{(1,58)}$ = 3.64, p = 0.06, ¦2 = 0.059, or the interactions of anaesthetic group, recovery time and pre-ECT HAM- D on post-3rd ECT HAM-D score, $F_{(1,58)}$ = 1.45, p = 0.2, ¦2 = 0.048 (Table 2).

Table 2: Acute effects analysis between Pre-ECT and Post-3rd ECT: HAM-D

Variables	df	Mean Square	F	Sig.	Partial Eta Squared (η^2)
Corrected Model	6	320.75	2813.67	<0.001	0.997
Intercept	1	8.43	73.99	<0.001	0.561
GROUP	**1**	**2.65**	**23.26**	**<0.001**	**0.286**
Recovery Time	1	0.16	1.42	0.2	0.024
Comorbidity	1	0.41	3.64	0.06	0.059
HAMD1	1	287.4	2521.49	<0.001	0.978
GROUP * Recovery Time * comorbidity * HAMD1	2	0.17	1.45	0.2	0.048

HAM-D: Hamilton Depression Scale; MMSE: Mini Mental State Examination; ECT: Electroconvulsive Therapy; Adjusted means for propofol = 28.65, SE 0.08, ketofol = 26.72, SE 0.06, p < 0.001; 5Øß2: Partial Eta Squared: Adjusted means:AdjM

For the MMSE ratings, there was no significant effect of anaesthesia type on post 3rd ECT MMSE score, $F_{(1,56)}$ = 0.382, ***P = 0.5***, ¦2 = 0.007, no significant effect of recovery time, $F_{(1,56)}$ = 0.1, p = 0.7, ¦2 = 0.002, no significant effect of presence of comorbidity, $F_{(1,56)}$ = 0.22, p = 0.6, ¦2 = 0.004, no significant effect of pre-ECT MMSE, $F_{(1,56)}$ = 2.11, p = 0.15, ¦2 = 0.036, no significant interactive effects of anaesthetic group, recovery time, presence of comorbidity and baseline MMSE score on post-3rd ECT scores, $F_{(1,56)}$ = 0.21, p = 0.8, ¦2 = 0.007 (Table 3).

Treatment effects (between pre-ECT, post-3rd ECT and post-ECT course)

Linear mixed models were used to examine group differences in the severity of depression and level of

Table 3: Acute effects analysis between Pre-ECT and Post-3rd ECT: MMSE

Variables	df	Mean Square	F	Sig.	Partial Eta Squared (η^2)
Corrected Model	6	7.91	2.41	0.04	0.205
Intercept	1	17.16	5.23	0.03	0.085
GROUP	**1**	**1.25**	**0.38**	**0.54**	**0.007**
Recovery Time	1	0.34	0.1	0.7	0.002
comorbidity	1	0.75	0.22	0.6	0.004
Baseline MMSE	1	6.91	2.11	0.15	0.036
GROUP * Recovery Time * comorbidity *Baseline MMSE	2	0.69	0.21	0.8	.007
Error	56	3.279			

HAM-D: Hamilton Depression Scale; MMSE: Mini Mental State Examination; ECT: Electroconvulsive Therapy; Adjusted means for propofol = 27.26, SE 0.52, ketofol = 27.19, SE 0.35, p = 0.09; 5Øß2: Partial Eta Squared: Adjusted means:AdjM

Table 4: Effects analysis between Pre-ECT, Post-3rd ECT and Post-ECT Course: MMSE

				95% CI		Tests of Fixed Effects	
Parameter	df	t	Sig.	Lower Bound	Upper Bound	F	P
Intercept	55.00	0.79	0.4	-15.8	36.3		
Ketofol Group	55.00	1.52	0.1	-1.2	9.3	2.3	0.1
Propofol Group	.	.	.	.	.		
Pre-ECT MMSE	.00	-.001	1.0	-1.7	1.7	0.00	1.0
Post-3rd ECT MMSE	.00	-0.85	1.0	-165.3	159.7	0.7	1.0
Recovery Time	216581833634.87	0.002	1.0	-567.5	568.4	0.00	1.0
Comorbidity	3437.40	0.19	0.9	-1.2	1.4	0.04	0.8
Ketofol group * Recovery time * Pre-ECT MMSE * Post-3rd ECT MMSE * Comorbidity	55.00	0.64	0.5	-1.3E-5	2.5	0.9	0.4

Adjusted post-ECT Course HAM-D means for propofol = 4.7, SE 1.0, ketofol = 5.4, SE 1.0, p = 0.7; HAM-D: Hamilton Depression Scale; MMSE: Mini Mental State Examination; ECT: Electroconvulsive Therapy

cognitive function over time (pre-ECT, post-3rd ECT and at the end of the ECT course). These data are displayed in Tables 4 and 5, respectively.

For HAM-D ratings, there was no significant effect of anaesthetic type on post-ECT course HAM-D score, $F_{(1)}$= 0.004, p = 0.9, no significant effect of

Table 5: Effects analysis between pre-ECT, post-3rd ECT and post-ECT course: HAM-D

				95% CI		Tests of Fixed Effects	
Parameter	**df**	**t**	**Sig.**	**Lower Bound**	**Upper Bound**	**F**	**P**
Intercept	57.0	.28	0.8	-27.19	35.48	0.04	0.9
Ketofol Group	57.0	1.0	0.3	-2.50	8.0	0.004	0.9
Propofol Group	.	.	.	.	.	-	-
Pre-ECT HAM-D	57.0	-1.24	0.2	-3.28	.75	0.00	1.0
Post-3rd ECT HAM-D	57.0	1.55	0.1	-.477	3.75	0.5	0.5
Recovery Time	57.0	1.30	0.2	-.007	.04	1.3	0.3
Comorbidity	57.0	1.59	0.1	-1.29	11.15	0.4	0.5
Ketofol group * Recovery time * Pre-ECT HAM-D * Post-3rd ECT HAM-D * Comorbidity	57.0	-1.51	0.1	-2.36	3.33	1.5	0.3

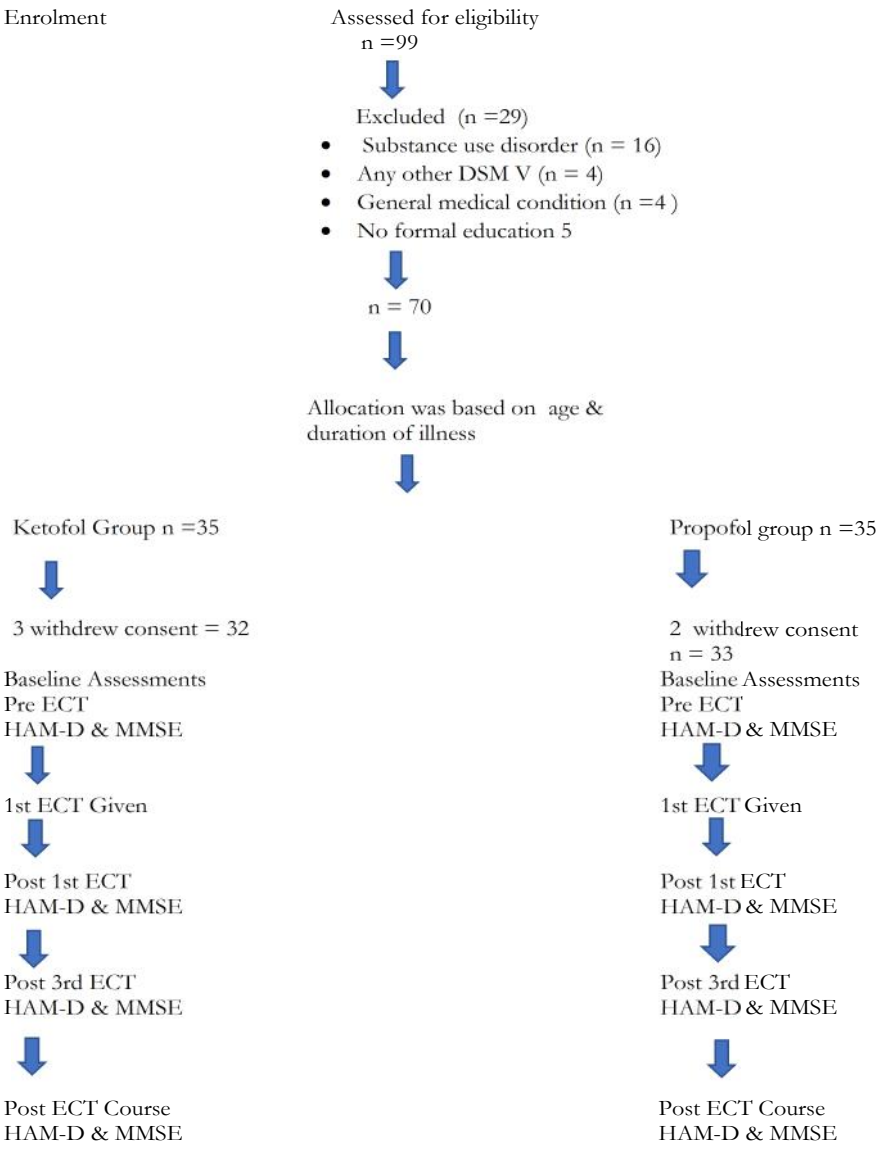


Figure 1: Consort flow chart

pre-ECT HAM-D score on post-ECT course HAM-D score, $F_{(1)}$= 0.00, p = 1.0, no significant effect of post-3rd ECT HAM-D score on post-ECT course scores. $F_{(1)}$= 0.5, p = 0.5, no significant effect of presence of comorbidity on post-ECT course HAM-D score, $F_{(1)}$= 0.4, p = 0.5, no significant effect of recovery time on post-ECT course HAM-D score, $F_{(1)}$ = 1.3, p = 0.3, no significant interactive effects anaesthetic group, recovery time, pre-ECT HAM-D, post-3rd ECT HAM-D and presence of comorbidity on post-ECT course HAM-D score, ($F_{(1)}$ = 1.5, *P* = 0.3 (Table 4).

For the MMSE ratings, there was no significant effect of anaesthetic group on post-ECT course MMSE scores, ($\boldsymbol{F}_{(1)}$ = 2.3, p = 0.1, no significant effect of recovery time on post-ECT course MMSE scores, ($\boldsymbol{F}_{(1)}$ = 0.0, p = 1.0, no significant effect of comorbidity on ECT course MMSE scores, ($\boldsymbol{F}_{(1)}$ = 0.7, p = 1.0, no significant effect of pre-ECT MMSE scores on post-ECT course MMSE scores, $\boldsymbol{F}_{(1)}$ = 0.00, p = 0.98 and no significant interacting effects of these factors on post-ECT course MMSE scores, $\boldsymbol{F}_{(1)}$ = 0.9, p = 0.5 (Table 5).

DISCUSSION

Contrary to our hypotheses, this prospective, randomized study showed that although the ketofol group demonstrated a lower HAM-D score post-3rd ECT, this was not so with the MMSE scores post-3rd ECT. There was also no significant difference in the severity of depression and cognitive function between the two groups post-ECT course.

The result presented at post-3rd ECT in which HAM-D scores were significantly lower in the ketofol group joins evidence that ketamine has limited efficacy as an antidepressant when it is used as an anaesthesia in ECT, with clinical evidence on an acute timescale.[34, 35] These observations were complemented by the results of another randomised controlled trials,[36] that compared ketamine with thiopental as the anaesthetics for ECT and found significantly lower levels of depression before the end of the 6-session ECT but no significant difference between the group at the end of the course. Contrarily, Rasmussen *et al.*,[37] found no significant differences in the depression scales during the entire ECT treatment course when ketamine was compared with methohexital anaesthesia in ECT. However, the randomized controlled trial of Wang *et al.*[18] found that decreases in depression rating scores were more significant in either Ketamine anaesthesia group or Ketofol compared with propofol only anaesthesia group, although all patients received only 1 ECT treatment and the assessments were daily for 4 days, followed by day 7.

As stated earlier, we did not find and significant reduction in the HAM-D score post-ECT course in the ketofol group. This finding is consistent with the result from a systematic review and meta-analysis, suggesting that the antidepressant effect of ketamine is not applicable when it is used as the anaesthetic in ECT.[35] Similarly, the "KANECT" study compared ketamine with propofol and found no significant difference in the HAM-D score post-ECT course.[38]

Although the cognition preserving function of ketamine anaesthesia during ECT has been documented in different literature,[4,11-13] the study reported herein showed that the addition of ketamine to propofol did not offer any protection against ECT-associated cognitive impairment as measured by the MMSE post ECT course. This is in support of the findings of McGirr *et al.*, in their systematic review and meta-analysis,[39] and the KANECT trial.[38] Another study that compared ketamine to 0.9% normal saline given as an adjunct before anaesthesia induction, did not also report any superior cognitive outcomes for adjunctive ketamine anaesthesia for ECT in depression.[40]

The major discrepancies between the results from previous studies and ours should be considered in the light of the fact that we used a mixture of ketamine and ketofol, while those studies used ketamine alone. The discrepancies could be considered, given differences in the sample size, variation in drug doses, and drug combination, measures of severity of depression and cognitive impairment, and differences in the frequency and duration of ECT treatment.

The mean number of ECT given to patients in the two groups reported in the current study ketofol (5.13 ± 1.31) vs propofol (4.93±1.12) is lower than the number of ECTs administered in previous studies, 8 by Okamotor[41] and 7.88 vs 7.26 for ketamine and propofol, reported in the KANECT trial.[38] This could have also contributed to the discrepancies between our findings and those from previous studies.[38,41]

Nevertheless, our study is adequately powered to detect if a difference exists between matched pairs. Our study was based on an effect size of 0.5, 34 patients per group would be recruited (2-tailed, power of 80%, critical *t* of 1.98). We achieved a sample size of 65. Our sample was larger than the KANECT trial (n = 40) and the sample size used by Okamoto et al (n=31).[41]

We observed a longer recovery time in ketofol group following ECT administration. This is in line with known pharmacological profiles of ketamine.[42,43]

However, this did not contribute to the MMSE model of the ketofol group. both at post-3rd ECT and the end of the ECT course.

Our study has implications for the choice of anaesthesia for ECT, not only in depression but also whenever ECT is indicated in patients with psychiatric disorders.

Strength and limitations

The major strength of this study is the research design and its ability to provide data for evidence-based clinical work. Our findings are also generalizable given the statistically determined sample and the research design. Our statistically calculated sample size is larger than previous studies of references.[40] This further increased the power of the study.

However, results are limited by a few factors, first, we placed no restrictions on the medication patients received both prior to and during the ECT course, except for anticonvulsants and benzodiazepines that were withdrawn before the ECT. This is important as concomitant psychotropic medications have differential implications on cognitive outcome and quality of seizure, which indirectly could have affected our results. However, the randomisation process should have minimized this and ensured a similarity between the group distribution.

We also did not evaluate the long-term effect of the two anaesthetic agents on the attenuation of ECT-associated cognitive impairment. Thus, further studies with a longer period of follow-up are recommended to fully explore the use of ketamine in ameliorating ECT-associated cognitive impairment. We also did not examine impairments in daily life, persistent autobiographical memory deficits and subjective cognitive impairment. Future studies should explore these.

CONCLUSION

In conclusion, the results of this double-blind, parallel-design, RCT demonstrate although ketamine-propofol anaesthesia in ECT is associated with temporary improvement of depressive symptoms, it has no superiority to propofol in cognitive outcome at any level of ECT treatment.

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