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Research paper

A randomized clinical trial of adjunctive ketamine anesthesia in electroconvulsive therapy for depression

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ABSTRACT

Background: Electroconvulsive therapy (ECT) is a rapid acting and effective treatment for both major depressive disorder (MDD) and bipolar disorder (BP). Both propofol and ketamine are commonly used anesthetic agents but recent clinical studies suggest that ketamine has rapid-acting antidepressant properties, itself, at sub-anesthetic doses.

Methods: A total of 77 inpatients (41 MDD and 36 BP) were randomly assigned to receive ECT with propofol (1 mg/kg) anesthesia or with ketamine (0.5 mg/kg) plus propofol (0.5 mg/kg). Depressive symptoms were assessed with the 24-item Hamilton Depression Rating Scale (HAMD-24) and Montgomery–Asberg Rating Scale (MADRS), before and after 1, 2, 4, and 6 ECT treatments, and 1–4 weeks following the last treatment. The MATRICS Consensus Cognitive Battery (MCCB) was evaluated at baseline,after the sixth ECT, and 1–4 weeks following the final ECT. Adverse effects were assessed at baseline and 4 weeks after the last treatment.

Results: There were no significant differences in depressive symptoms, MCCB performance, or adverse effects between the treatment groups at any time. The electrical dose required to generate seizures in the ketamine plus propofol group was lower than that of the propofol only group at every time point. The seizure energy index and seizure duration in the ketamine plus propofol group was higher and longer than those in the propofol only group.

Limitations: The diagnoses of MDD and BP were unevenly distributed across treatment groups.

Conclusions: Ketamine plus propofol anesthesia in the ECT treatment of MDD and BP was not superior on any measure to propofol alone.

1. Introduction

Depressive disorders, including both Major Depressive Disorder (MDD) and Bipolar Disorder (BP) are severe and chronic psychiatric illnesses that are associated with substantial morbidity and high health care costs, affecting approximately 350 million people worldwide each year (Oremus et al., 2015). The World Health Organization has predicted that depression will become the second largest cause of disability worldwide in 2020, with its highest prevalence among adolescents (Bayati et al., 2009). Psychopharmacological treatments, psychotherapy, and electroconvulsive therapy (ECT) have all been widely used to treat MDD and BP. However, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study found that a majority of patients do not achieve clinical remission after the first treatment and many become treatment resistant (Trivedi et al., 2006). Electroconvulsive therapy (ECT) had been demonstrated to be an effective therapy for major depressive disorder (Martensson et al., 2013), with a response rate of approximately 79%, and a remission rate of 75% (Tang et al., 2012). There is some evidence that adequate seizure duration and higher doses of electricity are essential to optimize the antidepressant effects of this treatment (Boylan et al., 2000). Propofol is a commonly used sedative and anesthetic agent for ECT. However, it has potent anticonvulsant properties, and thus may impact the quality of the induced seizure and hamper the effectiveness of ECT treatment (Bundy et al., 2010).

Ketamine, a phencyclidine hydrochloride derivative, is a non-competitive N-methyl-d-aspartate (NMDA) receptor antagonist. Ketamine is a well-known anesthetic agent, and recent clinical studies have shown that it can also produce rapid antidepressant effects in subanestehetic doses among patients suffering from depressive symptoms from either MDD or BP (Berman et al., 2000; Diazgranados et al., 2010; Serafini et al., 2014). Ketamine has also been found to reduce suicidality in

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treatment-resistant depression (TRD). Robust and rapid antidepressant effects have been observed after a single intravenous dose of ketamine (0.5 mg/kg) (Zarate et al., 2006) with benefits becoming apparent within 2 h after infusion and with thirty-five percent of subjects maintaining their response for at least 1 week (Zarate et al., 2006).

Ketamine has been used, specifically, in ECT anesthesia for many years and, in view of its antidepressant effects, may augment the therapeutic benefits of ECT (Loo et al., 2012; Zhong et al., 2016). Comparison of seizure duration, ictal EEG, and cognitive effects of ketamine and methohexital anesthesia with ECT showed ketamine to be well tolerated and associated with prolonged seizure duration, as well as with fewer cognitive side effects (Krystal et al., 2003). One previous study suggested that use of ketamine anesthesia may improve the efficacy of ECT as compared with propofol anesthesia (Okamoto et al., 2010) while another reported that at a dose of 0.5 mg/kg, given just before electroconvulsive therapy, ketamine did not enhance antidepressant effects (Abdallah et al., 2012).

Cognitive impairment is a common side effect of ECT, and one that is often observed after idiopathic grand mal seizures (MacPherson and Loo, 2008). Both anterograde and retrograde amnesia are produced by convulsive treatment in nonhuman primates (Moscrip et al., 2004). There is also evidence that ketamine may increase synaptic signaling proteins in the prefrontal cortex of rats (Li et al., 2010) and may thereby reduce cognitive impairment during ECT.

This randomized double blind clinical trial compared ECT with propofol anesthesia to ECT with ketamine and propofol together to determine whether ketamine could augment the effectiveness of ECT when used an an anesthetic agent. Outcomes included antidepressant effects, ECT parameters, cognitive function and side effects.

2. Methods

2.1. Subjects

Seventy-seven patients with clinical symptoms of depression were enrolled in a randomized trial of anesthetic strategies for modified ECT at the Department of Psychiatry of the Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital) between June 2014 and October 2015. To be eligible, participants met diagnostic criteria for either major depressive disorder (MDD) or bipolar disorder (BD), and were currently in a major depressive episode by ICD-10 criteria that had not showed an adequate clinical response with at least two antidepressant drugs of different pharmacological classes at adequate dosages for at least 6 weeks.

Patients were excluded if they had a primary psychiatric diagnosis other than MDD or BD, such as schizophrenia and dementia; or current severe physical illness or organic brain disease; as were those with other contraindications for ECT or for anesthesia. The study was approved by the ethics committee of the Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital). Written informed consent was obtained from all participants.

2.2. Treatment

ECT was performed using the Thymatron ® IV device (Somatics LLC, Lake Bluff, Illinois, USA) with bitemporal electrode placement. The seizure threshold was estimated using the half-age method (% energy = half current age) in each case (Chung and Wong, 2001). Seizure duration and the seizure energy index on the EEG were recorded during anesthesia. Systolic and diastolic blood pressures were recorded just before anesthesia and approximately 30 min following the ECT procedure. Patients were randomly assigned to receive propofol anesthesia alone, or propofol plus ketamine based on double blind random assignment such that the raters and the patients were blind to the anesthetic agent.

ECT treatment was performed three times per week for two consecutive weeks for a total of six treatments. No antipsychotic or antidepressive drugs were prescribed to the patients during the period of delivering ECT. The two groups first received atropine sulfate (1 mg). Then, they received propofol (1 mg/kg) alone, or ketamine (0.5 mg/kg) plus propofol (0.5 mg/kg) I.V. push for ECT anesthesia. Succinylcholine (1 mg/kg) was administered intravenously to all patients as a muscle relaxant after the induction of anesthesia.

2.3. Assessment of depressive and psychotic symptoms and adverse effects

The 24-item Hamilton Depression Rating Scale (HAMD-24) (Hamilton, 1960) and the Montgomery–Asberg Rating Scale (MADRS) (Montgomery and Asberg, 1979) were used to assess the severity of depressive symptoms at baseline or 1 day before the first ECT treatment, and 1 day after ECT treatments 1, 2, 4, and 6 and again 1–4 weeks following the last of the six treatments. The criterion for response was ≥ 50% decrease in the HAMD-24 total score from baseline, while the criterion for remission was having a MADRS total score ≤ 10. Adverse events were documented during hospitalization by a psychiatrist.

2.4. Assessment of neurocognitive function

Neurocognitive functioning was assessed at baseline; after 6 treatments and 1–4 weeks following the last treatment by a trained neuropsychological technician using a subset of the MATRICS Consensus Cognitive Battery (MCCB). The evaluation of all subjects followed procedures described previously (Zhou et al., 2015). Briefly, the Chinese version of the MCCB includes seven domains and nine subtests: (1) Speed of Processing (SoP), consisting of three tests: Category Fluency, Trail Making Test (TMT), and Brief Assessment of Cognition in Schizophrenia: symbol coding (BACS SC); (2) Attention/Vigilance(AV), using the Continuous Performance Test-Identical Pairs (CPT-IP); (3) Working Memory(WM), using the Wechsler Memory Scale-III (WMS III): Spatial Span; (4) Verbal Learning(Vrbl Lrng), using the Hopkins Verbal Learning Test-RevisedTM (HVLT-RTM); (5) Visual Learning(Vis Lrng), using the Brief Visuospatial Memory Test-Revised (BVMT-RTM); (6) Reasoning and Problem Solving(RPS), using the Neuropsychological Assessment Battery®, (NAB®): Mazes; and (7) Social Cognition(SC), measured by the Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEITTM): Managing Emotions. The reliability and validity of the Chinese version of the MCCB has been demonstrated previously (Shi et al., 2013). Each domain score was standardized to a T score with a mean of 50 and a standard deviation of 10. For the domain that includes more than one test, a composite T score was calculated by averaging standardized value of each test T score.

2.5. Statistical analysis

Baseline data are expressed as mean ± SD for continuous variables, as number (%) for categorical variables. Analysis proceeded in several steps. First, *t*-tests were used to compare treatment groups at baseline on continuous measures. Chi-square tests were used to examine baseline differences in sex, diagnosis, family history, suicidal behavior, alcohol consumption and tobacco smoking.

Secondly, the group comparisons of follow-up data (the HAMD-24, the MADRS, the treatment parameters of ECT, the T scores of MCCB and the side effects) were compared using linear mixed models which included terms for treatment group, time and the interaction of time and treatment group and which were adjusted for diagnosis (BP or MDD) which was included as a covariate. A power analysis was done to estimate the effectiveness of sample size, which were performed using PASS 11. A two-tailed p value < 0.05 was used as the criterion for significant group differences. All statistical analyses were performed using SPSS version 18.0 for windows.

Table 1
Clinical and demographic characteristics of ECT subjects.

Socio-demographics	Total (n = 77)	Ketamine plus Propofol Group (n = 43)	Propofol Group (n = 34)	t/x2	p
Gender(male/female)	36/41	19/24	17/17	0.258	0.612[a]
Age(years)	30.21 ± 10.15	31.47 ± 11.47	28.62 ± 8.06	−1.227	0.224[b]
Years of education	12.22 ± 2.87	12.14 ± 2.91	12.32 ± 2.87	0.271	0.787[b]
Age of onset	24.96 ± 10.26	26.49 ± 10.88	23.03 ± 9.22	−1.480	0.143[b]
Duration of the disease (years)	5.33 ± 4.66	5.06 ± 4.80	5.66 ± 4.53	0.553	0.582[b]
DUP(months)	25.3 ± 42.55	20.74 ± 37.00	31.13 ± 48.75	1.036	0.304[b]
Number of hospitalization	2.08 ± 1.12	2.02 ± 1.12	2.15 ± 1.21	0.464	0.644[b]
Family history(absence/presence)	56/21	28/15	28/6	2.844	0.092[a]
Suicidal behavior(absence/presence)	20/57	11/32	9/25	0.008	0.93[a]
Diagnose					
Major depression	41(53.2%)	28(65.1%)	13(38.2%)	5.511	**0.019**[a,*]
Bipolar depression	36(46.8%)	15(34.9%)	21(61.8%)		
Tobacco(absence/presence)	72/5	40/3	32/2		1.000[c]
Alcohol(absence/presence)	74/2	40/2	34/0		0.499[c]
MARDS at baseline (7 miss)	33.87 ± 8.45	34.00 ± 8.55	33.72 ± 8.46	−0.138	0.891[b]
HAMD-24 at baseline (9 miss)	35.12 ± 8.14	34.59 ± 8.72	35.74 ± 7.49	0.576	0.567[b]

Abbreviations: DUP, duration of untreated psychosis; HAMD-24, 24-item Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Rating Scale.
[a] $\chi 2$ test.
[b] T test.
[c] Fisher's exact test.
* $P < 0.05$.

3. Results

3.1. Demographic and clinical characteristics data

A total of 77 inpatients with depression who consented to ECT were enrolled, including 41 (53.2%) with MDD and 36 (46.8%) with BP. Patients were randomized into two groups, to received either propofol anesthesia (n = 34) or ketamine plus propofol (n = 43). Twenty-one patients (61.8%) in the propofol group and 15 (34.9%) patients in the ketamine plus propofol group were diagnosed with bipolar disorder. There were no significant differences in gender, age, years of education and baseline depression scores between the two groups, although diagnoses was significantly different ($p < 0.05$) (Table 1).

3.2. Depression outcomes

Improvements in depressive symptom were observed with both anesthetic regimens (see Fig. 1 and highly significant time effects in Table 2), The power analysis showed that the time effects power value both was 1.000 for HAMD-24 scores and MARRDS scores. But there were no significant differences between treatment groups (group effect in Table 2).

There was also no significant difference between treatment groups in the proportion who achieved remission at any time point. (Fig. 2A) or in the proportions meeting criteria for response at any time point (Fig. 2B). There was no significant main effect for the diagnostic covariate (BP vs MDD) in any analysis.

3.3. Cognitive function

No significant difference was found on the MCCB between the propofol group and the ketamine plus propofol group (Table 3). More specifically there were no significant differences between the groups on the T scores for any of the subscales of the MCCB. There was a significant time effect for Reasoning and Problem Solving(RPS) and Social Congnition(SC) but no significant group-by-time interaction effects.

3.4. Treatment parameters of ECT

As shown in Table 4, the Linear mixed models examining the effects of the treatment group on the electrical dose used showed a significant main effect for increased electrical dose over time (F = 43.986, p < 0.001) and the group comparison showed significantly lower electrical dose (F = 18.775, p < 0.001), higher scores on the seizure energy index and greater seizure duration in the ketamine plus propofol group (F = 7.199, p < 0.01; F = 7.134, p < 0.01, respectively). The group-by-time interaction for the electrical dose (F = 7.904,

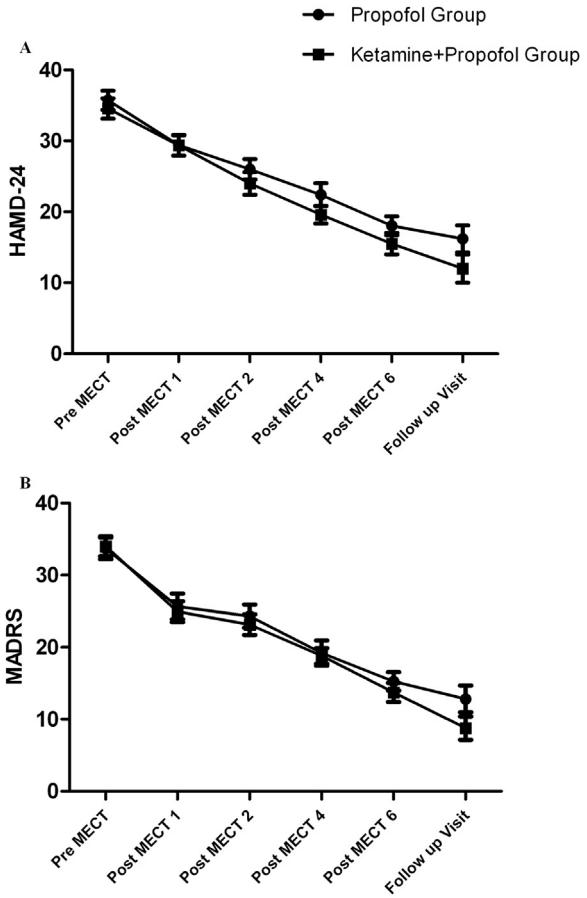

Fig. 1. Comparisons the change of the 24-item Hamilton Depression Rating Scale and Montgomery–Asberg Rating Scale at pre-ECT, after 1, 2, 4, 6 times ECT and follow-up visit between propofol group and ketamine plus propofol group. Data indicate the mean ± SEM.

Table 2
Total HAMD-24 and MARDS scores of ECT subjects analyze by covariates with diagonse in Linear mixed models.

	SUM		Main effect of time		Main effect of grouping factor		Group-by-time interaction	
Psychotic symptoms	Ketamine plus Propofol Group (n = 43)	Propofol Group (n = 34)	F	p	F	p	F	p
HAMD-24	22.63 ± 0.95	24.60 ± 1.03	98.943	< **0.001*****	1.368	0.246	0.628	0.679
MARDS	20.80 ± 1.04	21.50 ± 1.13	104.335	< **0.001*****	0.063	0.803	0.269	0.930

Abbreviations: HAMD-24, 24-item Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Rating Scale.
*** $P < 0.001$.

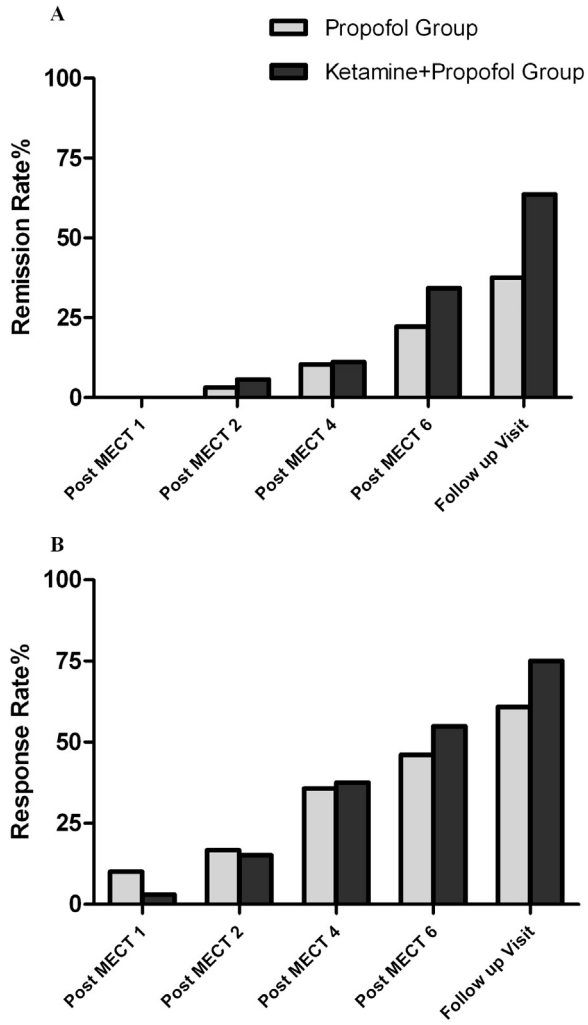

Fig. 2. The remission and response rates at after 1, 2, 4, 6 times ECT and follow-up visit in propofol group and ketamine plus propofol group.

p < 0.0010) showed progressively lower relative doses of electricity in the ketamine plus propofol group.

3.5. Adverse events

Analysis of systolic and diastolic blood pressures both showed higher values for the ketamine plus propofal group (F = 10.962, p = 0.001; F = 32.814, p < 0.001, respectively) although they were not in a dangerous range (Table 5). There was no difference in heart rate and breathing recovery time between two groups (Table 5). Analysis of consciousness recovery time detected a main effect of time (F = 3.941, p < 0.01), but not group or group-by-time interaction.

During the six ECT treatments, no major adverse effects were observed in patients who received ketamine plus propofol or propofol as the anesthesia agent. The majority of patients in two groups reported minimal transient adverse events, including rapid heartbeat and irritability. None of these side effects were severe enough to require discontinuation of the ECT treatment.

4. Discussion

This randomized clinical trial showed no greater benefits for the ketamine-propofol combination in reducing symptoms of depression or adverse cognitive effects, and had no more serious side effects except for a modest increase in blood pressure. The ketamine plus propofol group required a lower level of electric energy input, and showed increased seizure duration and a higher seizure energy index but, in the final analysis, ketamine plus propofol anesthesia in ECT for the treatment of depression in MDD and BP patients had no advantage over propofol alone.

To place this study in context, we note that following the emergence of strong evidence that subanesthetic doses of ketamine in both MDD and BP has rapid and robust antidepressant effects (Diazgranados et al., 2010; Zarate et al., 2006), multiple case reports been to appear suggesting that using ketamine as the anesthetic for ECT might enhance its therapeutic efficacy and reduce adverse cognitive side effects, possibly by lengthening seizure duration and lowering electric energy requirements needed to induce seizures (Krystal et al., 2003; Loo et al., 2010; McDaniel et al., 2006). However, since those preliminary reports, several randomized trials have yielded more negative or at best ambiguous results. The majority of studies found no evidence that ketamine anesthesia neither improved depression outcomes nor reduced cognitive side effects of ECT. These negative results appeared both with ketamine (0.8–1.0 mg/kg) alone (Rasmussen et al., 2014; Salehi et al., 2015; Yen et al., 2015); and with ketamine (0.5 mg/kg) as an adjunct to either thiopental (Abdallah et al., 2012) or profofol (Jarventausta et al., 2013). In addition, a meta-analysis of randomized controlled trials of ketamine anesthesia augmentation in ECT suggested a lack of clinical efficacy. Data relating to remission (31.3% ketamine vs 28.8% control, ns) and response rates (52.9% ketamine vs 57.6% control, ns) were synthesized from 3 RCTs, indicating no difference in outcome with ketamine anesthesia (McGirr et al., 2015). In contrast to these numerous negative trials one study found slightly greater antidepressant efficacy in the first week of ECT treatment with adjunct ketamine (0.5 mg/kg) anesthesia (Loo et al., 2012) and a second report found better cognitive performance with ketamine (1.0–2.0 mg/kg) anesthesia compared to thiopental, when assessed with the mini mental status examination (MMSE) (Yoosefi et al., 2014). Third report show that a ketofol 1:1 mixture (43 ± 11 mg propofol, and 43 ± 11 mg ketamine) was associated with a longer mean seizure time and better hemodynamic stability, without any important increased in side effects (Yalcin et al., 2012). In addition, two studies conducted in China both reported that ketamine (0.8 mg/kg) alone or ketamine (0.5 mg/kg) adjunct with propofol exhibited significantly faster and superior antidepressant effects with less severe cognitive side effects (Wang et al., 2012; Zhong et al., 2016). Since several other side effects have frequently been reported with ketamine including headache, nausea, short term delirum, restlessness and increased blood pressure (Rasmussen

Table 3
MCCB T scores of ECT subjects evaluated by covariates with diagonse in linear mixed models.

			Main effect of time		Main effect of grouping factor		Group-by-time interaction	
	Ketamine plus propofol group (n = 43)	Propofol group (n = 34)	F	p	F	p	F	p
Speed of Processing			1.148	0.323	1.300	0.260	0.765	0.469
Baseline (26/24)	31.04 ± 10.25	28.75 ± 12.31						
Post-ECT 6 (26/22)	31.42 ± 9.10	31.32 ± 7.40						
Follow-up Visit (15/20)	34.00 ± 11.89	29.35 ± 13.24						
Attention/Vigilance			2.171	0.122	0.000	0.998	0.245	0.783
Baseline (26/18)	37.00 ± 13.75	37.67 ± 11.71						
Post-ECT 6 (26/21)	38.35 ± 10.54	38.00 ± 8.60						
Follow-up Visit (15/16)	39.20 ± 13.29	40.50 ± 9.13						
Working Memory			0.832	0.439	0.745	0.392	2.404	0.097
Baseline (25/23)	43.28 ± 10.23	37.04 ± 10.42						
Post-ECT 6 (26/22)	40.42 ± 9.78	40.18 ± 12.16						
Follow-up Visit (15/20)	42.20 ± 12.02	42.95 ± 9.75						
Verbal Learning			3.052	0.053	0.105	0.747	0.909	0.407
Baseline (26/24)	39.92 ± 13.24	36.08 ± 14.10						
Post-ECT 6 (25/22)	38.56 ± 12.82	39.77 ± 7.10						
Follow-up Visit (15/20)	31.33 ± 9.40	33.55 ± 14.81						
Visual Learning			2.680	0.075	1.221	0.275	1.245	0.302
Baseline (25/22)	39.48 ± 12.78	37.45 ± 11.82						
Post-ECT 6 (26/22)	36.35 ± 9.34	36.32 ± 10.93						
Follow-up Visit (15/19)	39.93 ± 10.89	37.32 ± 10.09						
Reasoning and Problem Solving			4.043	**0.021***	1.236	0.272	1.255	0.291
Baseline (26/23)	39.73 ± 8.71	36.52 ± 9.62						
Post-ECT 6 (26/22)	42.92 ± 11.44	39.09 ± 10.30						
Follow-up Visit (15/20)	39.53 ± 10.72	42.25 ± 9.73						
Social Congnition			4.849	**0.010****	3.808	0.057	1.091	0.341
Baseline (24/20)	46.75 ± 10.14	40.00 ± 10.78						
Post-ECT 6 (24/21)	44.83 ± 11.34	41.90 ± 8.43						
Follow-up Visit (15/18)	49.47 ± 9.78	45.83 ± 8.58						

* $P < 0.05$.
** $p < 0.01$.

et al., 2014; Salehi et al., 2015; Wang et al., 2012; Yen et al., 2015), ketamine has been used at subanesthetic doses as an adjunct to low dose propofol as a recommended first choice in TRD patients (Wang et al., 2012; Zhong et al., 2016). It is important to note that one study did not support the use of adjunctive ketamine in routine ECT treatment in the NHS (Anderson et al., 2017). The results of that study showed that compared with saline, adjunctive ketamine (0.5 mg/kg) had no significant effect on neuropsychological outcomes, improvement in depression, the number of ECT treatments to remission, anxiety symptoms or quality of life (Anderson et al., 2017). Our study, however, provides further evidences that although stimulus intensity was significantly reduced and seizure duration was longer, ketamine used adjunctively with propofol neither enhances the antidepressant effect of ECT nor reduces the cognitive side effects. These results suggest that the antidepressant effect of ECT is so pronounced and rapid acting that it may mask any independent effects of ketamine (Okamoto et al., 2010).

Even though several evaluations of ketamine anesthesia in ECT have been published the present negative study was a rigorous double-blind randomized clinical trial that was designed to compare two highly salient study groups. While our findings support the general negative trend in the literature, several distinctive strengths deserve comment. First, we used an especially sophisticated neuropsychological battery, the MCCB to evaluate cognitive changes after ECT treatment. This extensive set of neurocognitive tests could have been expected to bo more sensitive in detecting adverse effects as compared with neurocognitive tests like the MMSE that have been used in some previous studies. Secondly we measured symptoms and cognitive functions longitudinally, at 6 different time point, from the pre-ECT baseline through 4 intermediate assesments to the final assessment 1–4 weeks after the final ECT treatment. This a dynamic and more sensitive evaluation of changes in depressive symptoms. Thirdly our study sample was relatively large and there was no loss of follow-up data. Since all

Table 4
Evaluated ECT treatment parameters of ketamine plus propofol groups and propofol group by covariates with diagonse in linear mixed models.

	SUM		Main effect of time		Main effect of grouping factor		Group-by-time interaction	
	Ketamine plus propofol group (n = 43)	Propofol group (n = 34)	F	p	F	p	F	p
Electric quantity (mC)	178.37 ± 11.50	259.41 ± 12.81	43.986	**< 0.001*****	18.775	**< 0.001*****	7.904	**< 0.001*****
Seizure energy index (%)	90.41 ± 0.96	86.55 ± 1.08	1.359	0.239	7.199	**0.009****	0.321	0.900
Seizure duration (second)	43.30 ± 2.82	30.01 ± 3.22	1.337	0.248	7.134	**0.009****	0.183	0.969

** $P < 0.01$.
*** $p < 0.001$.

Table 5
The side effects of ECT treatment of propofol group and ketamine plus propofol groups evaluated by covariates with diagonse in linear mixed models.

	SUM		Main effect of time		Main effect of grouping factor		Group-by-time interaction	
	Ketamine plus propofol group (n = 43)	Propofol group (n = 34)	F	p	F	p	F	p
Systolic blood pressures	127.81 ± 1.26	121.26 ± 1.40	2.101	0.065	10.962	**0.001****	0.500	0.777
Diastolic blood pressures	82.87 ± 0.80	75.27 ± 0.89	1.014	0.409	32.814	< **0.001*****	0.513	0.766
Heart rate	98.51 ± 1.27	96.21 ± 1.41	1.922	0.090	0.960	0.331	2.007	0.077
Breathing recovery time (minute)	3.00 ± 0.01	3.00 ± 0.01	1.023	0.403	0.428	0.513	1.013	0.409
Consciousness recovery time (minute)	22.34 ± 0.17	22.44 ± 0.19	3.941	**0.002****	0.009	0.924	2.032	0.074

** $P < 0.01$.
*** $p < 0.001$.

participants were hospitalized during the study patients could be closely observed and dropout avoided entirely.

4.1. Limitations

Several limitation also deserve comment. Firstly, the study samples were all from the same acute psychiatric hospital perhaps limiting the generalizability of the results to other facilities. Second, since all participants were hospitalized in a psychiatric hospital, they may have had more severe symptoms and more complicated presentations than patients treated on psychiatric wards of general hospitals or as outpatients. Thirdly diagnoses of MDD and BP were unevenly distributed across treatment groups potentially biasing the results. Statistical adjustment fir this imbalance did not change the results. Fourthly, a larger dose of ketamine was not assessed in present study. A pilot dose-response trial of ketamine found that antidepressant efficacy may be dose-related (Lai et al., 2014). High doses may thus have led to more positive results for the ketamine group. Finally, while the ECT treatment regimen of 6 treatments is widely accepted as adequate, some practitioners would suggest that a more extensive course of ECT treatments might have led to higher remission and response rates. Whether ketamine anesthesia would have shown greater benefit in the context of a more extensive course of ECT treatment is not known but may deserve further study. Thus there is still considerable scope for further research, examining the relationship between antidepressant effect and dose of ketamine with large sample sizes.

5. Conclusion

Although ketamine-propofol anesthesia reduced the stimulus intensity and increased the seizure duration of ECT treatment it did not enhance the speed or magnitude of antidepressant effects nor significantly reduce the cognitive impairment or other side effects. Since using a single agent may be simpler than using two, it may be preferable to use propofol alone as anesthesia for ECT except for those with high seziure threshold.

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