Highlights

To our knowledge, there is the first study comparing the antidepressant effect of ketamine alone (anesthetic concentration) and subanesthetic ketamine as an anaesthic induction for ECT in TRD treatment.

Both anesthetic and subanesthetic concentrations of ketamine have rapid antidepressant actions in ECT for TRD.

Anesthetic concentrations results in larger magnitudes of antidepression and cognitive protection.

Mood and Neuropsychological Effects of Anesthetic and Subanesthetic Concentrations of Ketamine in Electroconvulsive Therapy for Treatment-resistant Depression

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Abstract

Background: Treatment-resistant depression (TRD) is a growing clinical challenge. Electroconvulsive therapy (ECT) is one of the effective tools in the treatment of TRD. However, there remains a subset of patients do not respond to this treatment with common anesthetic agent. Ketamine, an NMDA receptor antagonist, also a noteworthy anesthetic agent, has emerged as augmentation to enhance the antidepressant efficacy of ECT. Trial of i.v. ketamine in TRD indicated dose-related antidepressant efficacy. We aimed to explore anesthetic and subanesthetic concentrations of ketamine in ECT for TRD regarding their impact on antidepressant efficacy, ECT parameters and cognitive protection.

Methods: Ninety TRD patients were randomly assigned to receive either ketamine (0.8 mg/kg) (n=30), subanesthetic ketamine (0.5 mg/kg) plus propofol (0.5 mg/kg) (known as ketofol, n=30) or propofol (0.8 mg/kg) (n=30) as anesthetic and underwent 8 ECT sessions.

Results: Ketamine group showed earlier improvement in HDRS-17, longer seizure duration, lower electric quantity, higher remission rate, and lower degree of executive cognitive impairment when compared to ketofol and propofol groups. Ketofol group showed earlier improvement in HDRS-17, longer seizure duration and seizure energy index when compared to propofol group.

Limitations: Psychopathology symptoms were measured by BPRS, so small magnitude of postoperative psychomimetic side effects was not fully assessed.

Conclusions: Both anesthetic and subanesthetic concentrations of ketamine have rapid antidepressant actions in ECT for TRD, while anesthetic concentrations results in larger magnitudes of antidepression and cognitive protection. ECT with ketamine anesthesia might be an optimized therapy for patients with TRD.

Key words: Treatment-resistant depression, Ketamine, Electroconvulsive therapy, Mood and neuropsychological effects

Introduction

Major depressive disorder is a widespread psychiatric illness, affecting approximately 350 million people worldwide and leading to severe health and socioeconomic consequences (Oremus et al., 2015). Despite a growing selection of psychopharmacological treatments is available, only 60–70% of major depressive disorder patients will respond to first-line treatment with antidepressant drugs. Evidence indicates that at least one-third of patients with major depressive disorder do not reach clinical remission and become treatment resistant (Oremus et al., 2015). Treatment-resistant depression (TRD) is defined as the failure to respond to adequate dosage and duration of at least two different therapeutic antidepressant drugs (Mathew, 2008). The treatment of TRD is challenging. Electroconvulsive therapy (ECT) is generally considered to be the most effective treatment for TRD (McGirr et al., 2015). However, the response rate of ECT using common anesthetic agent (such as propofol, thiopental and etomidate) is around 50%~60% (Shelton et al., 2010). This has resulted in stimulating interest in augmentation strategies which aim to increasing effectiveness of ECT for TRD treatment (McGirr et al., 2015). Ketamine, an N-methyl-D-aspartate (NMDA) receptor blocking agent, emerging as a novel, rapid-acting antidepressant even with low-dose intravenous, can effect rapid benefit in reducing depressive symptoms and suicidal ideation in patients with affective disorders (Naughton et al., 2014). A growing body of research demonstrates that the glutamatergic system play an important role in the pathophysiology of major depression and the mechanism of antidepressant effects. The rapid antidepressant effect of ketamine is due to activation of the mammalian target of rapamycin (mTOR) signaling pathway together with inhibitory phosphorylation of eukaryotic elongation factor 2 (eEF2) and glycogen synthase kinase-3 (GSK-3) (Gideons et al., 2014). Ketamine is a noteworthy anesthetic agent used mainly for starting and maintaining anesthesia. In additional, it has been suggested that ketamine may exhibit potential neuroprotective properties, showing particular benefit on cognitive protect post-ECT (MacPherson and Loo, 2008). Based on these findings, ketamine has emerged as a putative augmentation agent to enhance the antidepressant efficacy of ECT (Bryson et al., 2014; Erdil et al., 2015; Jarventausta et al., 2013; Kucuk et al., 2013; Loo et al., 2012; Rasmussen et al., 2014; Sartorius et al., 2015; Wang et al., 2012; Yalcin et al., 2012; Yoosefi et al., 2014). However, the results are inconsistent. Some studies reported a lack of clinical efficacy, and some

confirmed its efficacy in improving depressive symptomatology earlier when using ketamine as anesthesia agent or adjunctive agent to ECT compared with propofol, thiopental or methohexital anesthesia (Abdallah et al., 2012; Jarventausta et al., 2013; Loo et al., 2012; Okamoto et al., 2010; Rasmussen et al., 2014; Wang et al., 2012). Further studies are needed to provide evidence to this issue.

Previous study of ketamine administered with anesthetic concentration as augmentation in ECT for TRD indicated increased effect (Okamoto et al., 2010), while subanesthetic concentration showed no effect (Jarventausta et al., 2013). These studies suggest that the antidepressant efficacy may be influenced by the dose of ketamine used in ECT. The trial of i.v. ketamine in TRD patients provided evidence that increasing doses of ketamine produced more marked and more sustained antidepressant response (Lai et al., 2014). To our knowledge, there is no study comparing the antidepressant effect of ketamine alone (anesthetic concentration) and subanesthetic ketamine as an anaesthic induction for ECT in TRD treatment. It is still unknown which is the optimal mode of anesthesia.

The aim of the present study was to compare the effects of ketamine, subanesthetic ketamine / propofol combination (referred to by the portmanteau “ketofol”) and propofol as anesthesia on the antidepressant efficacy, ECT parameters, cognitive protection and side effects in patients with TRD.

Materials and methods

Subjects

The study was approved by the ethics committee of the Guangzhou Brain Hospital. Written informed consent was obtained from all participants. All patients were recruited from the wards of Guangzhou Brain Hospital. The ECT sessions were performed in the Department of ECT of Guangzhou Brain Hospital. Patients with TRD were included during the period between April 2011 and April 2014. All patients fulfilled the diagnostic criteria for major depression or bipolar disorder with a current major depressive episode according to the ICD-10 diagnostic criteria and had no clinical response to at least two antidepressant drugs with different pharmacological classes at adequate dosage for at least 6 weeks for their current depression episode. The exclusion criteria were as follows: schizophrenia, alcohol or drug abuse, intracranial hypertension,

cerebrovascular disorder, respiratory tract disease, and other contraindications for ECT or anesthesia.

Treatment

TRD patients were randomized to receive ketamine, ketofol or propofol as anesthesia. Both the rater and the patients were blind to the anesthetic agent. ECT treatment was performed three times per week for three consecutive weeks encompassing eight treatments. No antipsychotic or antidepressive drugs were prescribed to the patients during the period of ECT. All the three groups first received atropine sulfate（1mg）. Then they received ketamine (0.8 mg/kg), ketamine (0.5 mg/kg) plus propofol (0.5 mg/kg) and propofol (0.8 mg/kg) for ketamine, ketofol and propofol groups, respectively. Succinylcholine (1 mg/kg) was administered intravenously as muscle relaxant after induction of anesthesia.

Bitemporal ECT was performed using the Thymatron ® IV device (Somatics LLC, Lake Bluff, Illinois, USA). The seizure threshold was determined by the half-age method in each case. Seizure duration and seizure energy index on the EEG were recorded during anesthesia.

Psychopathology and cognitive assessment

The 17-item Hamilton Depression Rating Scale (HDRS) was used to assess the severity of depressive symptoms and treatment response. The Brief Psychiatric Rating Scale (BPRS) was used to evaluate general psychopathology symptoms. These two scales were administered at baseline and after treatments one, two, three, four and six on the mornings of next scheduled ECT and 48 to 72 hours after the last (eight) treatments.

Word Fluency Test, Digit Symbol Test, Digit Span test, Wisconsin Card Sorting test, Tower of Hanoi, Trail making Test and Visual Regeneration Test were used to assess the cognition at baseline and 48 to 72 hours after the eighth treatment.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) 18.0 software (SPSS, Chicago, IL, USA). The Kruskal-wallis H (K) test was used for skewed distributions, followed by Mann-Whitney U test with Bonferroni correction. The one-way analysis

of variance (ANOVA) was used for normal distributions, followed by post hoc least significant difference test with Bonferroni correction. Analysises of repeated-measures, including 17-item HDRS, BPRS, electric quantity, seizure duration and seizure energy index were conducted by General Linear Model (GLM) repeated-measures, with treatment group (ketamine, ketofol and propofol) as the between-subjects factor and time of assessment as the within-subject factor. To analyze the influence of different anesthesia method on neurocognition, the change in the scores of cognitive test were calculated (cognitive scores at baseline minus cognitive scores after the last ECT treatments), and Kruskal-wallis H (K) test was used for group comparison. A two tailed p value of 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics

Ninety patients with TRD were enrolled, and were randomized into ketamine (n=30), ketofol (n=30) and propofol (n=30) groups. The patients' mean age was 30.6 years (ranged between 15 and 67 years). Ten patients in the ketamine group, 13 patients in the ketofol group and 11 patients in the propofol group were diagnosed as bipolar disorder. The demographic data and baseline depression scores are presented in Table 1. No significant differences were found in age, gender, education and baseline depression scores among the three groups.

Antidepressant Effect

Three anesthesia conditions were associated with depressive symptom improvement. After Greenhouse–Geisser correction, GLM repeated-measures showed a strong main effect of time on HDRS (F=3084.8, p□0.001). Decreases in the total score on the HDRS-17 were seen in three groups as the number of treatments was increased (Figure 1). Significant group-by-time interaction (F=9.736, p□0.001) and significant group difference (ketamine vs. propofol , p□ 0.001, ketamine vs. ketofol, p=0.011, and ketofol vs. propofol, p=0.033, respectively) were also obtained (Table 2 and Figure 1). Bonferroni post-hoc analyses (Table 3) indicated that patients who received ketamine as anesthesia versus those who received propofol showed lower HDRS-17 scores after the first treatment (p=0.025). A more pronounced difference was observed between ketamine and propofol groups from the completion of the second treatment to the last treatment (the eighth treatment) (all p□0.001) . Patients who received ketofol as anesthesia versus those

who received propofol showed lower HDRS-17 scores after the second treatment (p=0.025). This difference became greater after the third (p=0.004), fourth (p=0.003) and sixth (p=0.001) treatments, but receded after the eighth treatment (p= 0.017) (Table 3). The comparison of antidepressant effect of ketamine and ketofol groups showed significantly lower HDRS-17 scores in patients who received ketamine versus those who received ketofol from the completion of the second treatment to the last treatment (the eighth treatment) (Table 3).

Antidepressant response was defined at a ≥50% reduction in HDRS-17 total score from baseline and remission as a HDRS-17 score≤7. As shown in Figure 2, we found no responders until the completion of the third treatment in three groups. Both the ketamine and ketofol groups showed statistically significant higher response rates after the third and fourth ECT compared to the propofol group. However, the significant difference disappeared after the sixth and eighth ECT. There was no difference in response rates between the ketamine and ketofol groups at any time point. With respect to the remission, group difference only reached significance after completion of the eighth treatment (Figure 3). Ketamine group showed statistically significant higher remission rate when compared to ketofol group (p 0.001) and propofol group (p 0.017) . Chi-Square test indicated that the remission rate in ketofol group was significant than that in propofol group (p=0.018). Nevertheless, this significance disappeared after Bonferroni correction.

Effect on psychopathology symptoms

Psychopathology symptoms were improved in all three treatment groups. GLM repeated-measures revealed a significant main effect of time on BPRS (Table 2 and Figure 4). However, there was no significant group-by-time interaction (Table 2). Significant main effect of group was observed. Bonferroni post-hoc analyses (Table 2) indicated that patients in ketamine group showed significant improvement in psychopathology symptom than patients in propofol group ($p<0.01$). No significant statistical difference was found between ketamine and ketofol groups or between ketofol and propofol groups.

Seizure parameters

GLM repeated-measures examining the effects of anesthesia agent on electric quantity showed significant main effect of time (Table 4 and Figure 5).The electric quantity required for ECT

became higher with increasing treatment times. Group comparison indicated that electric quantity in ketamine group was lower than that in propofol group or in ketofol group. No difference was found between ketofol and propofol groups. With respect to session variability, electric quantity required in ketamine group was lower than that of propofol group at every time point. Significant difference was observed between ketamine and ketofol groups at the second, fourth, sixth and eighth ECT treatments (all p 0.001). The group-by-time interaction (F=6.314, p<0.001) was significant (Table 5 and Figure 5).

There are significant main effect of group in seizure duration and seizure energy index (F=22.4, P < 0.001 and F=4.3, p < 0.05, respectively). Seizure duration in ketamine group was higher than that in propofol group or in ketofol group (Table 4). Higher seizure duration in ketofol group was obtained when compared to propofol group. Seizure energy index in ketofol group was higher than that in propofol group, while no difference was found between ketamine and ketofol groups or between ketamine and propofol groups (Table 4). There was no main effect of time and no significant group-by-time interaction for seizure duration or for seizure energy index Table 4, Figure 6 and Figure 7.

Cognitive function

There was no significant difference in cognitive function tests at baseline. After the completion of the eighth ECT treatment, the decline in the number of WCST categories completed and the decline in the number of steps to solve the Tower of Hanoi in propofol group were significant than those of ketamine group (p < 0.05) (Table 6). The decline in the number of WCST categories completed in ketofol group was more severe than that of ketamine group (p < 0.05). The propofol group had a significant decline in performance (increase in time to completion) on TMT Part A and Part B when comparing with ketamine group (p < 0.05) (Table 6). The degrees of cognitive impairment as measured by Word Fluency Test, Digit Symbol Test, Digit Span test and Visual Regeneration Test were not difference among the three groups p >0.05 (data not shown).

Side effects

During the eight ECT treatments, no major adverse effects were observed in patients who received ketamine, ketofol or propofol as anesthesia agent. Majority of patients in three groups reported

minimal transient adverse events, including headaches and nausea. These adverse events remitted spontaneously in 0.5-1 hour without any treatment. None of them were severe enough to require discontinuation of the ECT treatment.

Discussion

In this study, we compared anesthetic and subanesthetic concentrations of ketamine and propofol for ECT regarding their impact on antidepressant efficacy, seizure parameters, cognitive function and side effects in patients with TRD. We found a more rapid antidepressant effect, higher remission rate, lower electric quantity, higher seizure duration, higher seizure energy index and lower degree of cognitive impairment in ketamine group than those of propofol group. These observations highlight the clinical usefulness of ketamine in ECT for treatment of TRD.

TRD is an important clinical problem that continues to represent a major challenge to clinical psychiatry. ECT is one of the most effective tools in the treatment of TRD. However, there remains a subset of patients who failed to respond to ECT. Accumulating evidence suggests that a single intravenous infusion of ketamine exerts rapid antidepressant effects in patients with TRD (Murrough et al., 2013; Serafini et al., 2014). Repeated doses of ketamine intravenous ((0.5 mg/kg over 45 min) is as effective as ECT using thiopental as anesthetic agents in depressive symptom improvement in MDD patients and have more rapid antidepressant effects compared to the ECT (Ghasemi et al., 2014). Thus, using ketamine as anesthetic agents in ECT should be an optimized therapy for TRD. As expected, our study confirms that ketamine enhances the speed of response to ECT. Comparing to the propofol group, both patients in ketamine and ketofol groups showed a significant clinical improvement in depressive symptoms at the early stage of treatment (after the first ECT and after the second ECT, respectively). Our finding is consistent with the study of Okamoto N. et.al. indicating rapid antidepressant effects with ketamine anesthesia (Okamoto et al., 2010). However, Okamoto N. et.al. found the superiority disappeared after the completion of the sixth and eighth ECT (Okamoto et al., 2010). Contrary to this result, we observed greater improvement in depression symptom in the ketamine group than in the propofol group throughout eight sessions of ECT. In addition, when ketamine was used as an adjuvant to propofol, increased antidepressive effectiveness was also observed. This result is contrary to the study of Järventausta

K. et.al. , which showed no difference in the magnitude or speed of response compared to propofol (Jarventausta et al., 2013; Okamoto et al., 2010). The antidepressant efficacy of ketamine may be dose-related (Lai et al., 2014). A pilot dose-response trial of intravenous ketamine (0.1, 0.2, 0.3, 0.4 mg/kg) in TRD patients found two of four subjects achieved the greatest improvement at the highest dose received (Lai et al., 2014). In present study, the patients in ketamine group received a larger dose of ketamine relative to the patients in the ketofol group (0.8 mg/kg and 0.5mg/kg, respectively). We observed a greater improvement in depression symptom in the ketamine group comparing to the propofol group after the second ECT, and this superiority lasted until the eighth session of ECT. As to the speed of response, the ketamine and ketofol groups showed higher response rate at the completion of the third and fourth ECT; after that, the propofol group caught up with the ketamine and ketofol groups. The recovery rate was significant higher at the completion of eight ECT sessions in the ketamine group when compared with the ketofol and propofol groups. Our result suggests that both anesthetic concentrations of ketamine and subanesthetic ketamine in ECT have a rapid onset of antidepressant activity in the treatment of TRD. The antidepressant magnitude is associated with the dose of ketamine. Anesthetic concentration of ketamine reveals superior antidepressive effect and cognitive protection than subanesthetic ketamine. Meta-analysis of trials of ketamine augmentation in the ECT setting suggests a lack of clinical efficacy (McGirr et al., 2015), while we found high response and remission rates. This difference might be attributed to the fact that we included only TRD patients in our research, while the data of meta-analysis were synthesized from patients with major depressive episodes. Further multi-centre case-control studies are needed to verify the synergistic antidepressant effects with ketamine and ECT in TRD patients.

Prior studies have reported that ketamine anesthesia is associated with higher-quality seizures than propofol (Hoyer et al., 2014; Okamoto et al., 2010; Yalcin et al., 2012). We confirmed that the seizure durations in ketamine group and ketofol groups were longer than propofol group. This result suggests that, anesthetic concentration of ketamine or subanesthetic ketamine, resulted in significant changes in seizure duration. The electric quantity required for ECT in ketamine group was less than ketofol and propofol groups. This result may be due to

their pharmacological properties that ketamine has less anticonvulsant activity than propofol. Our study provided evidence that the use of ketamine in ECT is advantageous.

Patients after a grand mal seizure have a period of cognitive impairment (MacPherson and Loo, 2008). It is a common side effect after ECT. Some individuals with TRD forgo ECT over concern about adverse cognitive effects. The choice of anesthetic agent makes a difference in cognitive impairment following ECT, possible by affecting the seizure threshold, altering the required electrical dose, or affecting seizure expression (MacPherson and Loo, 2008). As mentioned above, patients in ketofol and propofol groups received significant higher electrical dose than ketamine group. Higher stimulation doses lead to greater cognitive side effects (MacPherson and Loo, 2008). In our study, ketamine was shown to be preferable to propofol or ketofol regarding the impairment of executive function following ECT. There are evidences that ketamine, an NMDA antagonist, can mitigate the excitotoxic neuronal damage mediated by the effect of glutamate on the N-methyl-D-aspartate (NMDA) receptor (Serafini et al., 2014), rapidly lead to increased synaptic signaling proteins (Li et al., 2010), and increase the number and function of new spine synapses in the prefrontal cortex of rats by activating the mTOR pathway (Li et al., 2010). Thus, ketamine's favorable impact on cognition may be related to the neuroprotection of ketamine and low electrical dosage.

It is important to point out some limitations of the present study. It is possible that the sympathomimetic feature of ketamine may play a role in the susceptibility of arrhythmias during ECT. The study ignored to assess the hemodynamic stability during anesthesia. Patients in ketamine group showed marked clinical improvement of their general psychopathology symptoms without worsening of the psychotic symptoms as measured by BPRS. Smaller magnitude of postoperative psychomimetic side effects may be detected if more detailed questionnaires were used. Future studies with large sample size focusing on hemodynamic profile and psychomimetic side effects of ketamine anesthesia are needed to provide evidences for clinical expansion.

TRD continues to represent a major challenge for treating clinicians. Ketamine has been used

rather hesitantly in ECT for its potential to provoke dissociative symptom. Our study demonstrates that both anesthetic and subanesthetic concentrations of ketamine enhance the effect of ECT for TRD. The use of anesthetic concentration of ketamine has superior antidepressant effects and neuroprotection against cognitive impairment than propofol and ketamine/propofol combination anesthesias. Ketamine anesthesia is optimal mode of drug administration recommended in the ECT for TRD.

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Table 1. Baseline Characteristics of the ketamine, ketofol and propofol groups

	Ketamine group (n = 30)	Ketofol group (n = 30)	Propofol group (n = 30)	F /χ^2value	*P* value
Age (years)	32.1±9.9	30.4±9.6	29.2±8.0	0.774	0.465

Women/men	16(53.3%)	18(60%)	20(66.7%)	1.111	0.574
Education (years)	11.5±3.2	12.0±3.7	12.1±3.1	0.256	0.775
HDRS-17 at baseline	26.7±1.6	26.7±2.0	26.0±2.8	0.958	0.388
BPRS at baseline	35.47±4.167	36.53±5.164	36.93±6.142	0.633	0.534

Abbreviations: HDRS-17, 17-item Hamilton Depression Rating Scale;
BPRS, Brief Psychiatric Rating Scale

Table 2 Main effect of time, main effect of grouping factor and group-by-time interaction on HDRS-17 and BPRS evaluated by GLM repeated measures analysis

		SUM	Main effect of time		Main effect of grouping factor		Group-by-time interaction	
			F	*P*	F	*P*	F	*P*
HDRS-17	Ketamine group	14.8±0.256*	3084.813	0.001	15.529	0.001	9.736	0.001
	Ketofol group	15.876±0.256*						
	Propofol group	16.814±0.256						
BPRS	Ketamine group	25.576±0.351**	597.498	0.001	5.901	0.004	0.339	0.797
	Ketofol group	26.567±0.351						
	Propofol group	27.276±0.351						

Group comparisons were performed by the one-way analysis of variance (ANOVA), followed by post hoc Bonferroni test

Compared with propofol group, *P 0.05, ** P 0.01, ***P 0.001

Compared with ketofol group, P 0.05 # P 0.01, P 0.001

Abbreviations: HDRS-17, 17-item Hamilton Depression Rating Scale; BPRS, Brief Psychiatric Rating Scale

Table 3. Hamilton Depression Rating Scale and Brief Psychiatric Rating Scale scores at baseline and after each treatment in ketamine, ketofol and propofol groups

		Base line	1st ECT	2nd ECT	3rd ECT	4th ECT	6th ECT	8th ECT
HDRS-17	Ketamine group	26.7±1.6	21.1±1.3*	16.7±1.2***□	13.5±1.2***#	11.0±1.0***#	8.6±0.7***#	6.0±0.7***□
	Ketofol group	26.7±2.0	22.0±1.8	17.9±1.9*	15.0±2.1*	12.5±2.1**	10.0±1.8**	7.1±1.6*
	Propofol group	26.0±2.8	22.5±2.6	19.2±2.0	16.5±1.9	14.1±1.8	11.2±1.5	8.2±1.9
	F value	0.958	3.748	15.769	21.039	25.468	24.613	16.154
	P value	0.388	0.027	□ 0.001	□ 0.001	□ 0.001	□ 0.001	□ 0.001
BPRS	Ketamine group	35.47±4.167	28.9±1.807	25.87±1.306	24.17+1.02	22.8±0.887	21.67±0.994	20.17±1.117
	Ketofol group	36.53±5.164	30.37±3.882	27.37±2.906	25.03±1.52	23.63±1.52	22.23±0.971	20.8±1.157
	Propofol group	36.93±6.142	31.2±4.262	27.93±2.9	25.7±1.557	24.4±1.522	23.07±0.98	21.7±0.988

Group comparisons were performed by the one-way analysis of variance (ANOVA), followed by post hoc Bonferroni test.

Compared with propofol group, *P □ 0.05, ** P □ 0.01, ***P □ 0.001

Compared with ketofol group, □P □ 0.05□ # P □ 0.01,□□□P □ 0.001

Abbreviations: ECT, Electroconvulsive Therapy; HDRS-17, 17-item Hamilton Depression Rating Scale; BPRS, Brief Psychiatric Rating Scale

Table 4 Main effect of time, main effect of grouping factor and group-by-time interaction on Electric Quantity, Seizure Duration and Seizure Energy Index evaluated by GLM repeated measures analysis

		SUM	Main effect of time		Main effect of grouping factor		Group-by-time interaction	
Electric Quantity (mC)	Ketamine group	141.05±10.358**#	29.675	0.001	8.292	0.001	6.314	0.001
	Ketofol group	189.8±10.358						
	Propofol group	195.2±10.358						
Seizure Duration (second)	Ketamine group	60.439±2.126***	0.711	0.571	39.513	0.001	0.959	0.463
	Ketofol group	46.406±2.126***						
	Propofol group	33.722±2.126						
Seizure Energy Index (%)	Ketamine group	87.572±0.394	0.196	0.95	7.369	0.001	0.727	0.679
	Ketofol group	88.378±0.394**						
	Propofol group	86.261±0.394						

Group comparisons were performed by the one-way analysis of variance (ANOVA), followed by post hoc Bonferroni test

Compared with propofol group, *P 0.05, ** P 0.01, ***P 0.001

Compared with ketofol group, P 0.05 # P 0.01, P 0.001

Abbreviations: HDRS-17, 17-item Hamilton Depression Rating Scale; BPRS, Brief Psychiatric Rating Scale

Table 5. Electric quantity, seizure duration and seizure energy index during each ECT in ketamine, ketofol and propofol groups

		1st ECT	2nd ECT	3rd ECT	4th ECT	6th ECT	8th ECT
Electric Quantity（mC）	Ketamine group	137.1±40.6*	137.9±41.5**	140.3±41.0**	141.1±41.4**	145.1±42.2**	145.0±41.3**
	Ketofol group	141.6±46.2	164.1±50.0	171.6±57.1	199.9±81.5	233.5±108.8	228.1±110.9
	Propofol group	160.3±37.5	178.1±50.1	189.3±55.0	199.7±70.7	217.1±89.3	226.7±100.7
	F value	2.623	5.592	6.967	7.747	9.227	8.443
	P value	0.078	0.005	0.002	0.001	＜0.001	＜0.001
Seizure Duration (second)	Ketamine group	60.1±17.1	58.6±13.0	61.6±11.2	59.8±9.4	60.0±9.8	62.5±16.0
	Ketofol group	48.5±21.8	48.5±19.4	47.3±17.5	46.0±17.0	44.4±15.7	43.8±14.2
	Propofol group	35.2±13.8	33.4±9.1	33.2±11.6	35.0±11.2	32.0±11.0	33.6±12.3
Seizure Energy Index (%)	Ketamine group	86.8±4.0	87.7±2.4	87.9±2.6	88.4±2.6	87.4±2.6	87.3±2.4
	Ketofol group	88.2±5.1	88.3±4.6	88.2±5.5	87.7±5.2	88.6±5.1	89.3±4.0
	Propofol group	87.0±5.3	85.4±3.7	86.8±4.2	86.4±6.7	86.0±4.3	86.0±5.2

Group comparisons were performed by the one-way analysis of variance (ANOVA), followed by post hoc Bonferroni

Compared with propofol group, *P < 0.05, ** P < 0.01, ***P < 0.001

Compared with ketofol group, P < 0.05 # P < 0.01, P < 0.001

Table 6. Comparisons of cognitive impairment after eight ECT treatments in Ketamine, ketofol and propofol groups

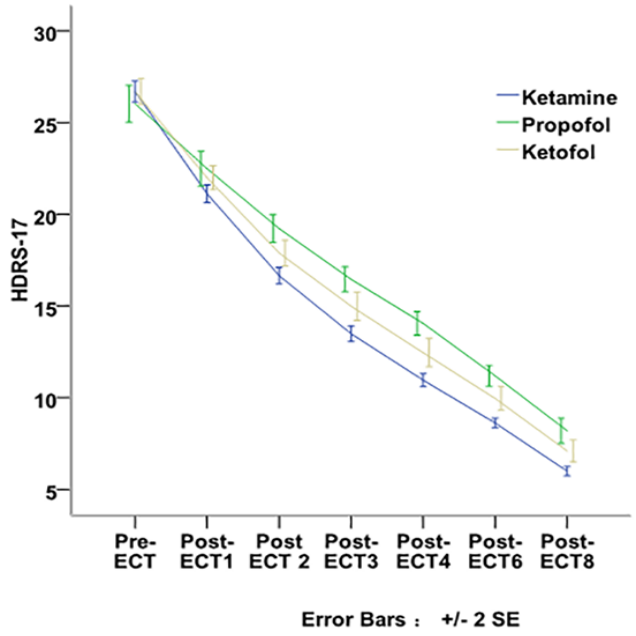
	Ketamine group (n = 30)	Ketofol group (n = 30)	Propofol group (n = 30)	χ^2value	*P* value
Decline in the number of WCST categories completed	1□1,1□*□	1(1,2)	1(1,2)	7.422	0.024
Decline in the number of steps to solve the Tower of Hanoi	1□1,1□**	1(1,2)	3□0.75,3)	8.802	0.012
Increase in time to complete TMT Part A	0.915(1.8075,0.5425)*	1.0250(0.2625, 3.5)	5.28(-1.99, 7.775,)	6.079	0.048
Increase in time to complete TMT Part B	1.355(0.92, 2.9425)**	1.64(-7.99, 12.97)	7.48(-2.875, 14.31)	6.534	0.038

Group comparisons were performed by the Kruskal-wallis H (K) test, followed by Mann-Whitney U test with Bonferroni correction.

Compared with propofol group, *P □0.05, ** P □0.01, ***P □0.001

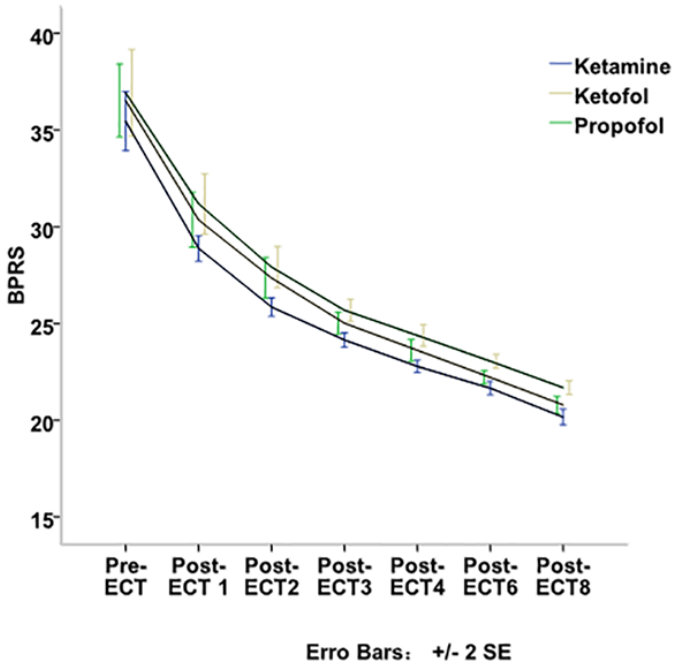
Compared with ketofol group□P □0.05□# P □0.01,□□□P □0.001

Figure 1. Hamilton depression rating scale over the ECT period



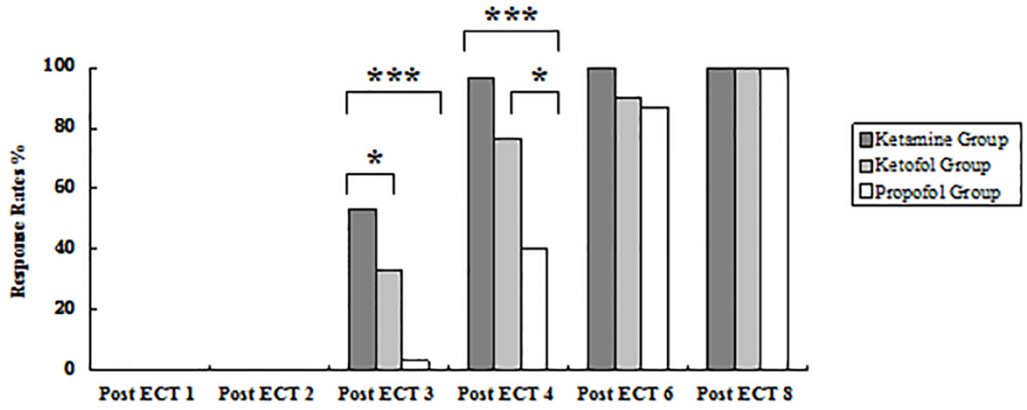
The antidepressant effect of ECT was significant over the treatment period in three groups.
There was significant group effect (ketamine vs. propofol , $p<0.001$, ketamine vs. ketofol, $p=0.011$, and ketofol vs. propofol, $p=0.033$, respectively) and group-by-time interaction ($p<0.001$).

Figure 2. Brief psychiatric rating scale over the ECT period



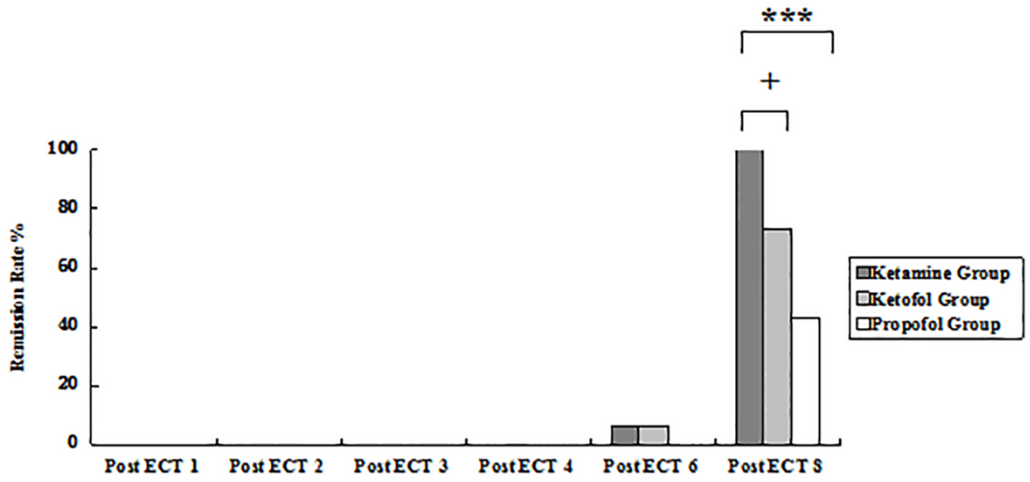
The psychopathology symptoms were significantly improved over the treatment period in three groups. Patients in ketamine group showed significant improvement in psychopathology symptom than patients in propofol group ($p<0.01$). However, there was no group-by-time interaction

Figure 3. Respond rates after each ECT



Compared with propofol group, *P ＜0.05, ***P ＜0.001

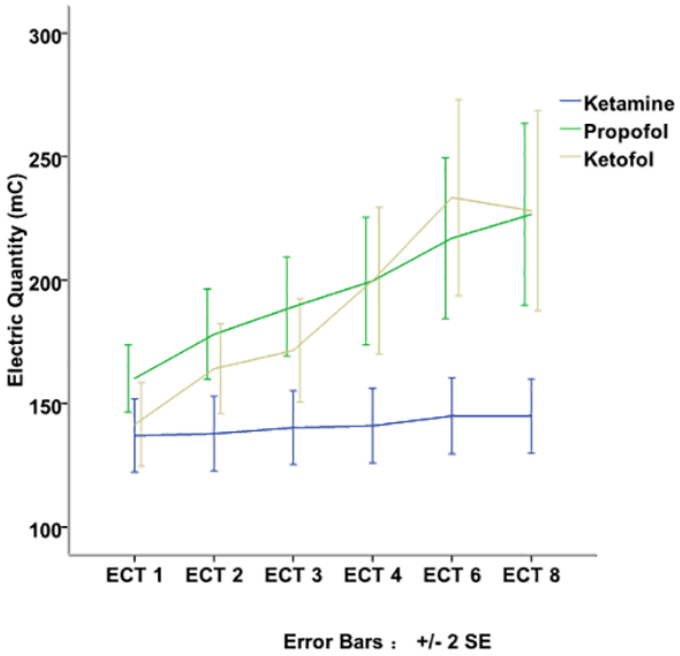
Figure 4. Remission rates after each ECT



Compared with propofol group, ***P ＜0.001

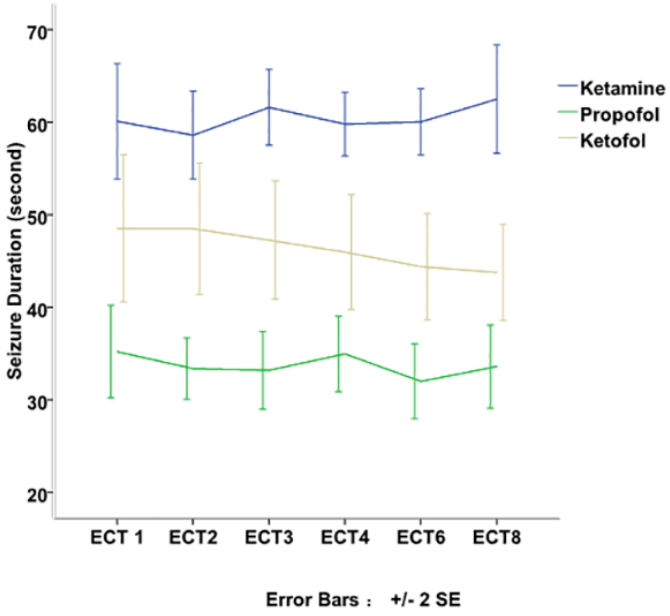
Compared with ketofol group, + P ＜0.05

Figure 5. The electric quantity required for ECT



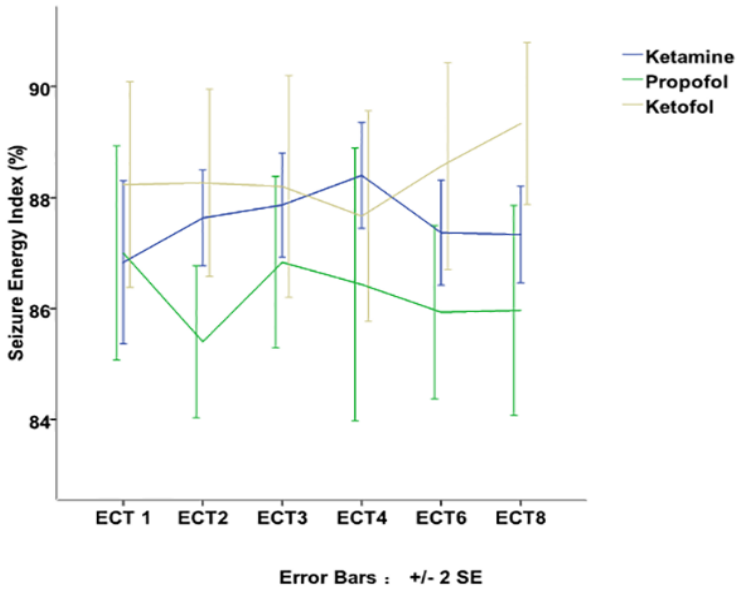
The electric quantity required for ECT became higher with increasing treatment times. Electric quantity in ketamine group was lower than that of propofol and ketofol groups. The group-by-time interaction was significant (P<0.001).

Figure 6. The eizure duration during ECT



The eizure duration in ketamine group was higher than that of propofol and ketofol groups. The seizure duration in ketofol group was higher than propofol group. However, there was no main time effect or group-by-time interaction.

Figure 7 The seizure energy index in ECT



The seizure energy index in ketofol group was higher than that of propofol group. No difference was found between ketamine and ketofol groups or between ketamine and propofol groups. There was no main time effect or group-by-time interaction.