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Research paper

Mood and neuropsychological effects of different doses 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 an effective tool for TRD treatment. However, there remains a subset of patients who do not respond to this treatment with common anesthetic agent. Ketamine, a noteworthy anesthetic agent, has emerged as an augmentation to enhance the antidepressant efficacy of ECT. Trials of i.v. ketamine in TRD indicated dose-related mood enhancing efficacy. We aimed to explore anesthetic and subanesthetic concentrations of ketamine in ECT for TRD with respect to their impact on mood and neuropsychological effects.

Methods: Ninety TRD patients (36 males, 54 females; average age, 30.6 years old) 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) (n=30) or propofol (0.8 mg/kg) (n=30) as an anesthetic and underwent 8 ECT sessions. The primary outcome measures were the 17-item Hamilton Depression Rating Scale (HDRS-17), cognitive assessments and seizure parameters.

Results: The ketamine group had an earlier improvement in HDRS-17, longer seizure duration, lower electric quantity, a higher remission rate, and a lower degree of executive cognitive impairment compared to the ketamine+propofol and propofol groups. The ketamine+propofol group showed earlier improvement in the HDRS-17, a longer seizure duration and a different seizure energy index when compared to the propofol group.

Limitations: The postoperative dissociative side effect was not assessed.

Conclusions: Both anesthetic and subanesthetic concentrations of ketamine have rapid mood enhancing 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.

1. 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 the growing selection of psychopharmacological treatments, 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 an 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). ECT affects multiple central nervous system components by inducing a bilateral general seizure. Seizure duration and electric quantity are the two most critical parameters in ECT. There is evidence that adequate seizure duration is necessary for antidepressant effects, and higher electric doses hasten the clinical response (Boylan et al., 2000). However, the response rate of ECT using a common anesthetic agent (such as propofol, thiopental and etomidate) is approximately 50–60% (Shelton et al., 2010). This result has stimulated interest in augmentation strategies that aim to increase the effectiveness of ECT for TRD treatment (McGirr et al., 2015).

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Ketamine, an N-methyl-D-aspartate (NMDA) receptor blocking agent, has emerged as a novel, rapid-acting antidepressant, and even when administered in low-doses intravenously, ketamine can rapidly reduce depressive symptoms and suicidal ideation in patients with affective disorders (Naughton et al., 2014). A growing body of research demonstrates that the glutamatergic system plays an important role in the pathophysiology of major depression and the mechanism of antidepressant effects. The rapid antidepressant effect of ketamine is due to the activation of the mammalian target of rapamycin (mTOR) signaling pathway together with the inhibitory phosphorylation of eukaryotic elongation factor 2 (eEF2) and glycogen synthase kinase-3 (GSK-) (Gideons et al., 2014). Ketamine is a noteworthy anesthetic agent used mainly for starting and maintaining anesthesia. Because of its anesthetic antidepressant effects, ketamine has emerged as a putative augmentation agent to enhance the antidepressant efficacy of ECT (Valentine et al., 2011; Wang et al., 2012; Yalcin et al., 2012; Jarventausta et al., 2013; Kucuk et al., 2013; Bryson et al., 2014; Rasmussen et al., 2014; Erdil et al., 2015; Sartorius et al., 2015). An increasing number of studies have tested the antidepressive effects of ketamine for ECT anesthesia in medication-free or antidepressant-antipsychotic drug combinations in patients with MDD or TRD (McGirr et al., 2015), while studies of intravenous ketamine without ECT were often performed in TRD patients or the ECT-resistant group (Serafini et al., 2014). Most studies of repeated-dose intravenous ketamine for TRD demonstrated rapid antidepressant effects (Serafini et al., 2014). However, the efficacy results of ketamine for ECT anesthesia are inconsistent. Some studies reported a lack of clinical efficacy and some confirmed its efficacy in improving depressive symptomatology earlier when using ketamine as an anesthesia agent or an adjunctive agent to ECT compared with propofol, thiopental or methohexital anesthesia (Okamoto et al., 2010; Abdallah et al., 2012; Loo et al., 2012; Wang et al., 2012; Jarventausta et al., 2013; Rasmussen et al., 2014). Further studies are needed to provide evidence regarding this issue.

A previous study of ketamine administered with anesthetic concentrations as augmentation in ECT for TRD indicated an increased effect (Okamoto et al., 2010), while subanesthetic concentrations 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 intravenous injection (i.v.) ketamine in TRD patients provided evidence that increasing doses of ketamine produced more marked and more sustained antidepressant responses (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. The optimal mode of ketamine anesthesia for ECT remains unknown.

In additional, cognitive impairment is common after ECT. The use of ECT is limited due to its adverse effects on cognitive function. Patients experience disorientation after each treatment and may have anterograde amnesia after the ECT course (Moscrip et al., 2004). Excitotoxic damage related to excessive glutamatergic transmission through the NMDA receptor during ECT is a postulated molecular mechanism for cognitive impairment (Loo et al., 2012). When ketamine is used in anesthetic doses, it exerts neuroprotection by inhibiting the NMDA-receptor activation, mediating beneficial changes in apoptosis-regulating proteins, and interfering with the inflammatory response to injury (Hudetz and Pagel, 2010). Ketamine as an anesthesia for ECT may exhibit potential cognitive protection.

The aim of the present study was to compare the effects of ketamine, the subanesthetic ketamine/propofol combination (ketamine+propofol) and propofol as anesthesia on the antidepressant efficacies, ECT parameters, cognitive protection and side effects in patients with TRD.

2. Materials and methods

2.1. Subjects

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. All patients were recruited from the wards of the Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital). The ECT sessions were performed in the Department of ECT of The Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital). Patients with TRD were enrolled 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 of different pharmacological classes at adequate dosages for at least 6 weeks for their current depression episode. The exclusion criteria were as follows: the existence of a mental disorder other than major depression or bipolar disorder with a current major depressive episode, such as schizophrenia and dementia; a history of seizures; a history of substance abuse including alcohol or drug abuse; pregnancy; the presence of neurological disorders or traumatic brain injury; the presence of any serious physical disease, such as intracranial hypertension, cerebrovascular disorder, respiratory tract disease; and other contraindications for ECT or anesthesia.

2.2. Research intervention

TRD patients were randomized to receive ketamine, ketamine+propofol 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 for a total of eight treatments. No antipsychotic or antidepressive drugs were prescribed to the patients during the period of ECT. All three groups first received atropine sulfate (1 mg). 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) I.V. push for anesthesia for the ketamine, ketamine+propofol and propofol groups, respectively. Succinylcholine (1 mg/kg) was administered intravenously as a muscle relaxant after the induction of anesthesia.

Bitemporal ECT was performed using the Thymatron ® IV device (Somatics LLC, Lake Bluff, Illinois, USA). The seizure threshold was determined using the half-age method (% energy=half the age) in each case. 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 10 min after the ECT procedure.

2.3. Psychopathology and cognitive assessment

The 17-item Hamilton Depression Rating Scale (HDRS-17) was used to assess the severity of depressive symptoms and the treatment response. The antidepressant response was defined at a $\geq$ 50% reduction in the HDRS-17 total score from baseline, and remission was considered a HDRS-17 score $\leq$ 7. The 18-item Brief Psychiatric Rating Scale (BPRS-18) 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 the next scheduled ECT and 48–72 h after the last (eight) treatments.

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

the selected scales have been demonstrated to have satisfactory reliability and validity for cognitive assessment and are commonly used in clinical settings.

2.4. Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 18.0 software (SPSS, Chicago, IL, USA). The Kruskal-Wallis H (K) test was used for skewed distributions, followed by the Mann-Whitney *U* test with Bonferroni correction. The one-way analysis of variance (ANOVA) was used for normal distributions, followed by the post hoc least significant difference test with Bonferroni correction. Analyses of repeated-measures, including the HDRS-17, the BPRS-18, electric quantity, seizure duration, the seizure energy index and the blood pressure were conducted by General Linear Model (GLM) repeated measures, with treatment group (ketamine, ketamine+propofol and propofol) as the between-subjects factor and time of assessment as the within-subject factor. To analyze the influence of different anesthesia methods on neurocognition, the changes in the scores of the cognitive test were calculated (cognitive scores at baseline minus cognitive scores after the last ECT treatment), and the Kruskal-Wallis H (K) test was used for group comparisons. A two-tailed p value of 0.05 was considered statistically significant.

3. Results

3.1. Demographic and clinical characteristics

Ninety patients with TRD were enrolled, including 36 men (40%) and 54 women (60%). The mean age (SD) was 30.6 (9.15) years (ranging from 15 to 67 years). The patients were randomized into the ketamine (n=30), ketamine+propofol (n=30) and propofol (n=30) groups. Ten patients in the ketamine group, 13 patients in the ketamine+propofol group and 11 patients in the propofol group were diagnosed with bipolar disorder. The demographic data and baseline depression scores are presented in Table 1. No significant differences were found in the age, gender, education, baseline depression scores, baseline systolic diastolic blood pressures and baseline diastolic blood pressures among the participants in the three groups.

3.2. 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 increased (Fig. 1). A significant group-by-time interaction ($F=9.736$, $p<0.001$) and significant group differences (ketamine vs. propofol, $p<0.001$, ketamine vs. ketamine+propofol, $p=0.011$, and ketamine+propofol vs. propofol, $p=0.033$) were also obtained (Table 2 and Fig. 1). Bonferroni post-hoc analyses (Supplementary Table 1) indicated that patients who received ketamine as an anesthesia versus those who received propofol had lower HDRS-17 scores after the first treatment ($p=0.025$). A more pronounced difference was observed between the 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 ketamine+propofol as an anesthesia versus those who received propofol had 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 ($p=0.017$) (Supplementary Table 1). A comparison of the antidepressant effect of ketamine and ketamine+propofol showed significantly lower HDRS-17 scores in patients who received ketamine versus those who received ketamine+propofol from the completion of the second treatment to the last treatment (the eighth treatment) (Supplementary Table 1).

As shown in Fig. 2, we found no responders until the completion of the third treatment among the three groups. Both the ketamine and ketamine+propofol groups showed statistically significantly 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 the response rates between the ketamine and ketamine+propofol groups at any time point. With respect to remission, the group difference only reached significance after the completion of the eighth treatment (Fig. 3). The ketamine group had a statistically significant higher remission rate compared to the ketamine+propofol group ($p<0.001$) and propofol group ($p<0.017$). The chi-square test indicated that the remission rate in the ketamine+propofol group was significantly greater than in the propofol group ($p=0.018$). Nevertheless, this significance disappeared after Bonferroni correction.

3.3. The effect on psychopathology symptoms

The psychopathology symptoms were improved in all three treatment groups. GLM repeated-measures revealed a significant main effect of time on total BPRS-18 scores (Table 2). However, there was no significant group-by-time interaction (Table 2). A significant main effect of group was observed. Bonferroni post-hoc analyses (Table 2) indicated that patients in the ketamine group had significantly improved psychopathology symptoms compared to patients in the propofol group ($p<0.01$). No significant difference was found between the ketamine and ketamine+propofol groups or between the ketamine+propofol and propofol groups on the total BPRS-18 scores. There were significant main effects of time on subscales of anxiety-depression, anergia, though disturbance, activity, and hostility-suspicion (all $p<0.001$)

Table 1
Baseline characteristics of the ketamine, ketamine+propofol and propofol groups.

	Ketamine group (n=30)	ketamine+propofol 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-18 at baseline	35.47 ± 4.167	36.53 ± 5.164	36.93 ± 6.142	0.633	0.534
Systolic blood pressures at baseline	117.2 ± 7.5	116.7 ± 6.1	114.6 ± 6.3	1.235	0.296
Diastolic blood pressures at baseline	74.1 ± 6.0	74.1 ± 8.2	71.9 ± 5.2	1.117	0.332

Abbreviations: HDRS-17, 17-item Hamilton Depression Rating Scale.
BPRS-18, 18-item Brief Psychiatric Rating Scale.

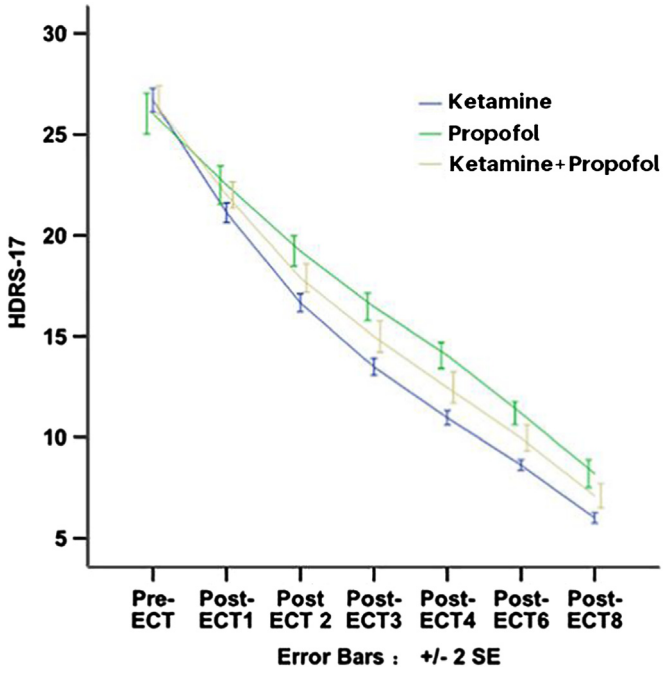

Fig. 1. Hamilton depression rating scale over the ECT period. The antidepressant effect of ECT was significant over the treatment period in three groups. There was significant group effect (ketamine vs. propofol, $p < 0.001$, ketamine vs. ketamine+propofol, $p = 0.011$, and ketamine+propofol vs. propofol, $p = 0.033$, respectively) and group-by-time interaction ($p < 0.001$).

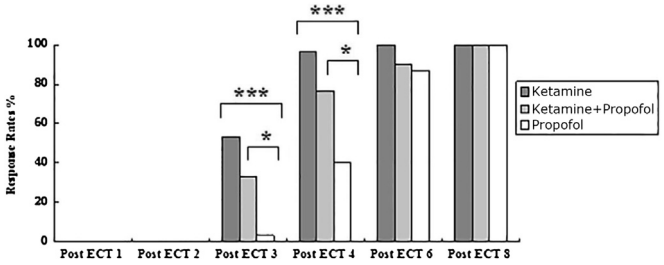

Fig. 2. Response rates after each ECT. The ketamine and ketamine+propofol groups showed statistically significantly higher response rates after the third and fourth ECT compared to the propofol group (ketamine vs. propofol, $p < 0.001$, ketamine vs. ketamine+propofol $p < 0.05$, respectively). The significant difference disappeared after the sixth and eighth ECT.

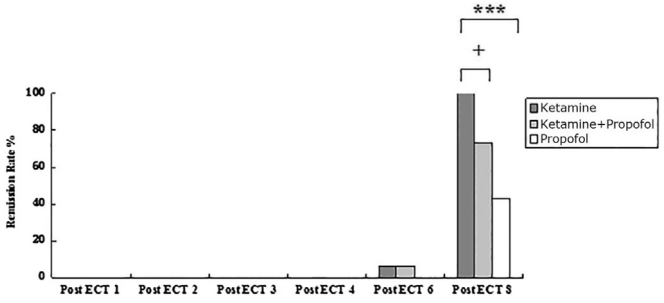

Fig. 3. Remission rates after each ECT. The ketamine group had a statistically significant higher remission rate compared to the ketamine+propofol group ($p < 0.001$) and propofol group ($p < 0.017$) after the eighth ECT.

(Supplementary Table 2). A significant main effect of group was observed on subscales of anxiety-depression. Bonferroni post-hoc analyses (Supplementary Table 2) indicated that patients in the ketamine group and ketamine+propofol groups had significantly improved emotional symptoms compared to patients in the propofol group ($p < 0.001$ and $p < 0.05$, respectively). Patients in the ketamine group showed lower scores on the subscale of anxiety-depression compared to patients in the ketamine+propofol group ($p < 0.01$).

3.4. Seizure parameters

GLM repeated-measures examining the effects of the anesthesia agent on the electric quantity showed a significant main effect of time (Table 3). The electric quantity required for ECT became higher with increasing treatment times. The group comparison indicated that the electric quantity in the ketamine group was lower than that in the propofol group or in the ketamine+propofol group. No difference was found between the ketamine+propofol and propofol groups. With respect to session variability, the electric quantity required in the ketamine group was lower than that of the propofol group at every time point. A significant difference was observed between the ketamine and ketamine+propofol groups at the second, fourth, sixth and eighth ECT treatments. The group-by-time interaction ($F = 6.314$, $p < 0.001$) was significant (Supplementary Table 3).

There is a significant main effect of group in the seizure duration and seizure energy index ($F = 22.4$, $p < 0.001$ and $F = 4.3$, $p < 0.05$, respectively). Seizure duration in the ketamine group was higher than in the propofol group or in the ketamine+propofol group (Table 3). Seizure duration was increased in the ketamine+propofol group when compared to the propofol group. The seizure energy index in the ketamine+propofol group was higher than in the propofol group, while no difference was found between the ketamine and ketamine+propofol groups or between the ketamine and propofol groups (Table 3). There was no main effect of time and no significant group-by-time interaction for seizure duration or for the seizure energy index (Table 3).

Table 2
The main effect of time, the main effect of the grouping factor and the group-by-time interaction of the HDRS-17 and total BPRS-18 evaluated by GLM repeated measures analyses.

		SUM	Main effect of time		Main effect of grouping factor		Group-by-time interaction	
			F	*p*	*F*	*p*	*F*	*p*
HDRS-17	Ketamine group	$14.8 \pm 0.256^{*,a}$	3084.813	< 0.001	15.529	< 0.001	9.736	< 0.001
	ketamine+propofol group	$15.876 \pm 0.256^{*}$						
	Propofol group	16.814 ± 0.256						
BPRS-18	Ketamine group	$25.576 \pm 0.351^{**}$	597.498	< 0.001	5.901	0.004	0.339	0.797
	ketamine+propofol group	26.567 ± 0.351						
	Propofol group	27.276 ± 0.351						

Abbreviations: HDRS-17, 17-item Hamilton Depression Rating Scale; BPRS-18, 18-item Brief Psychiatric Rating Scale.

[*] Compared with propofol group, $p < 0.05$.

[**] Compared with propofol group, $p < 0.01$.

[a] Compared with ketamine+propofol group, $p < 0.05$.

Table 3
The main effect of time, the main effect of the grouping factor and the group-by-time interaction on the electric quantity, seizure duration and seizure energy index evaluated by GLM repeated measures analyses.

		SUM	Main effect of time		Main effect of grouping factor		Group-by-time interaction	
Electric quantity (mC)	Ketamine group	141.05 ± 10.358**,b	29.675	< 0.001	8.292	0.001	6.314	< 0.001
	ketamine + propofol group	189.8 ± 10.358						
	Propofol group	195.2 ± 10.358						
Seizure duration (second)	Ketamine group	60.439 ± 2.126***,c	0.711	0.571	39.513	< 0.001	0.959	0.463
	ketamine + propofol 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
	ketamine + propofol group	88.378 ± 0.394**						
	Propofol group	86.261 ± 0.394						

** Compared with propofol group, $p < 0.01$.
*** Compared with propofol group, $p < 0.001$.
[b] Compared with ketamine + propofol group, $p < 0.01$.
[c] Compared with ketamine + propofol group, $p < 0.001$.

3.5. Cognitive function

There was no significant difference in the 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 the propofol group were significantly greater than those of the ketamine group ($p < 0.05$) (Supplementary Table 4). The decline in the number of WCST categories completed in the ketamine + propofol group was more severe than that of the ketamine group ($p < 0.05$). The propofol group had a significant decline in performance (an increase in time to completion) on TMT Part A and Part B compared to the ketamine group ($p < 0.05$) (Supplementary Table 4). The degrees of cognitive impairment as measured by the Word Fluency Test, the Digit Symbol Test, the Digit Span test and the Visual Regeneration Test were not different among the three groups ($p > 0.05$) (data not shown).

3.6. Side effects

During the eight ECT treatments, no major adverse effects were observed in patients who received ketamine, ketamine + propofol or propofol as the anesthesia agent. The majority of patients in all three groups reported minimal transient adverse events, including headaches and nausea. These adverse events remitted spontaneously in 0.5–1 h without any treatment. None of them were severe enough to require discontinuation of the ECT treatment.

Analysis of systolic blood pressure detected a main effect of group ($F = 40.962$, $p < 0.001$) and group-by-time interaction ($F = 2.615$, $p = 0.02$) (Table 4). Bonferroni post-hoc analyses indicated that patients in the ketamine and ketamine + propofol groups showed higher systolic blood pressure than the propofol group (Supplementary Table 5). There was no difference in the systolic blood pressure between the ketamine and ketamine + propofol groups at any time point (Supplementary Table 5). Analysis of diastolic blood pressure detected a main effect of treatment ($F = 39.939$, $p < 0.001$) but not time ($F = 1.968$, $p = 0.07$) (Table 4). Post-hoc tests confirmed that both ketamine and ketamine + propofol significantly increased diastolic blood pressure after each ECT treatment (Supplementary Table 5). The diastolic blood pressure was significantly higher in the ketamine group when compared with the ketamine + propofol group at most sessions of ECT (Supplementary Table 5).

4. Discussion

In this study, we compared the 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, a higher remission rate, lower electric quantity, increased seizure duration, a higher seizure energy index and a lower degree of cognitive impairment in the ketamine group than in the propofol group. These observations highlight the clinical usefulness of ketamine in ECT for the treatment of TRD.

TRD is an important clinical problem that continues to represent a major challenge in 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 intravenous ketamine (0.5 mg/kg over 45 min) are as effective as ECT using thiopental as anesthetic agents in improving the depressive symptoms of MDD patients, and ketamine has more rapid

Table 4
The main effect of time, the main effect of the grouping factor and the group-by-time interaction of the systolic and diastolic blood pressures evaluated by GLM repeated measures analyses.

		SUM	Main effect of time		Main effect of grouping factor		Group-by-time interaction	
			F	*p*	*F*	*p*	*F*	*p*
Systolic blood pressures	Ketamine group	128.9 ± 1.4***	2.615	0.02	40.962	< 0.001	1.356	0.190
	ketamine + propofol group	126.1 ± 1.4***						
	Propofol group	112.3 ± 1.4						
Diastolic blood pressures	Ketamine group	84.8 ± 1.0***,b	1.968	0.07	39.939	< 0.001	0.479	0.925
	ketamine + propofol group	72.5 ± 1.0***						
	Propofol group	80.0 ± 1.0						

*** Compared with propofol group, $p < 0.001$.
[b] Compared with ketamine + propofol group, $p < 0.01$.

antidepressant effects compared to ECT (Ghasemi et al., 2014). Thus, using ketamine as an anesthetic agent in ECT should be an optimized therapy for TRD. As expected, our study confirms that ketamine enhances the speed of response to ECT. Compared to the propofol group, both patients in the ketamine and ketamine+propofol groups showed a significant clinical improvement in depressive symptoms during the early stages of treatment (after the first ECT and after the second ECT, respectively). Our finding is consistent with the study of Okamoto et al. (2010) which indicated rapid antidepressant effects with ketamine anesthesia. However, Okamoto et al. (2010) found that the superiority disappeared after the completion of the sixth and eighth ECT. In contrast to this result, we observed greater improvement of the depression symptoms in the ketamine group than in the propofol group throughout the eight ECT sessions. In addition, when ketamine was used as an adjuvant to propofol, increased antidepressive effectiveness was also observed. This result is in contrast to the study of Järventausta et al. (2013) which showed no difference in the magnitude or speed of response compared to propofol (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, and 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 the present study, the patients in the ketamine group received a larger dose of ketamine relative to the patients in the ketamine+propofol group (0.8 mg/kg and 0.5 mg/kg, respectively). We observed a greater improvement in the depression symptoms in the ketamine group comparing to the propofol group after the second ECT, and this superiority lasted until the eighth session of ECT. Regarding the speed of the response, the ketamine and ketamine+propofol groups showed higher response rates at the completion of the third and fourth ECT; after that, the propofol group caught up with the ketamine and ketamine+propofol groups. The recovery rate was significantly higher at the completion of the eighth ECT session in the ketamine group when compared with the ketamine+propofol 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 concentrations of ketamine had superior antidepressive effects and cognitive protection compared to subanesthetic concentrations of ketamine. Our study show that both anesthetic and subanesthetic concentrations of ketamine show rapid mood enhancing actions, suggesting that ketamine enhances the effect of ECT for TRD. We should take into account that the anticonvulsant properties of propofol have negatively impact on seizure parameters. Another interpretation of this result is that propofol influences the antidepressant effect of ECT.

A meta-analysis of trials of ketamine augmentation in ECT settings suggested a lack of clinical efficacy (McGirr et al., 2015), while we found high response and remission rates. There are three major explanations for this conflicting result. Firstly, data in the meta-analysis were synthesized from 5 RCTs, with differences in the ketamine dose, concomitant anesthetic agents, stimulation parameters, and depressive symptom rating scales (McGirr et al., 2015). Secondly, no TRD patients were included in the meta-analysis, while we included only TRD patients in the present study. Thirdly, 17 of the 182 patients in the meta-analysis had bipolar disorder, while 34 of 90 patients in our study had bipolar disorder. The larger percentage of patients with bipolar disorder included in our study may contribute to the observed divergence. Further multi-center case control studies are needed to verify the synergistic antidepressant effects of ketamine and ECT in TRD patients.

Prior studies have reported that ketamine anesthesia is associated with longer seizure duration and more favorable central inhibition effects, with higher-quality seizures than propofol (Okamoto et al., 2010; Yalcin et al., 2012; Hoyer et al., 2014). We confirmed that the seizure durations in the ketamine and ketamine+propofol groups were longer compared to the propofol group. This result suggests that the anesthetic concentration of ketamine or subanesthetic ketamine resulted in significant changes in seizure duration. The electric quantity required for ECT in the ketamine group was less than in the ketamine+propofol and propofol groups. This result may be due to their pharmacological properties, as ketamine has less anticonvulsant activity than propofol. Our study provided evidence that the use of ketamine in ECT is advantageous.

After a grand mal seizure, patients have a period of cognitive impairment (MacPherson and Loo, 2008). Cognitive impairment is a common side effect following ECT. Some individuals with TRD forgo ECT due to concerns regarding adverse cognitive effects. The choice of the anesthetic agent makes a difference in cognitive impairment following ECT, possibly by affecting the seizure threshold, altering the required electrical dose, or affecting seizure expression (MacPherson and Loo, 2008). As mentioned above, patients in the ketamine+propofol and propofol groups received significant higher electrical doses than patients in the 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 ketamine+propofol in regards to the impairment of executive functioning following ECT. There is evidence 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 leading to increased synaptic signaling proteins (Li et al., 2010) and increasing 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 the low electrical dosage.

Ketamine has been reported to increase central sympathetic activity and catecholamine reuptake inhibition, resulting in raised blood pressures. In present study, we found an increase in systolic and diastolic blood pressures in the ketamine and ketamine+propofol groups. This finding is consistent with previous reports of ketamine infusion and ketamine anesthesia (Valentine et al., 2011; Yoosefi et al., 2014). At most sessions of ECT, we noted an increase in diastolic blood pressures in the ketamine group when compared to the ketamine+propofol group, suggesting that there may be dose-effect relation between the ketamine and diastolic blood pressures. Although ketamine anesthesia induced a significant rise in blood pressure, this side effect was temporary and without clinical significance. We consider that ketamine anesthesia was safe and well tolerated for ECT.

It is important to note some limitations of the present study. Although the rater and the patients were blind to the anesthetic agent in this study, the blinding wasn't tested. The trial's outcomes may have been biased by guesses about treatment allocation. Cognitive tests were performed at baseline and 48–72 h after the eighth treatment. We can't ascertain whether there is a practice effect. However, if there is a practice effect, its influence on cognitive function is comparable in the three groups. The study did not assess dissociative states which may be induced by ketamine anesthesia. It may be detected if scales such as the Clinician-Administered Dissociative States Scale (CADSS) were used. Future studies with large sample sizes focusing on the dissociative states of ketamine anesthesia are needed to provide evidence for clinical expansion.

TRD continues to represent a major challenge for treating clinicians. Although repeated doses i.v. of ketamine improved depressive symptoms in TRD patients, its application is limited for

the cardiovascular side effects and dissociative symptoms. Ketamine ECT may be a potential future direction for TRD treatment. Our study demonstrates that both anesthetic and subanesthetic concentrations of ketamine enhance the effect of ECT for TRD. The use of anesthetic concentrations of ketamine has superior antidepressant effects and neuroprotection against cognitive impairment compared to propofol and ketamine/propofol combined. Ketamine anesthesia is an optimal mode of drug administration recommended for the ECT for TRD.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2016.05.011.

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