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Intermittent administration of low dose ketamine can shorten the course of electroconvulsive therapy for depression and reduce complications: A randomized controlled trial

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ABSTRACT

This study aimed to investigate the efficacy and safety of intermittent low-dose ketamine on improving the efficacy of ECT. Patients diagnosed with Major Depressive Disorder (MDD) (n = 134) were randomized into 3 groups: routine ECT group (group E, n = 45); repeated ketamine-assisted ECT group (group RK, n = 43), and intermittent ketamine-assisted ECT group (group IK, n = 46). Patients in group RK were given ketamine at the dose of 0.3 mg/kg for each ECT treatment, patients in group IK were given ketamine once a week during ECT course. The depressive symptoms were assessed using the Hamilton Depression Rating Scale (HAM-D) at baseline, the end of ECT course, after 1 and 3 months, followed by an analysis of the psychiatric complications. Results indicated that ketamine-assisted ECT achieved a higher remission rate ($P < 0.05$), and no difference was observed between repeated and intermittent ketamine administrations. The total incidence rate of psychiatric complications in group RK (20.93%) was higher than that in group E (0%) and group IK (4.35%). In conclusion, intermittent administration of low dose ketamine in ECT significantly improved the effects of ECT and decreased psychiatric complications compared with repeated ketamine addition.

1. Introduction

Major Depressive Disorder (MDD) seriously affects patients' physical and mental health. Antidepressants have a slow effect on MDD, especially for patients with suicidal tendencies. Antidepressants may even increase suicide rate in the early stage of MDD. Thus, ECT is the preferred treatment for patients with severe depression, even though the remission rate of ECT in MDD is still unsatisfactory. ECT requires the use of general intravenous anesthetics, however, the commonly used anesthetics such as propofol and etomidate have been shown to have no antidepressant effects.

Ketamine is a commonly used intravenous anesthetic with a rapid and lasting antidepressant effect (Erdil et al., 2015; Salehi et al., 2015). In addition, it is currently used as an anesthetic in ECT (Nugent et al., 2019; Thomas et al., 2018). High-dose and repeated use of ketamine may lead to delirium as well as other psychiatric complications, while low-dose ketamine is safer (Hayhurst et al., 2018) and has the potential to enhance the efficacy of ECT in MDD patients (Li et al., 2017). In addition, current studies have confirmed that a single low dose of ketamine can maintain a long-term antidepressant effect, which can last for more than 7 days (Romeo et al., 2015; Pennybaker et al., 2017). Based on this, the repeated administration pattern of ketamine in each ECT course has been challenged.

However, it is not yet clear whether intermittent administration of ketamine can produce the same enhanced effects of ECT. The current study has been designed to investigate the role of intermittent administration (once a week) of low-dose ketamine in improving the efficacy of ECT, and to compare the treatment-associated complications and the antidepressant effects of ECT between patient groups administered with repeated and intermittent ketamine.

2. Materials and methods

2.1. Participants

This study included 172 patients with unipolar MDD. The inclusion criteria were unipolar MDD, age from 16 to 65 years, NYHA grading I–II level and ASA grading I–II level . The exclusion criteria were severe cardiovascular or cerebrovascular diseases, illiteracy, drug addiction and abuse, history of drug allergy, mental retardation or other

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neurological disorders affecting cognitive function assessment, other psychiatric disorders affecting medical experiences, including schizophrenia and post-traumatic stress disorder. The elimination criteria were severe adverse reactions, the development of bipolar depression or anxiety, changes in the treatment due to the development of the disease, refusing to participate in the experiment, missing of contact, and other factors that affecting experimental observation or data collection.

2.2. Experimental design

Patients were recruited consecutively from The Department of Psychiatry, The First Affiliated Hospital of Chongqing Medical University from January 2018 to January 2019. The protocol was approved by the medical ethics committee of the university, and the clinical study has been registered at www.clinicaltrials.gov/ (identifier number: NCT02305394). Patients were first diagnosed by psychiatrists according to the DSM-5 criteria and MDD patients requiring ECT were enrolled to participate in the trial. All participants provided written informed consent to receive ECT and to participate to this study. The enrolled patients were randomly divided into three groups according to the differences in the ketamine administration patterns: ECT control group (Group E), repeated ketamine administration group (group RK), and intermittent ketamine administration group (group IK). Random number software was used to generate a sequence of random numbers containing only 1, 2 and 3 before the study. According to the time and sequence of starting treatment, the patients were randomly divided into group E (1), group RK (2) and group IK (3).

2.3. Anesthetic treatments

The ECG, blood pressure and pulse oxygen saturation were monitored routinely. Patients in all three groups were treated with ECT after having been anesthetized with 1–1.5 mg/kg propofol (Corden Pharma S.P.A, No: X17073B) administered as an intravenous injection and 0.8–1 mg/kg suxamethonium chloride (Shanghai Xudong Haipu Pharmaceutical CO. LTD, No: AA151201) also administered as an intravenous injection. Patients in group RK were given an intravenous injection with 0.3 mg/kg ketamine (Fujian Gutian Pharmaceutical CO. LTD, No: 1707033) before the administration of anesthesia during each ECT, while patients in group IK were given 0.3 mg/kg ketamine as an intravenous injection before the administration of anesthesia once a week during the course of ECT.

2.4. ECT procedures

All the patients were given ECT with electrodes placed on both temporal sides three times a week, i.e. on Mondays, Wednesdays and Fridays. The initial energy was set based on the patient's age, energy percent = age (years) × 0.5%. The energy percent was increased by 5% in the next treatment if the inhibition index was less than 80%. The instruments used for ECT was Thymatron System IV (Somatics, LLC, Venice, FL United States). The frequency of ECT was based on the manifestations of the symptoms. A course of treatment usually comprised of 6–15 sessions of ECT. A course was considered to be completed when depressive symptoms achieved the standard of cure (HAM-D scores < 8). However, if the total number of ECT administration reaches 15 times without inducing any relief of symptoms, then ECT is stopped and the condition is considered uncured.

2.5. Measures

2.5.1. Assessment of ECT outcomes

The convulsion seizure time and energy inhibition index of EEG were collected and recorded for each ECT treatment by a Thymatron System IV instrument, and the average value of each ECT during the entire course of ECT was used as the patient's value for statistical analysis. The number and maximum energy of ECT of all patients was record.

The HAM-D depression scores, including 24 depression scales (with a total score of 78) were used to evaluate the degree of depression on the day before the administration of the ECT course, and then on 1 day, 1 month and 3 months after the end of the entire ECT course. Depression was considered to be relieved if the HAM-D score reduced by more than 50% and HAM-D score <20. It was considered to be clinical cured when the depressive symptoms were not observed anymore and the HAM-D score was less than 8. The patient was considered as not cured if the HAM-D score was still higher than 8 after 15 times ECT treatment.

2.5.2. Analysis of complications

Montreal Cognitive Assessment (MoCA) scale was used to evaluate the cognitive function of the patients one day before the ECT course, 1 day, 1 month and 3 months after the completion of the entire ECT course. The MoCA scale included eight items with a total score of 30, including visual space and executive function, naming, memory, attention, language, abstraction, delayed recall and orientation. Education duration <12 years plus 1. A total score of less than 26 was considered as cognitive impairment (Moirand et al., 2018).

The psychiatric complications incompatible with depression including hallucinations, irritability, impulsive behavior, delusions, delirium, etc. were recorded during the course of ECT and considered to be ketamine-related.

2.6. Statistics

The sample size calculation test level was $\alpha = 0.05$, and the test efficiency $1 - \beta = 0.9$. The minimum sample size of each group was more than 42 according to the main indicator of HAM-D scores. SPSS Statistics 19.0 software was used for data processing. The normal distribution measurements were expressed as the mean ± standard deviation. Analysis of variance (ANOVA) was used for comparison among groups. SNK-q was used for intergroup comparison. Variance analysis of repeated measurements and the LSD-*t*-test were used for intragroup comparison. The Fisher's exact test was used to compare the occurrence of complications. The chi-squared test was used for comparing the antidepressant medication case, remission rate and cure rate. The Bonferroni correction was used for intergroup comparison. The results were considered to be statistically significant when $P < 0.05$.

3. Results

3.1. General materials

A total of 172 patients were enrolled in this study, out of which 38 patients were eliminated and 134 cases were actually completed and followed up. The group E comprised of 45 completed cases, the group RK comprised of 43 complete cases and the group IK comprised of 46 complete cases (Fig 1).

There was no significant difference in gender, age and years of education in the three groups ($P > 0.05$). There was no significant difference in the use of antidepressant drugs (Table 1).

The ECT data ($N = 134$) was analyzed and the result is shown in Table 2. The inhibitory index of EEG in group E was lower than that in groups RK and IK, but there was no significant difference in seizure time among the three groups ($P > 0.05$). Compared with conventional ECT (group E), the number and the maximum energy of ECT were lower in the groups RK and IK when depression was relieved as well as when it was clinically cured ($P < 0.01$), and there was a higher remission rate in adjunctive ketamine patients ($P < 0.05$). The HAM-D scores in the three groups at the end of the ECT course and at the 1 month follow up were significantly lower than those before treatment, and the HAM-D scores of patients with adjunctive ketamine were lower than those in

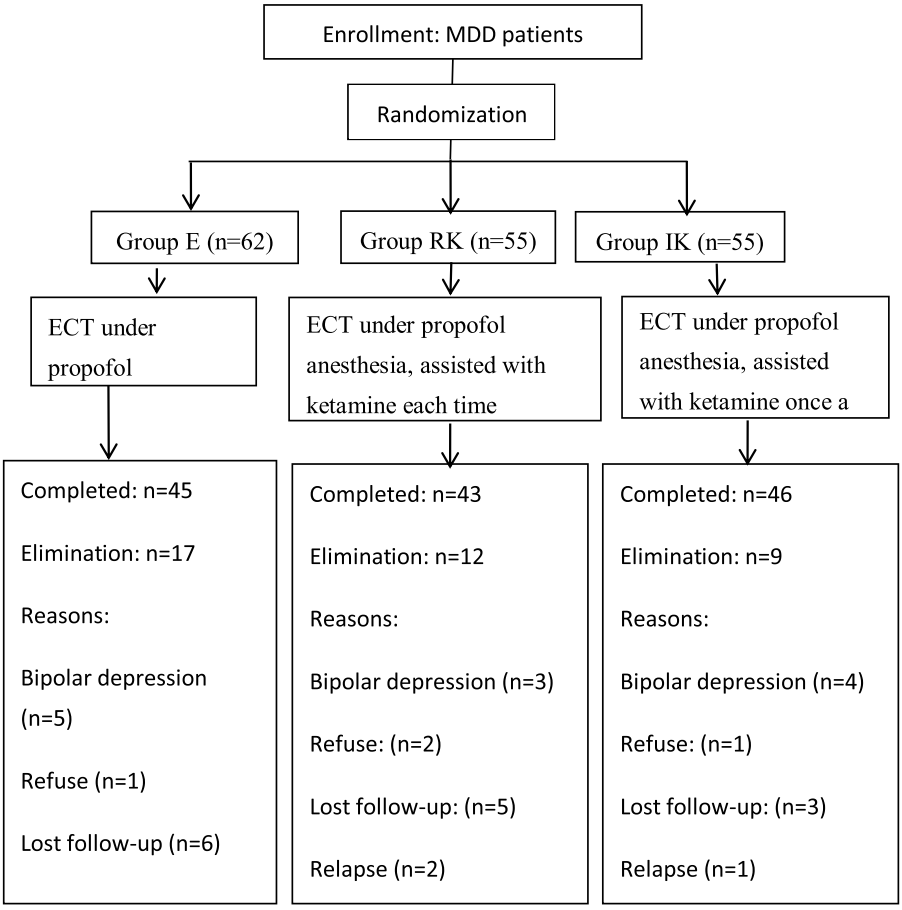

Fig. 1. The study design.

group E ($P < 0.01$). There was no significant difference in the number of ECTs, the maximum energy, HAM-D scores between groups RK and IK ($P > 0.05$). There was no significant difference in clinical cure rate among these three groups.

In this study, 10 cases in group E, 2 cases in group RK and 3 cases in group IK did not reach the remission standard when the ECT course was completed. The ECT data of remission patients was further analyzed and the results are shown in Table 2. The number of ECT treatments required for achieving remission of symptoms in groups RK and IK was lower than that in group E ($P < 0.01$). There was no significant difference in seizure time, inhibitory index, number and energy of relief, and HAM-D scores at the end of the ECT course as well as at the 1 month and 3 month follow up among the three groups ($P > 0.05$).

3.2. Psychiatric complications

Cognitive function was measured by MoCA after ECT treatment. MoCA scores in the three groups were improved after ECT ($P < 0.05$). However, as shown in Table 3, there was no significant difference in the MoCA scores among the three groups after ECT ($P > 0.05$).

The total incidence rate of psychiatric complications in group RK (20.93%) was higher than that in group E ($P = 0.004$) and group IK ($P = 0.04$). There was no significant difference in the incidence rate between the groups E and IK ($P > 0.05$). Two cases in the IK group

Table 1
Baseline patient data.

Demographics	Group E (n = 45)	Group RK (n = 43)	Group IK (n = 46)	F	P–value
Gender					
Male (n/percentage)	22/48.9%	18/41.9%	25/54.3%	*1.391*	*0.499*
Female(n/percentage)	23/51.1%	25/58.1%	21/45.7%	–	–
Age					
Mean	35.67 ± 12.78	36.79 ± 15.08	35.61 ± 11.29	*0.113*	*0.893*
CI 95%	31.83–39.51	32.15–41.43	32.26–38.96	–	–
Years of Education (year)					
Mean	12.76	13.19	13.30	*0.326*	*0.722*
CI 95%	11.62–13.89	12.17–14.20	12.38–14.22	–	–
Antidepressant medication (n/percentage)					
SSRI	25/55.56%	22/51.16%	24/52.17%	*0.189*	*0.910*
SNRI	7/15.56%	6/13.95%	6/13.04%	*0.121*	*0.941*
NASSA	9/20.93%	6/13.95%	8/17.39%	*0.568*	*0.753*

Measurement data are shown as the means ± standard deviation. The data were analyzed with ANOVA, P values were determined with SNK-q test, Compared with entering the room, a$P < 0.05$; Compared with before ECT, b$P < 0.05$; Compared with leaving the room, c$P < 0.05$.

Table 2
Comparison of EEG seizures and ECT Effects.

		All patients (N = 134) Group E (n = 45)	Group RK (n = 43)	Group IK (n = 46)	F	P–value
Seizure time of EEG (s)		29.82 ± 4.55	31.14 ± 3.88	31.04 ± 3.31	*1.55*	*0.216*
Inhibitory index of EEG		80.62 ± 4.89	83.14 ± 3.50	82.02 ± 6.01	*2.88*	*0.007*
ECT Number of relief		5.91 ± 1.28	4.37 ± 1.00[a]	4.46 ± 1.50[a]	*20.40*	*<0.001*
ECT energy of relief(%)		30.44 ± 8.52	24.89 ± 6.94[a]	25.76 ± 7.07[a]	*6.99*	*0.001*
ECT number of cure		10.47 ± 1.92	8.77 ± 1.84[a]	8.89 ± 2.01[a]	*10.79*	*<0.001*
ECT energy of cure (%)		41.22 ± 10.51	34.88 ± 9.10[a]	36.09 ± 6.99[a]	*6.28*	*0.002*
Remission rate (n/percentage)		35/77.8%	41/95.3%[a]	44/95.7%[a]	*32.64*	*<0.001*
Cure rate (n/percentage)		32/71.1%	38/88.4%	40/86.9%	*5.584*	*0.061*
HAM-D (score)	Before ECT	29.69 ± 2.71	30.07 ± 2.80	30.39 ± 2,30	*0.83*	*0.440*
	End of ECT	8.44 ± 3.95[b]	6.88 ± 2.83[a,b]	6.93 ± 2.89[a,b]	*3.30*	*0.040*
	1 month follow-up	7.62 ± 2.77[b]	6.40 ± 1.22[a,b]	6.20 ± 1.05[a,b]	*7.82*	*0.001*
	3 month follow-up	7.27 ± 2.13[b]	6.63 ± 1.80[b]	6.48 ± 1.66[b]	*2.26*	*0.108*
		Remission patients (N = 119) Group E (n = 35)	Group RK (n = 41)	Group IK (n = 43)	F	P-value
Convulsive time of EEG (S)		31.45 ± 3.51	31.44 ± 3.89	31.52 ± 2.99	*0.01*	*0.100*
Inhibitory index of EEG		82.43 ± 2.79	83.59 ± 2.83	83.44 ± 3.90	*1.41*	*0.248*
ECT Number of relief		5.54 ± 0.95	4.24 ± 0.83	4.14 ± 1.51	*24.14*	*<0.001*
ECT Number of cure		9.63 ± 0.65	8.46 ± 1.23	8.40 ± 1.17	*15.52*	*<0.001*
ECT Energy of relief (%)		28.29 ± 7.66	25.00 ± 7.07	25.58 ± 6.47	*2.294*	*0.105*
ECT Energy of cure (%)		38.00 ± 8.68	34.63 ± 9.18	35.58 ± 6.56	*1.68*	*0.191*
HAM-D (score)	Before ECT	29.69 ± 2.71	30.07 ± 2.80	30.39 ± 2,30	*0.83*	*0.440*
	End of ECT	6.26 ± 0.82	6.17 ± 0.95	6.09 ± 0.95	*0.31*	*0.731*
	1 month follow-up	6.34 ± 0.76	6.20 ± 0.75	6.02 ± 0.83	*1.62*	*0.202*
	3 month follow-up	6.26 ± 0.61	6.29 ± 0.90	6.09 ± 0.75	*0.79*	*0.453*

Measurement data are shown as the means ± standard deviation. The data were analyzed with ANOVA, P values were determined with SNK-q test, Remission rate and cure rate were shown as a percentage, and P values were determined with chi-squared test. Compared with group E.
[a] $P<0.05$;Compared with before ECT
[b] $P<0.05$.

were irritable, while in the in RK group, 4 cases of hallucination, 3 cases of irritability and 2 cases of delirium were recorded.

4. Discussion

These results were obtained after a one year long study and they show that low-dose ketamine (0.3 mg/kg) significantly shortened the relief and cure times of ECT and improved the remission rate of depressed patients. However, adjunctive low-dose ketamine administration in ECT did not affect the cure rate and HAM-D scores of remission depression patients. There were similar improving effect on depressed symptoms between repeated administration (each ECT treatment) and intermittent administration (once a week) of ketamine, but repeated ketamine administration increased psychiatric complications such as hallucination and delirium.

Intravenous anesthesia is the most commonly used anesthesia for ECT. Studies have confirmed that propofol, a commonly used intravenous anesthetic, has no significant effect on the efficacy of ECT for depression (Jun et al., 2010). Ketamine is another commonly used intravenous anesthetic in clinical settings, but the specific roles of ketamine in ECT remains controversial. Krystal JH found that low-dose ketamine had some degree of antidepressant effects (Krystal et al., 2007), and thus, extensive research has been done on the application of ketamine in depression (Chen et al., 2017). Studies have shown that a single injection of low-dose ketamine can have a rapid and long-lasting antidepressant effect in most depressive patients. A study with 27 depressive patients injected with ketamine showed that the rate of response and symptom relief after 24 h was 59% and 40.7%, respectively. Montgomery-Asberg Depression Rating Scale (MADRS) relief was achieved in 48% of the patients, with more than 50%, and 37% of the patients meeting the clinical relief criteria (MADRS < 7) within 7 days (Correia-Melo et al., 2017), which suggested that the antidepressant effect of ketamine after a single injection for depression maintained at least for more than a week. Adjunctive ketamine reduced the number of

Table 3
MoCA Cognitive function score and ketamine-related complications.

Parameters	Group E (n = 45)	Group RK (n = 43)	Group IK (n = 46)	F	P-value
MoCA (score)					
Before ECT	23.30 ± 1.69	23.63 ± 1.76	23.93 ± 1.53	1.727	0.182
End of ECT	23.73 ± 1.39[d]	24.49 ± 1.58[a,c]	24.78 ± 1.85[a,c]	5.058	0.008
1 month follow-up	24.56 ± 1.32[c,d]	24.81 ± 1.44[c]	24.93 ± 1.20[c]	0.975	0.380
3 months follow-up	25.38 ± 1.66[c]	25.51 ± 1.35[c]	25.54 ± 1.24[c]	0.171	0.843
Ketamine-related psychiatric complications (n/percentage)					
Totality during ECT	0/0%	9/20.93%[a,b]	2/4.35%	*15.49*	*<0.001*

Measurement data are shown as the means ± standard deviation. The data were analyzed with ANOVA, P values were determined with SNK-q test, the incidence rate is shown as a percentage, and P values were determined with Fisher's exact test. Compared with group E.
[a] $P < 0.05$; Compared with group IK.
[b] $P < 0.05$. Compared with before ECT.
[c] $P < 0.05$;Compared with 3 months follow-up.
[d] $P < 0.05$.

ECTs required in patients of depression and reduced MADRS by 50% after two ECT treatments, while patients with propofol anesthesia need at least four ECT treatments to achieve the same results. In addition, the depression remission rate of ECT with adjunctive ketamine reached 100% (Gamble et al., 2018). In this study, 24 HAM-D scales were used to evaluate the improvement of depressive symptoms. We found that the average number of ECT treatments after which symptom relief (HAM-D scores reduced by 50%) is achieved with simple propofol anesthesia was 6 times, while in the case of adjunctive ketamine-assisted patients, it was 4 times. The average number of ECT treatments after which patients were clinically cured (HAM-D scores < 8) was 10 times in patients with simple propofol anesthesia but 8 times in the case of adjunctive ketamine-assisted patients. The clinical remission rate of ketamine-assisted patients was over 95%, while that of simple propofol patients was only 77%. Repeated and intermittent adjunctive ketamine had the same effects in reducing the number of treatments and improving the remission rate in our study and this suggested that single adjunctive ketamine might enhance ECT effects within one week. Therefore, repeated or intermittent adjunctive low-dose ketamine can significantly accelerate the onset time of ECT in depressive patients and shorten the course of ECT. In addition, low-dose adjunctive ketamine not only improved the therapeutic effects of ECT, but also improved the HAM-D score of patients within one month after the ECT course, whereas conventional ECT patients achieved the same effect only after three months. Thus, ECT in combination with adjunctive ketamine has the potential to improve depressive symptoms of patients faster and more durably.

In this study, the EEG inhibitory index in patients with low-dose ketamine was significantly higher than that in conventional ECT patients. Previous studies have also shown that ketamine-assisted ECT can induce epileptic-like seizures with lower energy consumption (Zhang et al., 2018; Zhong et al., 2016), and make higher seizure energy index and longer seizure duration (Zavorotnyy et al., 2017). Higher EEG suppression index and seizure intensity after ECT tended to achieve better efficacy (Duthie et al., 2015; Tiller and Ingram, 2006). This indicated that the improvement effects of low-dose ketamine on depression might be related to the increase of ECT electric convulsion intensity.

It is noteworthy that some studies and meta-analyses considered that ketamine did not significantly affect the efficacy of ECT (Ren et al., 2018; Gálvez et al., 2017). Some researchers found that only ketamine used as an anesthetic did not improve the efficacy of ECT (Carspecken et al., 2018; Rasmussen et al., 2014). Another study showed that ketamine (2 mg/kg) did not improve depressive symptoms compared with propofol (2.5 mg/kg) in severely depressed patients during ECT treatment courses (Fernie et al., 2017). This data suggests that anesthetic dosage of ketamine had no enhancement effect on the efficacy of ECT with regards to depression. Therefore, it is recommended that low doses of ketamine, i. less than 0.5 mg/kg, can be supplement ECT treatment.

This study analyzed the outcomes of remission in depression patients within one single ECT course. The results showed that low-dose ketamine did not affect EEG inhibition index and duration of epileptic seizures, and there were no significant difference in the HAM-D scores of the patients during ECT treatment and 3 months after the ECT course. Our study suggested that low-dose ketamine might mainly increase the sensitivity of depressed patients to ECT and enhance the efficacy and clinical remission rate of ECT. These results indicate that the improvement of depressive symptoms in patients receiving ketamine-assisted ECT might only be the antidepressant effect of low-dose ketamine but not the enhancement effect of ketamine on ECT (Ghasemi et al., 2014). The specific roles of low-dose ketamine on ECT need further study.

Current studies suggest that low-dose ketamine in combination with ECT has no harmful effects on the cognitive function of depressive patients, indeed it even has a positive effect (Shams et al., 2015). In our study, MoCA was used to assess cognitive function. We found that the cognitive function of depressive patients undergoing ECT assisted with low-dose ketamine improved, although this improvement disappeared after one month of ECT, which indicated that low-dose ketamine could effectively improve cognitive function for a short time period. One of the biggest safety concerns regarding ketamine is that it is associated with a high risk of delirium, hallucination and other sperm complications. Especially high dose and continuous administration of ketamine can further increase complications (Salehi et al., 2015). It is known that depression requires a long course and several courses (>10) of ECT treatment. However, long-term and continuous use of ketamine in ECT might increase the risk of psychiatric complications. Previous studies have shown that more than 27% of the patients given low-dose ketamine (0.5 mg/kg intravenous infusion) experienced at least one adverse event, of which transient psychological effects and psychiatric symptoms were the most common (Anderson et al., 2017). In our study, the incidence of delirium, irritation and hallucination increased significantly in patients with repeated low-dose ketamine at each ECT treatment, and the total incidence of psychiatric symptoms was about 20.93%. The incidence of psychiatric symptoms decreased significantly in patients with intermittent ketamine once a week, which was only 4.35%, and compared with patients with propofol anesthesia alone, there was no difference. This indicated that intermittent low dose ketamine administration in ECT treatment was safe and feasible.

In conclusion, low-dose ketamine (0.3 mg/kg) in combination with ECT treatment can improve the remission rate of depression, significantly shorten the onset time, especially for patients who are not sensitive to ECT. Moreover, intermittent and repeated adjunctive administration modes of ketamine have the same effect on improvement of ECT, but the intermittent administration of ketamine reduced the occurrence of psychiatric complications.

Declaration of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.112573.

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