Comparing Effects of Ketamine and Thiopental Administration During Electroconvulsive Therapy in Patients With Major Depressive Disorder

A Randomized, Double-Blind Study

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Objectives: Recently, ketamine has attracted attention for induction of anesthesia during electroconvulsive therapy (ECT). This study compared the effects of thiopental and ketamine in patients undergoing this procedure.

Method: This randomized, double-blind clinical trial included inpatients, with major depressive disorder, undergoing ECT. Subjects were randomly allocated to receive either ketamine or thiopental. Mini-Mental State Examination and Hamilton Depression Rating Scale were used to assess memory and depression, respectively, before the first and second ECT sessions as well as a few days and 1 month after the sixth session. The electrical charge, seizure duration, blood pressure, and heart rate were also recorded.

Results: Of the 31 patients, 17 met the criteria for the ketamine group but 2 dropped out of the study. Therefore, 15 patients received ketamine and 14 received thiopental. Each patient underwent 6 ECT sessions. At the end of the study, depression improved significantly in both groups. However, a significant difference in depression improvement was noted only before the second ECT with ketamine compared with thiopental. Despite a significant decline in Mini-Mental State Examination scores in both groups after the first ECT, cognitive function improved afterward but was only significant in ketamine group. Seizure duration was found to be significantly longer with ketamine. Stimulus intensity used for each ECT increased gradually and linearly with a greater increase observed in thiopental group.

Conclusions: Ketamine administration during ECT is well tolerated and patients may experience earlier improvement in depressive symptoms, longer seizure duration, and better cognitive performance when compared with thiopental.

Key Words: ketamine, thiopental, electroconvulsive therapy, ECT, depressive disorder, Hamilton Depression Rating Scale, HAM-D

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Depression is one of the most debilitating and widespread illnesses[1,2] affecting up to 20% of individuals in their lifetime.[3] Electroconvulsive therapy (ECT) has been considered as a valuable option in the treatment of severe or treatment-resistant depression for a long time.[4–6] This procedure is performed under general anesthesia.[7] Thiopental is the leading anesthetic agent used for ECT in Iran due to the unavailability of methohexital, the anesthetic drug of choice[8] for this procedure.

Despite of the high efficacy of ECT as a treatment option in many psychiatric disorders, one of the remarkable drawbacks to its use is cognitive dysfunction.[9] The intensity and the length of cognitive impairment can be affected by the anesthetic drug itself or by the indirect impact of the agent on parameters such as seizure threshold, electrical dose needed during ECT, or seizure presentation.[10] Recently, anesthetic drugs in ECT have been considered not only as anesthesia-inducing agents but also as active agents that may impact the cognitive outcome of the procedure.[10]

Ketamine, a noncompetitive antagonist of glutamate at the *N*-methyl-D-aspartate (NMDA) receptor,[11] has been shown to have some extent of neuroprotective effects.[12] Recently, special attention has been given to ketamine due to the proposed role for glutamate pathway in both depression[13] and ECT-induced memory impairment.[11] Despite lack of precise knowledge on the exact mechanisms underlying ECT-induced cognitive impairment, NMDA receptors and glutamatergic systems are suggested to be involved in this bothersome adverse effect.[9]

Long-term potentiation, defined as "long-term changes in synaptic connection strength," seems to be an inevitable part of learning and memory and is affected by NMDA receptors.[14] Using NMDA antagonists during ECT has demonstrated beneficial effects on long-term potentiation in animal models, and therefore, decreasing impairment of cognitive function. For instance, Brun et al[15] reported that memory of the spatial information was not impaired in rats undergoing electrical stimulation of the hippocampus with 3-(2-carboxypiperazin-4-yl) propyl-1-phosphonicacid, an NMDA antagonist. Another study in rats, anesthetized with ketamine for induction of electroconvulsive seizures, suggested that administration of this drug could reduce memory impairment.[9] NMDA receptors have been noted to be involved in the pathology of major depression and anxiety.[1]

In many animal models, notable antidepressant and anxiolytic properties have been observed by ketamine administration.[2,13]

Garcia et al compared the effects of ketamine with imipramine and saline on rats' hippocampus and suggested that ketamine significantly raised brain-derived neurotrophic factor, a protein with important roles in the nervous system[1] and evidences of

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reverse correlation with severity of depression.[16] Engin et al[17] also noted the antidepressant and anxiolytic effects of ketamine in rats in forced swim test and elevated-plus-maze, respectively. Additionally, human studies have also reported beneficial effects with ketamine. For instance, ketamine has shown to affect mood in patients undergoing surgery.[18] Ibrahim et al conducted a study on patients with treatment-resistant major depressive disorder (MDD) who either did not respond to previous ECT or had not received ECT. Both groups showed a significant improvement after 230 minutes postinfusion of a single open-label infusion of ketamine (0.5 mg/kg).[5]

In another study, antidepressant property of ketamine was noted after administration of 6 infusions during 12 days in 10 medication naive, resistant, depressed patients. After the sixth infusion, patients experienced 85% reduction in Montgomery-Åsberg Depression Rating Scale scores.[19]

The most important advantage of ketamine antidepressant property is its rapid onset of effects. In 1 preliminary study, Machado-Vieira et al[2] administered ketamine to 7 patients with treatment-resistant depression and observed decreased symptoms within 72 hours postinfusion. One of the characteristics of an ideal anesthetic agent for ECT is to have minimal inhibitory effect on seizure duration.[20,21] Thiopental like other barbiturates has clear anticonvulsant properties and has been estimated to reduce seizure duration as much as 25% or more during ECT and tends to increase seizure threshold.[10,20] On the other hand, ketamine has been proposed to have less inhibitory effects on convulsion.[14]

Despite the mentioned benefits of ketamine, its widespread use in the setting of ECT is a subject of concerns due to its adverse effects such as increases in systolic blood pressure (BP), pulse rate, and intracranial pressure (ICP).[6,10,14]

However, despite of what many clinicians believe, ketamine does not raise ICP in head trauma and neurosurgical patients when the ventilation of the patient is optimal. In fact, in normocapnic patients, administration of ketamine has no effect on ICP.[22–24]

Benefits of the administration of ketamine in psychiatric settings has made researchers conduct a number of comparative studies between ketamine and other anesthetic agents like etomidate,[11] methohexital,[14,25] and thiopental[26] in patients receiving ECT.

However, most of these studies were performed as retrospective or open-label trials. To the best of our knowledge, double-blind, randomized clinical trials comparing the effects of ketamine and thiopental in the management of depression and cognitive function as well as hemodynamic parameters are lacking. The primary objective of this randomized clinical trial was to compare the efficacy of ketamine with thiopental in patients receiving ECT. Besides, comparing the effects of these drugs on the cognitive consequences, seizure parameters, and hemodynamic factors of ECT were considered as the secondary objectives.

METHOD

Patients between 20 and 50 years participated in this randomized double-blind parallel group study. Subjects who were recruited among inpatients indicated to receive ECT in Roozbeh Psychiatric Hospital affiliated with Tehran University of Medical Sciences entered this study.

Patients with a diagnosis of MDD according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* criteria and with a Hamilton Depression Rating Scale (HAM-D) of equal or greater than 18 were included in this study.

The exclusion criteria included history of any serious medical disease, such as cardiovascular disease (including BP > 140/90 mm Hg and ischemic heart disease), renal failure, neurologic disease (eg, epilepsy); presence of a "space occupying lesion" in the brain; history of substance abuse or dependence in the preceding 6 months; presence of any other Axis I psychiatric disorder; receiving ECT in the preceding 6 months; presence of hearing or communication problems interfering with memory performance and cognitive tests; having criteria of American Society of Anesthesiologists Physical Status Classes 3 to 6; and pregnancy. Additionally, the protocol of the study required reporting any unexpected emergency situation to the principal investigator for immediate performance of necessary medical interventions accordingly.

The study was approved by the ethic committee of Tehran University of Medical Sciences and all patients signed the informed consent. This clinical trial was registered at www.irct.ir with an identifier number of IRCT201201247202N3.

On the day before the first ECT, all subjects underwent pre-ECT evaluations such as (psychiatric interview and physical examination, routine blood tests, chest x-ray, electrocardiography, and urine analysis). Patients were required to fast for at least 8 hours and to void before the procedure.

Anesthesia and ECT Procedure

Electroconvulsive therapy was performed 3 times a week using Thymatrone DGX with bilateral electrode placement. A dose-titration protocol was used according to patients' age in the first ECT session and dosage was adjusted accordingly over the course of therapy. After recording the baseline variables, 0.5 mg of atropine was administered intravenously. Then patients were randomized by the research executive manager (one of the investigators) based on a table of random numbers and received either 1 to 2 mg/kg ketamine or 2 to 3 mg/kg thiopental as an induction agent for anesthesia. The study patients, the anesthesiologist (primary investigator), and the rater of the scales were all blind to the intervention allocation status.

When patient became unconscious, the muscle relaxant, succinylcholine (0.5 mg/kg), was administered. Patients were ventilated with bag and mask supported with 100% oxygen during the procedure and was continued until complete awakening of the patients.

Assessments

Memory and depression were evaluated by using Mini-Mental State Examination (MMSE) and HAM-D, respectively. Evaluation of cognitive function and depression were repeated on a regular scheduled basis as follows: before the first ECT, 48 hours after the first ECT (before the second session), 3 to 7 days after the sixth ECT, and 1 month after the sixth ECT. Depression response was defined as 60% reduction in the score of the baseline HAM-D.

The electrical charge was recorded and seizure duration was measured at every ECT session. This measurement was clinically performed by using the cuff method. In this method, the blood flow to the right foot is restricted by inflating a BP cuff before administration of the muscle relaxant. Additionally, in each ECT session, systolic and diastolic BP, mean arterial pressure (MAP), heart rate (HR), and oxygen saturation (by using pulsoxymeter) were recorded just before administration of atropine and 10 minutes after the procedure.

Statistical Analysis

Statistical analysis was performed using SPSS-13 software. Descriptive information was presented through their

TABLE 1. Baseline and Follow-up Values for Depression and Cognitive Function

Parameter		Ketamine	Thiopental	*P*
Depression	HAM-D1	23.60	22.86	0.61
	HAM-D2	16.13	20.00	0.002
	HAM-D3	17.20	17.71	0.57
	HAM-D4	17.07	17.29	0.86
Cognition	MMSE1	25.60	24.79	0.44
	MMSE2	24.87	21.36	0.014
	MMSE3	27.13	23.64	0.004*
	MMSE4	27.87	25.79	0.023*

*Mann-Whitney test.

means. The 2 independent sample *t* tests were used in the baseline analysis. Because some of the variables of interest did not follow a normal distribution, nonparametric tests (Mann-Whitney) were applied rather than *t* test. Repeated measurement analyses were used to compare the mean values of HAM-D, MMSE, seizure duration, BP, and HR over time in the 2 treatment groups.

RESULTS

Of the 120 subjects screened for this study, 31 met the inclusion criteria. Seventeen patients were allocated to receive ketamine and 14 to receive thiopental. There were 2 dropouts in the ketamine group, one due to significant increase in BP after the first ECT and the other one due to changing treatment center.

Twenty-nine patients with a mean age of 43.83 years completed this randomized double-blind clinical trial between November 2009 and November 2010. Seven women and eight men received thiopental. Average age of patients in this group was 47 years. In ketamine-receiving group, the average age of patients was 40.87 years and 7 patients were women. There was no significant difference between ages in both groups.

Each patient received 6 ECT treatments and the total number of 174 ECT treatments was performed. No significant differences were found in baseline values for HAM-D, MMSE, hemodynamic measures of HR, and MAP between the 2 groups.

Depression Improvement

As shown in Table 1, mean baseline HAM-D of patients who received ketamine and thiopental was 23.60 and 22.86, respectively ($P = 0.61$). A significant reduction in the HAM-D in ketamine group was noted only in the second follow-up when compared with that in the thiopental group ($P = 0.002$). Repeated-measures analysis of variance (ANOVA) showed significant reduction in HAM-D in both groups compared with the baseline values ($P < 0.0001$). Furthermore, when adjusted for repeated times of measurement, no significant difference was detected between the 2 treatment groups regarding the means of HAM-D ($P = 0.285$); whereas the interaction between the treatment and repetition was found to be significant ($P < 0.0001$). Changes in HAM-D in both groups are also shown in Figure 1.

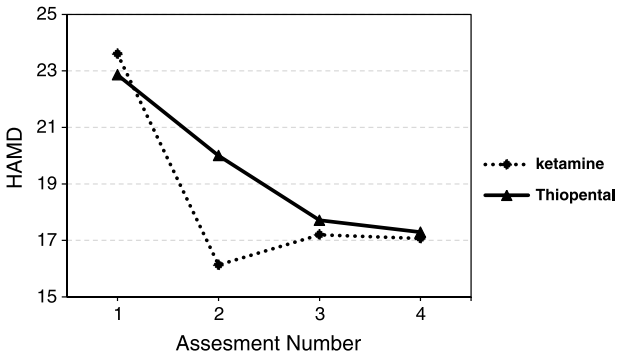

FIGURE 1. Change in HAM-D between the baseline and in different assessments in patients receiving ketamine and thiopental.

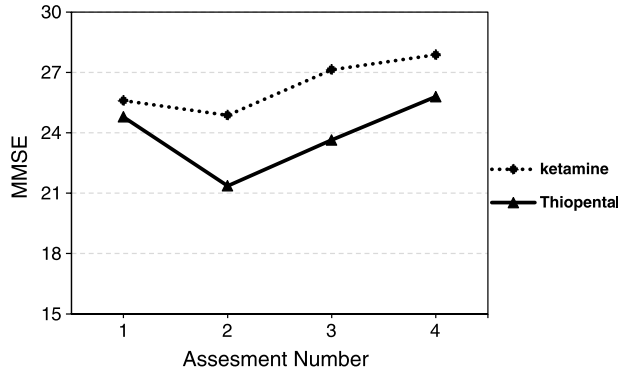

FIGURE 2. Change in MMSE between the baseline and in different assessments in patients receiving ketamine and thiopental.

Cognitive Assessment

Repeated-measures ANOVA of MMSE scores showed a significant difference between the 2 groups which was in favor of ketamine when adjusted for repeated times of measurements ($P = 0.004$). In fact, results of paired *t* test analysis of MMSE scores between baseline and the last assessment showed improvement in cognitive function after ECT in both groups; patients receiving ketamine showed a significant improvement in their cognitive function ($P = 0.004$), whereas this improvement was not significant in patients receiving thiopental ($P = 0.37$). Mini-Mental State Examination scores in both groups are summarized in Table 1. As shown in this table, the baseline cognitive function was not significantly different between the 2 groups ($P = 0.44$). However, a significantly better cognitive performance was evident in ketamine-receiving group. In addition, the interaction between the treatment and repeated times of measurements was not noted to be statistically significant ($P = 0.052$).

After the first ECT, a significant decline in MMSE scores was noted in both groups ($P = 0.005$), but in the third assessment, this was reversed and the scores increased in both groups. Changes in MMSE scores are shown in Figure 2.

We also outlined a multiple end point setting for MMSE and HAM-D (memory and depression) to compare the 2 main end points simultaneously between the 2 treatment groups. Because end points were measured in repeated times, using global statistical tests that are routinely applied in cases of multiple end points were not possible in our study. Therefore, a Doubly Multivariate Repeated Measures Design that exploits an *F* exact test statistic for Wilks λ was used to fit the data. The results reflected a significant overall difference between the 2 drugs regarding the 2 main end points, HAM-D and MMSE ($P = 0.021$). Furthermore, this difference was also found over the repeated times of measurements ($P = 0.003$).

TABLE 2. Comparison of Seizure Duration and Electrical Dose in Patients Receiving Ketamine and Thiopental

	Ketamine	Thiopental		Ketamine	Thiopental	
Assessment	Seizure Duration, s		*P*	Electrical Dose		*P*
1	31.87	25.57	0.028	28.67	36.43	0.075
2	30.87	21.71	0.002	29.67	43.57	0.005
3	30.07	21.86	0.001	31.33	48.93	0.001
4	29.13	21.21	<0.001	33.33	53.21	0.001
5	27.60	19.21	0.001	34.67	58.21	<0.001
6	27.47	24.93	0.593*	36.00	62.86	<0.001

*Mann-Whitney test.

Seizure Duration and Electrical Charge

Repeated-measures ANOVA of mean seizure durations showed significantly prolonged seizures in patients receiving ketamine compared with those who received thiopental in the first 5 ECT sessions ($P = 0.001$). The duration of seizures was longer with ketamine as shown in Table 2, which summarizes the duration of motor seizures in seconds for both groups for each ECT session. By increasing the number of ECT treatments, the seizure duration decreased in both groups; the rate of decline was significant in the ketamine-receiving patients ($P < 0.0001$) but not in the thiopental-receiving patients ($P = 0.63$)

In terms of electrical charge, stimulus intensity used for each ECT increased gradually and linearly in both groups, however, this increase was greater in the thiopental group ($P < 0.0001$). Moreover, in the repeated measurement analysis, no significant interaction between treatments and repeated times of measurements was noted ($P = 0.347$).

Hemodynamic Changes

In both groups, baseline values of HR and MAP were not shown to be significantly different (Table 3). Comparison of MAPs 10 minutes after induction of general anesthesia in both groups showed a significant difference throughout all ECT treatments (except the first treatment) with higher values observed in ketamine-receiving patients.

Despite a trend toward greater increase in HR in patients receiving ketamine, this did not reach the clinical significance between the 2 groups ($P = 0.681$). By increasing the number of ECT treatments, there was a trend toward higher HR in ketamine group and vice versa in the thiopental group.

Table 4 summarizes the mean systolic and diastolic BP of patients receiving either ketamine or thiopental after the induction of ECT. When ketamine was compared to thiopental, the differences between the systolic BPs were found to be significant after 3 ECT sessions for systolic BP and after 4 ECT sessions for diastolic BP (no regular pattern was noted).

DISCUSSION

Although different anesthetic agents are used for the induction of ECT, ketamine is the only one with suggested antidepressant effects. Different mechanisms of action have been proposed to explain its antidepressant effects (eg, restimulation of mammalian target of rapamycin pathway,[27] interaction with sigma receptors,[3] stimulation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors,[28] and "increased activity in the anterior cingulate cortex[26]").

For the previously mentioned reason, this double-blind, randomized trial was aimed to compare the effects of ketamine and thiopental on depression in patients with MDD who underwent ECT procedure. Furthermore, cognitive and hemodynamic effects as well as duration of seizure were also compared in these 2 groups. To the authors' knowledge, this is the first prospective study conducted to compare ketamine and thiopental administration during ECT.

In 5 consecutive ECT sessions performed for each patient in our study, seizure duration was significantly longer in ketamine-receiving patients compared with thiopental. Although response to ECT is not related to seizure duration alone[8] and this relationship still remains unclear, it is generally accepted that a minimum of 15 seconds is necessary for seizure duration to be considered therapeutic.[7]

Our finding is consistent with a study by Krystal et al[14] in which a significant seizure prolongation was reported after a switch from methohexital to ketamine. This switch was made

TABLE 3. Comparison Between HR and MAP After Induction of ECT in Patients Receiving Ketamine and Thiopental

	Ketamine	Thiopental		Ketamine	Thiopental	
Follow-up	Mean HR		*P*	Mean MAP		*P*
1	89.47	93.64	0.545	103.80	94.43	0.144
2	90.07	89.71	0.958	104.53	82.00	0.005
3	95.27	92.29	0.663	98.13	84.64	0.055
4	94.73	91.29	0.604	101.60	83.43	0.016
5	96.00	88.36	0.187	101.60	103.47	0.083*
6	96.00	88.57	0.087	103.40	86.14	0.003*

*Mann-Whitney test.

TABLE 4. Comparison Between Mean SBP and DBP After Induction of ECT in Patients Receiving Ketamine and Thiopental

	Ketamine	Thiopental		Ketamine	Thiopental	
Follow-up	**Mean SBP**		***P***	**Mean DBP**		***P***
1	136.40	126.21	0.194	90.00	79.07	0.055
2	136.20	108.43	0.007*	89.20	69.29	0.006
3	128.00	113.71	0.131	83.67	70.50	0.033
4	133.47	110.86	0.030*	86.20	70.21	0.013*
5	134.53	120.07	0.090	88.40	77.64	0.092
6	133.93	116.64	0.029	88.60	71.36	0.001

*Mann-Whitney test.

DBP indicates diastolic blood pressure; SBP, systolic blood pressure.

mainly because of ineffective seizure duration despite maximum stimulus intensity in patients receiving methohexital.

We also investigated the relationship between ketamine and thiopental use with energy delivered to induce acceptable seizure duration. The present study noted that patients anesthetized with ketamine received significantly lower electrical dose when compared with those who received thiopental from the second ECT session through the final session. In fact, prolongation of seizures in ketamine-receiving patients was not achieved with the cost of higher electrical dosage utilization. However, in a study by Kranaster et al,[26] no significant differences in the stimulation doses and in the motor response time were observed between ketamine and thiopental groups. This retrospective study reviewed data of 42 treatment-resistant, depressed patients who underwent ECT and were anesthetized with ketamine or thiopental.

The beneficial effect of ketamine on cognitive function after ECT that was observed in our study showed consistency with the results of a prospective study by McDaniel et al[11] in depressed patients undergoing ECT. In that study, patients' memory function was evaluated by being asked to recall 4 objects out of 4 words. Significantly better short-term memory function was observed in subjects anesthetized with ketamine, which was attributed to the protective effects of ketamine on memory function. Moreover, Krystal et al[14] showed that anesthesia with ketamine when compared with methohexital was associated with a shorter reorientation time and therefore, with a less retrograde amnesia post-ECT. In contrast, a clinical trial by Loo et al[29] suggested that adding ketamine or placebo to thiopentone would not result in a significant difference in neuropsychological performance of depressed patients who were receiving ultrabrief pulse-width right unilateral ECT.

The present study also found that ECT did not result in decreasing baseline MMSE scores and significantly better cognitive performance was noted in ketamine-receiving patients ($P = 0.004$). Some explanations for this result are as follows. It is widely accepted that cognitive impairment is evident in patients with MDD[30] even in those with its first episode.[31]

By considering the linkage between depression and cognitive impairment, it is theoretically possible to observe improvement in cognitive performance after treating depression.

Moreover, as noted by Kranaster et al,[26] lack of cognitive performance decline after ECT has been reported. In their study, MMSE scores in patients receiving ketamine not only did not decrease after ECT but also slightly increased; however, a slight decrease in MMSE scores was noted with thiopental that was in contrast to what was observed in our study. Another study by Porter et al[32] did not note any significant change in cognitive function at different time points in the course of ECT treatment based on modified MMSE.

The outstanding aspect of our results is the persistency of the beneficial effects of ketamine on cognitive function in patients undergoing ECT that remained even 1 month after the sixth session of this procedure.

Our study found a significantly more improvement in depression (based on HAM-D) of patients who received ketamine 48 hours after the first session of ECT. The rapid onset of antidepressant effects of ketamine has been reported in the literature. Machado-Vieira et al[33] reported that treatment-resistant MDD patients experienced improvement in depression within 2 hours after the administration of a single dose of ketamine. A case report about a severely depressed man noted a decrease in depressive symptoms even within 8 hours of ketamine administration during ECT procedure.[18]

On the basis of the observation that patients who received ketamine needed fewer sessions of ECT compared with those who received thiopental, Kranaster et al[26] suggested that patients receiving ketamine had a more rapid recovery of depression.

On the contrary, a study by Abdallah et al[34] showed that addition of ketamine to thiopental did not result in increasing the antidepressant effect of ECT when compared with thiopental alone. However, it should be noted that the doses of ketamine administered in the previously mentioned study was 0.5 mg/kg, which was lower than the dose used in our study.

Our study showed that the improvement in depression of patients receiving thiopental was not significantly inferior to that of ketamine after the second session of ECT.

An open-label study of 31 treatment-resistant, depressed patients, who underwent ECT and received either ketamine or propofol, showed an earlier improvement in symptoms of depression in the ketamine group. Significantly more rapid improvement in HAM-D was observed after the second and fourth ECT treatments in the ketamine group; however, the difference was no more significant after the sixth session.[13] Similarly, Wang et al noted that the improvement of depression was significantly greater in patients who received ketamine or ketamine plus propofol compared with those who received propofol alone on days 1, 2, and 3 after a single ECT session. However, the differences between groups were not significant 7 days after the ECT procedure.[35]

The early onset of antidepressant effects of ketamine may be extremely important, especially, in suicidal patients or when a later response to treatment could result in a hazardous event.

Basic hemodynamic parameters were also monitored in both groups in our study. It is generally accepted that a systemic

release of catecholamines and decreased catecholamine reuptake results in raised HR and BP as seen with ketamine.[12,26,36]

Our study noted an increase in BP 10 minutes after induction of general anesthesia that was significantly different between groups at most sessions of ECT.

A single-blinded study by Valentine et al[37] showed that ketamine was well tolerated in MDD patients, and despite a statistically significant rise in systolic BP, this rise was not clinically significant.

Similarly, some other studies have also considered ketamine as a safe option for ECT anesthesia with regard to changes in BP.[10]

The increase in HR was not significantly different between the 2 groups of ketamine and thiopental in the present study. However, the authors agree with other investigators to still recommend using ketamine with caution in patients with ischemic heart disease or hypertension.[26,36] Furthermore, electrocardiography before ketamine administration and close observation by an anesthesiologist during ECT deems to be helpful.[19]

Any adverse effect reported by the patients or nurses were recorded by the clinical pharmacist in charge. Additionally, none of the patients in our study experienced psychotogenic adverse effects like hallucination with ketamine despite of the concerns noted in the literature with this drug.[38] This observation may be due to the reversal of ketamine action by the resultant opening of the NMDA ion channel and depolarization after the induction of seizure during ECT.[14]

Limitations of this study are as follows:

Our study included a small number of patients due to the strict exclusion criteria. Additionally, due to the unavailability of the ECT apparatus equipped with electroencephalography, the researchers were unable to record seizure durations by EEG. We should also note that MMSE is not a specific scale to evaluate cognitive function impairment. However, it was used in our study due to its extensive use in similar studies.

Our study encourages the use of ketamine as an anesthesia for ECT because its use can result in enhanced seizure duration, an earlier improvement of depressive symptoms, and better cognitive profile. Additionally, it should be mentioned that due to the sample size of the current trial, the assessment of less common adverse effects was not practically possible and therefore was not detected in our study.

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REFERENCES

1. Garcia LSB, Comim CM, Valvassori SS, et al. Acute administration of ketamine induces antidepressant-like effects in the forced swimming test and increases BDNF levels in the rat hippocampus. *Prog Neuropsychopharmacol Biol Psychiatry.* 2008;32:140–144.
2. Machado-Vieira R, Salvadore G, DiazGranados N, et al. Ketamine and the next generation of antidepressants with a rapid onset of action. *Pharmacol Ther.* 2009;123:143–150.
3. Robson MJ, Elliott M, Seminerio MJ, et al. Evaluation of sigma (σ) receptors in the antidepressant-like effects of ketamine in vitro and in vivo. *Eur Neuropsychopharmacol.* 2012;22:308–317.
4. Merkl A, Heuser I, Bajbouj M. Antidepressant electroconvulsive therapy: mechanism of action, recent advances and limitations. *Exp Neurol.* 2009;219:20–26.
5. Ibrahim L, Diazgranados N, Luckenbaugh DA, et al. Rapid decrease in depressive symptoms with an *N*-methyl-D-aspartate antagonist in ECT-resistant major depression. *Prog Neuropsychopharmacol Biol Psychiatry.* 2011;35:1155–1159.
6. Gregory-Roberts EM, Naismith SL, Cullen KM, et al. Electroconvulsive therapy-induced persistent retrograde amnesia: could it be minimised by ketamine or other pharmacological approaches? *J Affect Disord.* 2010;126:39–45.
7. Hooten WM, Rasmussen KGJ. Effects of general anesthetic agents in adults receiving electroconvulsive therapy: a systematic review. *J ECT.* 2008;24:208–223.
8. Calarge CA, Crowe RR, Gergis SD, et al. The comparative effects of sevoflurane and methohexital for electroconvulsive therapy. *J ECT.* 2003;19:221–225.
9. Pigot MB, Andrade C, Franzcp CL. Pharmacological attenuation of electroconvulsive therapy-induced cognitive deficits: theoretical background and clinical findings. *J ECT.* 2008;24:57–67.
10. MacPherson RD, Loo CK. Cognitive impairment following electroconvulsive therapy—does the choice of anesthetic agent make a difference? *J ECT.* 2008;24:52–56.
11. McDaniel WW, Sahota AK, Vyas BV, et al. Ketamine appears associated with better word recall than etomidate after a course of 6 electroconvulsive therapies. *J ECT.* 2006;22:103–106.
12. Copeland J, Dillon P. The health and psycho-social consequences of ketamine use. *Int J Drug Policy.* 2005;16:122–131.
13. Okamoto N, Nakai T, Sakamoto K, et al. Rapid antidepressant effect of ketamine anesthesia during electroconvulsive therapy of treatment-resistant depression: comparing ketamine and propofol anesthesia. *J ECT.* 2010;26:223–227.
14. Krystal AD, Weiner RD, Dean MD, et al. Comparison of seizure duration, ictal EEG, and cognitive effects of ketamine and methohexital anesthesia with ECT. *J Neuropsychiatry Clin Neurosci.* 2003;15:27–34.
15. Brun VH, Ytterbø K, Morris RGM, et al. Retrograde amnesia for spatial memory induced by NMDA receptor-mediated long-term potentiation. *J Neurosci.* 2001;21:356–362.
16. Hashimoto K. Brain-derived neurotrophic factor as a biomarker for mood disorders: an historical overview and future directions. *Psychiatry Clin Neurosci.* 2010;64:341–357.
17. Engin E, Treit D, Dickson CT. Anxiolytic- and antidepressant-like properties of ketamine in behavioral and neurophysiological animal models. *Neuroscience.* 2009;161:359–369.
18. Goforth HW, Holsinger T. Rapid relief of severe major depressive disorder by use of preoperative ketamine and electroconvulsive therapy. *J ECT.* 2007;23:23–25.
19. Rot M, Collins KA, Murrough JW, et al. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biol Psychiatry.* 2010;67:139–145.
20. Datto C, Rai AK, Ilivicky HJ, et al. Augmentation of seizure induction in electroconvulsive therapy: a clinical reappraisal. *J ECT.* 2002; 18:118–125.
21. Geretsegger C, Nickel M, Judendorfer B, et al. Propofol and methohexital as anesthetic agents for electroconvulsive therapy: a randomized, double-blind comparison of electroconvulsive therapy seizure quality, therapeutic efficacy, and cognitive performance. *J ECT.* 2007;23:239–243.
22. Schmittner MD, Vajkoczy SL, Horn P, et al. Effects of fentanyl and S(+)-ketamine on cerebral hemodynamics, gastrointestinal motility, and need of vasopressors in patients with intracranial pathologies: a pilot study. *J Neurosurg Anesthesiol.* 2007;19:257–262.
23. Bourgoin A, Albanese J, Wereszczynski N, et al. Safety of sedation with ketamine in severe head injury patients: comparison with sufentanil. *Crit Care Med.* 2003;31:711–717.

24. Bourgoin A, Albanese J, Leone M, et al. Effects of sufentanil or ketamine administered in target-controlled infusion on the cerebral hemodynamics of severely brain-injured patients. *Crit Care Med*. 2005;33:1109–1113.

25. Rich CL, Smith NT. Anaesthesia for electroconvulsive therapy: a psychiatric viewpoint.*Can Anaesth Soc J.* 1981;28:153–157.

26. Kranaster L, Kammerer-Ciernioch J, Hoyer C, et al. Clinically favourable effects of ketamine as an anaesthetic for electroconvulsive therapy: a retrospective study. *Eur Arch Psychiatry Clin Neurosci*. 2011;261:575–582.

27. Tokita K, Yamaji T, Hashimoto K. Roles of glutamate signaling in preclinical and/or mechanistic models of depression. *Pharmacol Biochem Behav.* 2012;100:688–704.

28. Koike H, Iijima M, Chaki S. Involvement of AMPA receptor in both the rapid and sustained antidepressant-like effects of ketamine in animal models of depression. *Behav Brain Res*. 2011;224:107–111.

29. Loo CK, Katalinic N, Garfield JB, et al. Neuropsychological and mood effects of ketamine in electroconvulsive therapy: a randomised controlled trial. *J Affect Disord.* 2012;142:233–240.

30. McDermott LM, Ebmeier KP. A meta-analysis of depression severity and cognitive function. *J Affect Disord*. 2009;119:1–8.

31. Lee RSC, Hermens DF, Porter MA, et al. A meta-analysis of cognitive deficits in first-episode Major Depressive Disorder. *J Affect Disord*. 2012;140:113–124.

32. Porter R, Heenan H, Reeves J. Early effects of electroconvulsive therapy on cognitive function. *J ECT.* 2008;24:35–39.

33. Machado-Vieira R, Salvadore G, Luckenbaugh DA, et al. Rapid onset of antidepressant action: a new paradigm in the research and treatment of major depressive disorder. *J Clin Psychiatry.* 2008;69:946–958.

34. Abdallah CG, Fasula M, Kelmendi B, et al. Rapid antidepressant effect of ketamine in the electroconvulsive therapy setting. *J ECT.* 2012;28:157–161.

35. Wang X, Chen Y, Zhou X, et al. Effects of propofol and ketamine as combined anesthesia for electroconvulsive therapy in patientswith depressive disorder. *J ECT.* 2012;28:128–132.

36. Moy RJ, Le Clerc S. Ketamine in prehospital analgesia and anaesthesia. *Trends Anaesthesia Crit Care*. 2011;1:243–245.

37. Valentine GW, Mason GF, Gomez R, et al. The antidepressant effect of ketamine is not associated with changes in occipital amino acid neurotransmitter content as measured by [^{1}H]-MRS. *Psychiatry Res*. 2011;191:122–127.

38. Loo C, Simpson B, MacPherson R. Augmentation strategies in electroconvulsive therapy. *J ECT.* 2010;26:202–207.