Effect of the Addition of Ketamine to Sevoflurane Anesthesia on Seizure Duration in Electroconvulsive Therapy

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Objectives: We evaluated the effects of a subanesthetic dose of ketamine, which was administered as an adjunct to sevoflurane, on duration of seizure activity, hemodynamic profile, and recovery times during electroconvulsive therapy in patients with major depression.

Methods: Patients were randomly allocated to a group receiving either sevoflurane-ketamine (group SK) or sevoflurane-saline (group SS). Sevoflurane was initiated in both groups at 8% for anesthesia induction until loss of consciousness was achieved, at which point it was discontinued. After loss of consciousness, ketamine was administered to the group SK in the form of a 0.5-mg/kg intravenous bolus. Patients in the group SS received saline in the same manner. Mean arterial pressure (MAP) and heart rate were recorded before anesthetic induction (T1); after anesthetic induction (T2); as well as 0, 1, 3, and 10 minutes after the seizure had ended (T3, T4, T5, and T6, respectively). Motor and electroencephalogram seizure durations were recorded.

Results: Motor and electroencephalogram seizure durations in the group SS were similar to those observed for the group SK. The heart rate increased significantly during T2 to T6 in both group SS and group SK compared with the baseline. The MAP increased in the group SS during the period between T3 and T6 as well as in the group SK during the same period compared with the baseline. The MAP increased more in the group SK, in comparison with the group SS, during T2 ($P < 0.05$).

Conclusions: The addition of ketamine at subanesthetic doses, for the purposes of anesthetic induction with sevoflurane, yielded results similar to those in the control group in terms of both seizure duration and hemodynamic stability.

Key Words: electroconvulsive therapy, seizures, major depression, sevoflurane, ketamine

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Electroconvulsive therapy (ECT) is a well-established treatment for severe depression in patients unresponsive to pharmacotherapy. Successful ECT requires that induction of generalized seizure activity and maintenance of seizure be carried out. The minimum amount of time for sufficient antidepressant activity has been stated as 25 seconds, although there is no proven correlation between seizure duration and clinical outcome.[1]

Many drugs, such as sevoflurane, thiopental, etomidate, propofol, and ketamine, are used for ECT anesthesia. The ideal anesthetic agent for ECT should be short acting, ensure rapid recovery with minimal confusion after treatment, and have a minimal effect on seizure threshold. Sevoflurane provides a rapid induction and emergence from anesthesia. It can be helpful for intravenous catheter application in patients who are frightened, sad, or psychiatrically agitated in a way that affects their ability to cooperate.[2,3] However, some studies report brief seizure durations with sevoflurane.[4,5]

There has been growing interest in recent years in the use of ketamine in psychiatric patients as an anesthetic for ECT.[6–9] Ketamine acts as an anesthetic agent in ECT with favorable seizure induction action and increased seizure duration in addition to being an effective *N*-methyl-D-aspartate receptor antagonist. Ketamine was associated with longer seizure durations when used as the sole anesthetic or as an adjunct.[7,10] However, the effect of ketamine in prolonging the duration of ECT-induced seizure activity was not evaluated in the presence of a standardized dose of sevoflurane. Seizure duration may thus be elongated if subanesthetic doses of ketamine are added to sevoflurane.

We evaluated the effects of a subanesthetic dose of ketamine (0.5 mg/kg), which was administered as an adjunct to sevoflurane, on duration of seizure activity, hemodynamic profile, and recovery times during ECT in patients with major depression.

MATERIALS AND METHODS

After receipt of the Inonu University Ethics Committee's approval and patients' written informed consent, 84 patients with major depression with no other major medical problems were enrolled in this prospective, randomized, parallel trial. We excluded patients who were younger than 18 years; pregnant; or had a history of myocardial infarction in the previous 6 months, atrial fibrillation or flutter, heart block, unregulated hypertension, cerebrovascular diseases, or a known drug allergy. Use of all long-term psychiatric medications was permitted to continue.

The patients were randomly allocated via computer-generated random numbers to a group receiving either a sevoflurane-ketamine (group SK) or a sevoflurane-saline (group SS) for ECT session. The study drug was prepared by an anesthesiologist not involved in the study in a 10-mL syringe diluted with 0.9% saline and labeled as "study drug." Placebo was 0.9% saline. None of the patients were premedicated. American Society of Anesthesiologists monitorization was applied to all patients, and anesthetic induction was achieved via 8% sevoflurane; seizure thresholds were determined via a dose-titration method for the patients' first ECT sessions. Energy was increased by 50% in the subsequent treatment. Electroconvulsive therapy was applied 3 times per week to all patients. Sessions 2 to 4 were included in the study. Sevoflurane was initiated, in both groups, at 8% for anesthesia induction until loss of consciousness was achieved, at which point it was discontinued. After loss of consciousness, ketamine was administered to the group SK (n = 41) in the form of a 0.5-mg/kg intravenous bolus. The patients in the group SS (n = 43) received saline in the same manner. Each patient received the same induction agent during their complete course of treatment. A pneumatic tourniquet was applied to the arm and inflated to isolate circulation and allow for accurate assessment of motor seizure. Succinylcholine (1 mg/kg) was then administered intravenously; ventilation was facilitated using 100% oxygen, via face

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TABLE 1. Patients' Seizure Durations and Recovery Times

	Group SS (n = 43)	Group SK (n = 41)	*P*
Seizure activity, s			
EEG seizure	35.5 (9.2)	36.7 (10.5)	0.566
Motor seizure	26.2 (6.2)	23.7 (5.3)	0.059
Peak HR	129.6 (13.3)	131.1 (15.5)	0.626
PSI	72.2 (10.7)	76.8 (10.2)	0.048
Recovery time, min			
Spontaneous breathing	4.8 (1.3)	4.8 (1.2)	0.977
Open eyes	7.1 (1.3)	7.8 (1.4)	0.016
Obeying commands	7.5 (1.2)	8.2 (1.3)	0.014

Values are presented as means (SD).

P values are for between-group comparisons (unpaired *t* test).

mask, in both groups. The investigators were blinded to the identity of the study drug used.

Mean arterial pressure (MAP) and heart rate (HR) were recorded before anesthetic induction (T1); after anesthetic induction (T2); as well as 0, 1, 3, and 10 minutes after the seizure had ended (T3, T4, T5, and T6, respectively). The patients were discharged from the recovery room once they met the discharge criteria.

Electrical stimuli were delivered via bifrontotemporal electrodes using a Thymatron System IV ECT instrument (Somatics Inc, Lake Bluff, Ill). The duration of the motor seizure was recorded as the time from application of the ECT stimulus to the cessation of tonic-clonic motor activity in the isolated arm. Electroencephalogram (EEG) tracing was recorded continuously from 2 frontal electrodes. The duration of the EEG seizure and postictal suppression index (PSI) were recorded from the EEG trace, and peak HR during the convulsion was recorded from the electrocardiogram. Times were recorded from the end of succinylcholine administration until the patients breathed spontaneously, opened their eyes, and obeyed commands. The primary outcome was on durations of seizure activity. Secondary outcomes were the changes of MAP, HR, PSI, and the recovery times.

Power analysis suggested minimum of 41 subjects in each group with an electromyography difference of 4, an estimated SD of 5.5, as well as a significance level (α) of 0.05 and (β) of 0.10. Statistical analyses were performed using Statistical Package for the Social Sciences for Windows (version 22.0; SPSS Inc Headquarters, Chicago, Ill). Categorical variables are reported as frequencies (*n*) and percentages (%). Continuous variables are reported as mean (SD) or median (minimum-maximum) values. The normality of continuous variables in the groups was confirmed using the Shapiro-Wilk test. Baseline and postbaseline measurements were compared via repeated-measures analysis of variance followed by Bonferroni test. *U* unpaired *t* test was used for between-group comparisons. $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Six patients were excluded from the study: 1 patient from each of the 2 groups developed severe hypertension during ECT; 1 patient in the group SS and 2 patients in the group SK refused further study treatments after the initial study treatment; and 1 patient in the group SK was excluded because of problems associated with the ECT equipment. The group SS comprised 19 men and 24 women, with a mean (SD) age of 39.3 (8.5) years and a mean weight of 72.5 kg (12). The group SK comprised 21 men and 20 women, with a mean (SD) age of 42.1 (7.8) years and a mean weight of 73.6 kg (10.8). Across groups, a total of 252 ECTs were delivered in 3 successive sessions.

Motor and EEG seizure duration in the group SS (26.2 [6.2] seconds and 35.5 [9.2] seconds, respectively) were similar to those observed for the group SK (23.7 [5.3] seconds and 36.7 [10.5] seconds, respectively). The PSI value was higher in the group SK (76.8 [10]) in comparison with the group SS (72.2 [10.7]; $P = 0.048$). There was no statistically significant difference between the group SS (129.6 [13.3]) and the group SK (131.1 [15.5]) with respect to peak HR. Time taken to open eyes and obey commands was longer in the group SK ($P = 0.016$ and $P = 0.014$, respectively). There was no group difference in spontaneous respiration. Motor seizure duration, EEG seizure duration, PSI and peak HR value, as well as recovery time are shown in Table 1.

There were no group differences in baseline measures of HR and MAP. The HR increased significantly during T2 to T6 in both the group SS ($P < 0.001$ for T2 and T5-T6; $P = 0.001$ for T3-T4) and the group SK ($P = 0.001$ for T2-T6) compared with the baseline. There was no change in HR during any period in either group. The MAP increased in the group SS during the period between T3 and T6 ($P < 0.001$ for T3-T6) as well as in the group SK

TABLE 2. Hemodynamic Parameters

	HR, bpm			MAP, mm Hg		
Time	Group SS (n = 43)	Group SK (n = 41)	*P*	Group SS (n = 43)	Group SK (n = 41)	*P*
T1	78.8 (11.3)	77.3 (10.4)	0.519	94.8 (11.6)	95.6 (10.5)	0.720
T2	84.5 (11.4)*	84.2 (10.8)*	0.892	90.1 (12.2)	100.3 (13.9)	0.001
T3	87 (13.6)*	88.2 (10.9)*	0.659	115.5 (14.2)*	119.8 (12.1)*	0.135
T4	88.5 (14.8)*	86.7 (13.2)*	0.549	115.6 (14.6)*	119 (14.1)*	0.288
T5	90.6 (14)*	89.5 (13)*	0.691	113.4 (14.1)*	111.1 (12.5)*	0.431
T6	91 (13.1)*	89.8 (12.6)*	0.682	106.5 (13.3)*	105.1 (12.4)*	0.629

Values are means (SD).

P values are for group comparisons (unpaired *t* test).

*$P < 0.05$ compared with T1 (repeated-measures analysis of variance followed by Bonferroni test).

bpm indicates beats per minute.

during the same period ($P < 0.001$ for T3-T6) compared with the baseline. The MAP increased more in the group SK, in comparison with the group SS, during T2 ($P = 0.001$). The HR and MAP data are shown in Table 2.

DISCUSSION

In our study, the addition of subanesthetic doses of ketamine to sevoflurane to induce anesthesia in patients with major depression was not associated with significant changes in seizure duration; conversely, MAP and PSI increased, and time to open eyes and obey commands was increased.

The proconvulsant, or reduced anticonvulsant, effects of ketamine in the context of ECT have been documented previously.[6,7] However, results pertaining to seizure duration when ketamine and another anesthetic agent are used in combination are equivocal. Our study was similar to those of Abdallah et al[8] and Loo et al,[9] with no change in EEG duration when subanesthetic doses of ketamine were added to the standard dose of an anesthetic agent administered for the purposes of ECT. In contrast, Yalcin et al[10] reported that propofol and ketamine, in combination, engender increased seizure duration in anesthetic induction compared with propofol. However, the propofol dose in the propofol-ketamine combination in this study was 50% lower in comparison with the control group. Dose-contingent anticonvulsant properties of the sedative and hypnotic agents used for anesthetic induction are well documented; decreasing the dose of these agents might precipitate decreases in the seizure threshold.[11]

We found only a single controlled study in the literature that included different combinations of anesthetic agents with sevoflurane for the purposes of ECT anesthesia. The study in question by Wajima et al[4] reported that motor seizure duration was very short in both sevoflurane and sevoflurane-propofol groups. We used 8% sevoflurane for inhalation anesthesia in ECT, in accordance with the recommendation of Rasmussen et al,[2] and discontinued supply of the agent as soon as anesthetic induction was achieved.

Although the use of EEG is an indicator of the efficacy of ECT, it has been proposed that clinical efficacy is associated primarily with more intense seizure activity and PSI.[12] The degree to which EEG amplitude "flattens" after the completion of a seizure is described by PSI and relates to the intensity or generalization of the seizure rather than to its duration.[13] Krystal et al[7] reported, for the first time, that ketamine anesthesia tends to be associated with greater seizure intensity as indexed by measures of ictal amplitude and PSI. Another retrospective study showed that ketamine increased PSI. The mean PSI value was 75 in the ketamine group, which was similar to what was reported in the present study.[14] However, a limitation of our study is that the sample size may be too small to fully determine its clinical significance.

The typical cardiovascular response to ECT consists of generalized autonomic nervous system stimulation, with an initial parasympathetic-induced bradycardia lasting 10 to 15 seconds, immediately followed by a more prominent sympathetic response that results in tachycardia and hypertension with duration of at least 5 minutes.[15] Although MAP and HR increased to their basal values (after ECT) in our study, this increase was within expected limits.[16] Because ECT is frequently administered in an outpatient setting, any anesthetic agents used should have rapid recovery profiles. Although the recovery periods in our study, aside for spontaneous breathing, were significantly longer in the group SK, their durations were nonetheless quite brief in comparison with the only other study to use the sevoflurane-propofol combination.[4]

An additional confounding factor when comparing ECT trials concerns whether ketamine has been used at a high dose. Anesthetic doses of ketamine may cause psychotogenic adverse effects, such as delirium and fear upon waking, in addition to hemodynamic effects.[6,7] Accordingly, it has been proposed that addition of subanesthetic doses of different anesthetic agents, in an adjuvant capacity, might be an effective strategy for decreasing the dose-related effects of ketamine.[17] We also used a subanesthetic dose of 0.5-mg/kg ketamine and observed no adverse affects either hemodynamically or psychomimetically, as have been documented in other studies.[9,10]

A few studies have suggested a potential benefit of ketamine as having antidepressant effects when administered as an anesthetic agent. It is of particular interest for patients with depression because ketamine has a synergistic effect together with ECT and is therefore influential in the course of the illness.[18] Another limitation of our study is the absence of evaluating antidepressant effects of ketamine after ECT session.

In conclusion, the addition of ketamine at subanesthetic doses, for the purposes of anesthetic induction with sevoflurane, yielded results similar to those in the control group in terms of both seizure duration and hemodynamic stability. Moreover, after ECT, PSI increased. Further clinical trials are required to determine the potential clinical effects of subanesthetic doses of ketamine during ECT and to assess the impact on treatment efficacy.

REFERENCES

1. Weiner RD. *The Practice of Electroconvulsive Therapy. Recommendations for Treatment, Training and Privileging*. American Psychiatric Association: Washington, DC, 2001.
2. Rasmussen KG, Spackman TN, Hooten WM. The clinical utility of inhalational anesthesia with sevoflurane in electroconvulsive therapy. *J ECT*. 2005;21:239–242.
3. Rasmussen KG, Laurila DR, Brady BM, et al. Anesthesia outcomes in a randomized double-blind trial of sevoflurane and thiopental for induction of general anesthesia in electroconvulsive therapy. *J ECT*. 2007;23: 236–237.
4. Wajima Z, Shiga T, Yoshikawa T, et al. Propofol alone, sevoflurane alone, and combined propofol-sevoflurane anaesthesia in electroconvulsive therapy. *Anaesth Intensive Care*. 2003;31:396–400.
5. Calarge CA, Crowe RR, Gergis SD, et al. The comparative effects of sevoflurane and methohexital for electroconvulsive therapy. *J ECT*. 2003;19:221–225.
6. Okamoto N, Nakai T, Sakamoto K, et al. Rapid antidepressant effect of ketamine anesthesia during electroconvulsive therapy of treatment-resistant depression. *J ECT*. 2010;26:223–227.
7. 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.
8. Abdallah CG, Fasula M, Kelmendi B, et al. Rapid antidepressant effect of ketamine in the electroconvulsive therapy setting. *J ECT*. 2012;28: 157–161.
9. Loo CK, Katalinic N, Garfield JB, et al. Neuropsychological and mood effects of ketamine in electroconvulsive therapy: a randomized controlled trial. *J Affect Disord*. 2012;142:233–240.
10. Yalcin S, Aydoğan H, Selek S, et al. Ketofol in electroconvulsive therapy anesthesia: two stones for one bird. *J Anesth*. 2012;26:562–567.
11. Avramov MN, Husain MM, White PF. The comparative effects of methohexital, propofol, and etomidate for electroconvulsive therapy. *Anesth Analg*. 1995;81:596–602.
12. Gazdag G, Kocsis N, Tolna J, et al. Etomidate versus propofol for electroconvulsive therapy in patients with schizophrenia. *J ECT*. 2004;20:225–229.

13. Geretsegger C, Rochowanski E, Kartnig C, et al. Propofol and methohexital as anesthetic agents for electroconvulsive therapy (ECT): a comparison of seizure-quality measures and vital signs. *J ECT*. 1998;14:28–35.
14. Hoyer C, Kranaster L, Janke C, et al. Impact of the anesthetic agents ketamine, etomidate, thiopental, and propofol on seizure parameters and seizure quality in electroconvulsive therapy: a retrospective study. *Eur Arch Psychiatry Clin Neurosci*. 2014;264:255–261.
15. Ding Z, White PF. Anesthesia for electroconvulsive therapy. *Anesth Analg*. 2002;94:1351–1364.
16. Saito S. Anesthesia management for electroconvulsive therapy: hemodynamic and respiratory management. *J Anesth*. 2005;19: 142–149.
17. Loo C, Simpson B, MacPherson R. Augmentation strategies in electroconvulsive therapy. *J ECT*. 2010;26:202–207.
18. Kranaster L, Ciernioc JK, 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.