Objective: We aimed to evaluate the effect of anaesthesia with thiopental (4 mg kg$^{-1}$), ketamine (1 mg kg$^{-1}$) and ketamine–thiopental (1 mg kg$^{-1}$ and 4 mg kg$^{-1}$, respectively) combination during electroconvulsive therapy (ECT) on the Hamilton Depression Rating Scale (HDRS) and Hamilton Anxiety Rating Scale (HAM-A) and haemodynamic variables in patients with resistant major depression.

Methods: Patients with HDRS scores above 17 were included. The patients were randomly divided into three groups according to the anaesthesia used. Group 1 was given thiopental (4 mg kg$^{-1}$), Group 2 was given ketamine (1 mg kg$^{-1}$) and Group 3 was given ketamine (1 mg kg$^{-1}$) and thiopental (4 mg kg$^{-1}$). Succinylcholine (1 mg kg$^{-1}$) was administered in all patients for muscle relaxation. HDRS and HAM-A scores were evaluated before ECT, after 3, 6, ECT and after the final ECT. Systolic and diastolic blood pressures, heart rates and oxygen saturations were recorded before and after anaesthesia induction and after the ECT procedure. Seizure duration was recorded.

Results: Fifty-eight patients were included in the study. Thirty (52%) patients were male and 28 (48%) were female. The mean age was 42.7±15.8 years in Group 1, 44.8±11 years in Group 2 and 38.6±6.8 years in Group 3. In all groups, HDRS scores were reduced compared with the baseline values. There was no statistical significant difference between the groups regarding HDRS scores. HAM-A scores were higher in Group 2 and Group 3. Systolic and diastolic blood pressures and heart rate values were lower in Group 1 and the difference was statistically significant.

Conclusion: In this study, anaesthesia induced with thiopental, ketamine and thiopental–ketamine combination was observed to not result in a difference in ECT for patients with treatment-resistant depression. Ketamine at a dose of 1 mg kg$^{-1}$ given just before ECT did not enhance the antidepressant effect of ECT; however, anxiety scores were increased with ketamine application.

Keywords: Depression, anxiety, thiopental, ketamine, electroconvulsive therapy

Introduction

Depression is a severe mental disease that negatively affects the quality of life (1). In total, 10%–30% of women and 7%–15% of men encounter this disease during their lifetime; the disease is clinically and biologically heterogeneous. The morbidity and mortality rates of depression are high, and it may cause severe social and economic impacts (2).

Antidepressant drugs and electroconvulsive therapy (ECT) are used for its treatment. It is indicated that ECT is effective in treating major depression at the rate of 80%–90%. Despite this, the existence of psychotropic drugs hinders the use of ECT as the first preferred treatment and limits it use with only treatment-resistant cases. The Hamilton Depression Rating Scale (HDRS) is among the most commonly used scales in evaluating depression and measuring its intensity (5, 6). A 50% decrease in the scale score has been accepted as response and falling to the score of 7 and below has become the criterion (7, 8).

Ketamine is an anaesthetic agent that exerts its effect through N-methyl D-aspartate (NMDA), opioid, muscarinic and some still unexplained receptors (9, 10). Ketamine plays a role in the treatment of major depression by having an impact on the monoaminergic targets of serotonin and noradrenaline; however, the results are not definite (11-18).
In our study, we aimed to determine the effects of ketamine (1 mg kg\(^{-1}\)), thiopental (4 mg kg\(^{-1}\)) and the combination of ketamine–thiopental in anaesthesia induction for ECT treatment in major depression cases resistant to drug treatment on HDRS, Hamilton anxiety rating scale (HAM-A) and haemodynamics.

**Methods**

The study was conducted by the Anaesthesiology and Reanimation Department on the patients diagnosed with major depression by the Çukurova University Medicine Faculty Department of Psychiatry. After having received approval from the Faculty Ethics Committee (10/24/2013–9/23) and written informed consents of the patients, adult patients (between the ages of 18 and 65 years) resistant to the treatment and diagnosed with major depression according to DSM-IV diagnostic criteria were included in the study. Patients with cardiovascular disease, intracranial hypertension, respiratory system illness, fracture, glaucoma, artery aneurysm and those who did not give consent were excluded from the study.

Preoperative evaluation was conducted a day before ECT, and information about the method to be applied was given to the patients and their family. The HDRS and HAM-A scores of all the patients were recorded.

The fasting time was planned to start from at least 8 h before ECT. All patients taken to the intervention room in supine position were monitored for electrocardiogram (EKG) findings, non-invasive systolic (SAB) and diastolic artery blood pressure (DAB), heart rate (HR) and peripheral oxygen saturation (SpO\(_2\)) follow-up. They were monitored with the Drager–Fabius anaesthesia device monitor.

In Group 1 (Gr TS, n=21): Thiopental [4 mg kg\(^{-1}\) intravenous (IV)],

In Group 2 (Gr KS, n=19): Ketamine (1 mg kg\(^{-1}\) IV)

In Group 3 (Gr KTS, n=18): Ketamine (1 mg kg\(^{-1}\) IV) and thiopental (4 mg kg\(^{-1}\) IV) were administered.

After administering the study drug, succinylcholine (1 mg kg\(^{-1}\)) was used as the neuromuscular agent in all cases. Then, the cases were ventilated with 100% oxygen (6 L dk\(^{-1}\)). The tongue was protected with an appropriate airway device during ECT. After conducting general anaesthesia according to the groups, ECT operation was conducted by a psychiatrist who did not know which anaesthesia method was applied. Thymatron System IV ECT device was used in ECT applications.

SAB, DAB, HR and SpO\(_2\) values before and after induction and after ECT were recorded. Eight sessions of ECT totally as bilateral, bitemporal and 3 times in a week (preferably every other day) were applied to all the patients. The anaesthesia agent used in the first ECT in one case was also used in other sessions. It was planned to administer atropine (0.015 mg kg\(^{-1}\)) in the cases with severe bradycardia and esmolol (0.5 mg kg\(^{-1}\), bolus) in the cases with severe hypertension and tachycardia during and after ECT application, and the other possible complications were noted.

Ventilation was continued until the spontaneous ventilation came back to normal after ECT. Patients who were stabilised with respect to haemodynamics and having sufficient spontaneous ventilation were taken into the recovery room. If there was no side effect or complication in 1 hour following ECT in the postoperative recovery room, the cases were transferred to the psychiatry ward.

HDRS and HAM-A evaluations were repeated after the 3rd and 6th ECT and at the end of ECT therapy. As drug applications, a 50% decrease in the HDRS scores was evaluated as response to the ECT.

**Statistical analysis**

The Statistical Package for Social Sciences (SPSS Inc., Chicago IL, USA) 15.0 statistics package program was used for the statistical analysis of the data. Categorical measurements were summarized as number and percentage, and continuous measurements were presented as mean and standard deviation. The chi-square test was used for the comparison of categorical variables. The statistical significance level in all tests was taken as <0.05.

**Results**

Sixty-one patients were included in the study. However, ECT therapy was discontinued in three patients of Group 2 (because of the development of confusion in one patient and severe anxiety in two patients). There was no statistically significant difference with respect to age and gender in the groups. The demographic features of the groups are displayed in Table 1.

**Haemodynamic changes**

There was no difference among the groups in SAB values measured before ECT. SAB and DAB values measured following anaesthesia induction after ECT were determined to be significantly low in Group 1 compared with those in Group 2 and Group 3 in all sessions (p<0.05). HR values recorded after anaesthesia induction and after ECT were found to be significantly lower in Group 1 than those in Group 2 and Group 3 in all sessions (p<0.05).

**Hamilton Anxiety and Depression Rating Scales**

It was detected that HAM-A values recorded at the end of ECT were significantly low in Group 1 compared with those in Groups 2 and 3 (Table 2).

HDRS results detected before ECT did not display any difference among the groups. It was observed that HDRS results decreased over time after ECT applications compared with the beginning results in all the three groups. There was no difference detected with respect to HDRS results among the groups at the end of ECT (Table 2).
Seizure duration
It was determined that the seizure duration after ECT was shorter in Group 3 than the other two groups. There was no difference between Groups 1 and 2. The mean seizure durations during each ECT operation are displayed in Table 3.

Side effects
ECT was discontinued upon the development of confusion in one patient in Group 2 after ECT. Two cases in Group 2 willingly discontinued ECT upon developing anxiety. Esmolol (0.5 mg kg\(^{-1}\)) was administered intravenously in seven patients who developed hypertension. All of these cases were in Group 2. Atropine sulphate (0.5 mg) was administered intravenously in three cases who developed severe bradycardia. Two of these cases were in Group 1, and the other one case was in Group 3. Except these complications, no respiratory or cardiovascular problems were encountered.

Discussion
Major depressive and bipolar affective disorders are psychiatric diseases that are often persistent and affect the quality of life (19). The effectiveness of traditional antidepressants is limited in the treatment of these diseases because of the lack of guidelines having valid evidence levels (20). Therefore, the development of new and effective antidepressants is required.

Ketamine is used frequently in anaesthesia practice because of its safe anaesthetic profile and has been recently administered as an antidepressant in treatment-resistant patients with depression (11). The rationality of the use of this indication of ketamine stems from its availability in clinical use and its use as the single non-competitive blocking agent. Although the pathology of depression is not exactly known, it has been proven that an increased number of arterial activity in NMDA receptors arises.

Kudoh et al. (13) suggested that single-dose ketamine (0.5 mg kg\(^{-1}\)) improved the state of the patient with depression who underwent orthopaedic surgery. Berman et al. (14) detected a regression in depression symptoms according to the HDRS scores using IV ketamine infusion in sub-anaesthetic doses (0.5 mg kg\(^{-1}\)) in depressive patients. Similarly, Zarate et al. (15) suggested that there was an improvement in depressive symptoms on the first day in 12 of the 18 patients administered with single-dose ketamine infusion. Because a limited number of randomised controlled trials have been conducted, the lack of an active placebo agent and insufficiency of long-term results prevent ketamine to be used routinely (16). The antidepressant effectiveness of ketamine was investigated in a comprehensive study in which 67 patients were included. Although the response rate was 64% in the patients administered with ketamine in the first 24 h, it was 28% in the group administered with midazolam as the active placebo. Dissociative side effects related with ketamine arose just after the

<table>
<thead>
<tr>
<th>Table 1. Demographic features of the groups</th>
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<tbody>
<tr>
<td>Group 1 (n=20)</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Age (years)</td>
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*Chi-square test
One-way ANOVA test

<table>
<thead>
<tr>
<th>Table 2. HDRS and HAM-A values of the groups</th>
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<tbody>
<tr>
<td>Before ECT</td>
</tr>
<tr>
<td>HDRS 17.6±4.9</td>
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<tr>
<td>HAM-A 10.2±4.3</td>
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<tr>
<td>After 3rd ECT</td>
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<tr>
<td>HAM-A 7.1±3.4</td>
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<tr>
<td>After 6th ECT</td>
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<tr>
<td>HAM-A 4.0±2.5</td>
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<tr>
<td>Completion of ECT</td>
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<td>HAM-A 1.4±0.8</td>
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</table>

*Kruskal–Wallis test results.
Statistically significant difference: Between Group 1 and Group 2 and Group 1 and Group 3 (p<0.017)
ECT: electroconvulsive therapy; HDRS: Hamilton depression rating scale; HAM-A: Hamilton anxiety rating scale

<table>
<thead>
<tr>
<th>Table 3. Seizure durations of groups</th>
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<tr>
<td>Seizure durations</td>
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<tr>
<td>1. ECT 35.4±16.3</td>
</tr>
<tr>
<td>2. ECT 32.4±11.8</td>
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<tr>
<td>3. ECT 32.8±10.9</td>
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<tr>
<td>4. ECT 29.5±16.2</td>
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<tr>
<td>5. ECT 24.7±11.1</td>
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<tr>
<td>6. ECT 31.3±14.1</td>
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<tr>
<td>7. ECT 32.8±12.0</td>
</tr>
<tr>
<td>8. ECT 25.7±11.5</td>
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</table>

ECT: electroconvulsive therapy
*Kruskal–Wallis test results.
Statistically significant difference between the groups with Bonferroni- corrected Mann–Whitney U-test:
Between Group 1 and Group 3 and Group 2 and Group 3 (p<0.017)
Between all the groups (p<0.017)
Between Group 1 and Group 2 and Group 2 and Group 3 (p<0.017)
Between all the groups (p<0.017)
Between Group 1 and Group 3 and Group 2 and Group 3 (p<0.017)
Between Group 2 and Group 3 (p<0.017)
Between Group 1 and 2 and Group 1 and 3 (p<0.017)
Between Group 1 and Group 2 and Group 1 and 3 (p<0.017)
application and disappeared 2 h later (17). Szymkowicz et al. (18) administered 0.5 mg kg$^{-1}$ IV ketamine to four patients over 65 years of age with treatment-resistant major depressive disorder and observed that antidepressant effects did not arise in all of the cases. They considered that this stemmed from the age-related changes in NMDA receptors.

ECT is a treatment accepted to be rapid and effective in treating unipolar and bipolar depression. On an average, 5–7 sessions are required to observe a remarkable improvement in the symptoms (21). Although there are studies indicating that the use of ketamine during ECT has a positive effect on depression symptoms, there are also studies with findings indicating that it has not received any positive contribution (11-18, 22-25). Ketamine is a rarely administered anaesthetic agent during ECT application in our clinic. Thiopental (frequently) and propofol (rarely) are administered for this purpose.

In the study of Katalinic et al. (23), in which thiopental-ketamine and thiopental-placebo were compared during ECT operation, no neuropsychological difference was detected between the two groups after ECT. In the randomized study of Abdallah et al. (25), thiopental and thiopental-ketamine (0.5 mg kg$^{-1}$) were compared with ECT in the patients with major depressive disorder or bipolar disorder, and the HDRS scores were evaluated at the beginning of ECT, after 1st ECT and 24–72 h after the 6th ECT. It was observed that ECT had a significant antidepressant effect in both groups. In addition, no difference was observed between the groups and HDRS scores of the groups according to time. These results support that 0.5 mg kg$^{-1}$ ketamine administered before ECT did not increase the antidepressant effect of ECT. Similar to this study, our study did not detect a difference with respect to HDRS results between the groups. The HDRS scores being 50% lower than the initial values support that the depression improved. It was observed that the mean HDRS scores even after the third ECT <17 and depression improved. The HDRS score of 17.6±4.9 before ECT application in Group 1 fell to 3.7±1.6 after the 8th session, it fell from 20.0±4.0 to 4.8±3.4 after the 8th session in Group 2 and it fell from 19.7±4.3 to 4.2±1.4 in Group 3. No difference was detected at the end of ECT sessions among the groups. Although there was no significant difference in the HDRS scores among the groups before ECT, it is remarkable that it was higher in Group 2 and Group 3 than in Group 1.

A seizure duration of 25 s is accepted as standard during ECT application, and shorter seizure durations are associated with poor clinical results (29). It was observed in our study that seizure durations were shorter in Group 3 than those in the other groups. This effect can be explained by the application of two different anaesthetic agents together without lowering the dose and the deep anaesthesia effect. Although the mean seizure duration being longer than 25 s in Group 1 was observed only in one session, it was detected in three sessions in Group 3. Although it is suggested that the seizure duration with ECT is beneficial for the improvement of depression symptoms, there was no difference with respect to depression symptoms in our patient groups.

Conclusion

We are of the opinion that the HDRS scores decreased compared with the initial values in all groups in ECT application and there was no difference between these measurements at the end of ECT, ketamine was not superior to thiopental in treating depression symptoms and the HAM-A scores, in contrast, were higher in the groups administered with ketamine. The evaluation of the antidepressant effect and anxiety side effect of ketamine with different doses in new studies will provide more detailed information about this drug.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Çukurova University (24.10.2013-23/9).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.


Conflict of Interest: No conflict of interest was declared by the authors.

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