

Administration of Sub-anesthetic Dose of Ketamine and Electroconvulsive Treatment on Alternate Week Days in Patients with Treatment Resistant Depression: A Double Blind Placebo Controlled Trial

By Murat Altinay, Harish Karne, Amit Anand

ABSTRACT~ Introduction and Background: Patients with depression who fail to respond to at least two antidepressants in their current episode are considered to have Treatment Resistant Depression (TRD). ECT is an effective treatment of TRD but cognitive side effects limit its use. Ketamine elicits a rapid antidepressant response in sub-anesthetic repeated doses. ECT and ketamine may be modulating the glutamate system, therefore when administered in an interleaved fashion, they could have a synergistic effect. **Methods:** 15 TRD patients were recruited and 12 were included in the analysis. Patients were randomly assigned to an ECT + iv. ketamine or ECT + iv. placebo (midazolam). At baseline and before each infusion, depression severity scales were administered. At baseline, halfway through and at the end of the study, cognitive tests were administered. **Results:** There was no difference between the ketamine and placebo arms, per change in 17-item Hamilton Depression Scores (HAM-D), Young Mania Rating Scores or cognitive tests. Per HAM-D scores, 3 ECT + ketamine subjects (42%) showed early remission (HAM-D < 8) and maintained euthymia for 3 additional visits. None of the ECT + midazolam subjects (0%) achieved early remission. This difference showed a trend level significance (Chi square P-Value = 0.0910). **Conclusion:** The results of the study were limited due to the small sample size. However, a trend level difference in rates of early remission was seen, suggesting that ketamine + ECT may lead to a faster symptom relief. A larger sample size is needed for statistical confirmation. *Psychopharmacology Bulletin. 2019;49(1):8-16.*

Altinay, MD, Karne, BS, Anand, MD, Center for Behavioral Health, Cleveland Clinic, Cleveland, Ohio.

To whom correspondence should be addressed: Murat Altinay, MD, Center for Behavioral Health, Cleveland Clinic, 9500 Euclid Avenue/P57, Cleveland, Ohio 44195. E-mail: altinam@ccf.org

INTRODUCTION AND BACKGROUND

Major Depressive Disorder (MDD) is one of the most prevalent psychiatric disorders (10–15% prevalence). Patients who fail to respond to at least two antidepressant trials in their current depressive episode are considered to have Treatment Resistant Depression (TRD). The monoamine hypothesis only partially explains the pathophysiology of depression and conventional antidepressants fail to treat TRD. There is a growing evidence that glutamate metabolism plays a role in depression,^{1–3} learning and memory.^{4,5}

Electroconvulsive Therapy (ECT) is one of the safest, most effective and robust treatments for TRD. There have been different theories of ECT's mechanism of action, one of which is the glutamate system. An increased glutamergic activity in dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) was shown after ECT, which was not seen in hippocampus^{6–8}—this might explain its cognitive side effects. In animals, electroconvulsive shock (ECS) therapy decreased N-Methyl-D-Aspartate (NMDA)-NR2B expression, which is associated with memory function.^{9–11} Human studies support these findings, where ECT was shown to decrease glucose metabolism in left medial temporal lobe, which plays a major role in memory.¹²

Ketamine (an NMDA channel blocker) was shown to elicit a rapid (1–5 hours) antidepressant response in sub-anesthetic repeated doses,¹³ which was shown to remain in effect (≥ 48 hours) beyond its half-life.^{14–19} This effect was hypothesized to be mediated via non-NMDA receptors²⁰: NMDA receptor blockade would increase the release of post-synaptic glutamate, which would then act on AMPA and kainate receptors. This action has been shown to increase dopamine release in the striatum and frontal cortex.

The differential effects on NMDA and non-NMDA receptors may explain the efficacy and side-effect profile of ECT and ketamine: while ECT's increased NMDA-related glutamatergic neurotransmission might lead to memory impairment, ketamine's NMDA blockade may lead to cognitive enhancement.²¹ On the other hand, both ECT and ketamine induced non-NMDA receptor mediated glutamatergic neurotransmission may cause the antidepressant effect. It follows therefore that an ECT-ketamine combination could have a synergistic antidepressant effect with minimum cognitive side effects. Clinical evidence shows faster reorientation and improved post-ECT word recall with ketamine as an anesthetic for ECT.^{20,22} But the studies that used ketamine as an adjunct treatment show negative results;^{23,24–26} possibly due to ECT-modulated acute profound NMDA neurotransmission negating or diluting ketamine's effects. Therefore, in this proof of

concept study, we administered ketamine on alternate days interleaved with ECT days. Our hypothesis was that interleaved ketamine treatment would enhance ECT effects, would lead to a greater and a more robust decrease in the depression scores, decrease the number of ECT treatments needed to achieve response and remission and reduce cognitive impairment due to ECT.

METHODS

15 patients with TRD, who were referred to the Cleveland Clinic outpatient depression clinic or ECT service, were recruited in the study. 1 subject withdrew consent after the baseline visit and 2 patients were lost to follow up after the screening visit. 12 patients were included in the analysis. Eligible patients went through a screening process, which involved a full psychiatric assessment and administration of Mini Neuropsychiatric International Interview (MINI) Plus (English Version 5.0.0) to confirm the diagnosis.

Inclusion criteria were: (i) males/females between 18–65 years of age, (ii) meet DSM-IV criteria for Major Depression or Bipolar Disorder, depressed phase that has lasted a minimum of 4 weeks, as determined by a clinician's diagnostic evaluation and confirmed by the MINI PLUS 5.0.0, (iii) MADRS score of ≥ 23 , (iv) YMRS score ≤ 10 , MoCA score ≥ 23 , (v) have 3 or more trials of antidepressants/augmentation strategies.

Exclusion Criteria were: (i) meeting DSM-IV criteria for schizophrenia, schizophreniform disorder, schizoaffective disorder, mental retardation, pervasive developmental disorder, (ii) meeting DSM-IV criteria for other substance/alcohol dependence within the past 6 months or abuse in the past 3 months, (iii) women who are pregnant or breastfeeding, (iv) intellectual disability, or IQ score of < 85 , (v) meeting exclusion criteria for ECT, (vi) meeting exclusion criteria for ketamine and midazolam.

Behavioral Measures

Patients were rated at baseline on the Clinical Global Impression of Severity Scale (CGI-S), MINI Plus (English Version 5.0.0), Montgomery Asberg Depression Rating Scale (MADRS), Hamilton Depression Scale (HAM-D-17), Neuroticism/Extraversion/Openness- Five Factor Inventory (NEO-FFI), Hamilton Anxiety Rating Scale (HAM-A), Columbia Suicide Severity Rating Scale (CSSRS), Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool (LIFE-RIFT) and Young Mania Rating Scale (YMRS).

Patients who were deemed eligible after the screening visit were scheduled for a baseline visit for baseline cognitive testing. (Montreal Cognitive Assessment (MOCA), Hopkins Verbal Learning Test – Revised (HVLN-R), Self-Reported Global Self Evaluation of Memory, Controlled Oral Word Association Test (COWAT), Trail Making Test, Part A and Trail Making Test, Part B). Study staff was trained by a psychometrist to administer the tests. To prevent practice effects on cognitive tasks and memory measures, different versions of these tests were used. Following the baseline visit, eligible subjects were randomly assigned to either subanesthetic dose of ketamine (0.5 mg/kg over 40 minute infusion) or active placebo (midazolam) (0.045 mg/kg over 40 minute infusion). Midazolam has recently been used as a placebo in other clinical trials^{16-19,23} due to its similar sedative effect to that of ketamine, but its effects are time limited to the duration of the infusion.

All subjects received ECT treatments on Mondays Wednesdays and Fridays and infusions on Tuesdays and Thursdays. Prior to each infusion, the patients were rated on MADRS, HAMD-17, CSSRS, LIFE-RIFT, YMRS and CGI-I. For all patients, the same ECT parameters were used: Bi-frontal (BF) brief pulse (0.5 msec) ECT administered by using Thymatron ECT machine. After 4th and 9th (last) ECT treatment the patients received MOCA, HVLN-R, AMI-SF and Self-Reported Global Self Evaluation of Memory. The patients, the treating psychiatrist and the nursing staff were kept blinded in this study. An unblinded pharmacy personnel, who was also in charge of the randomization process provided the team with the blinded infusion bag. The success of blinding was tested at the end of the study with a questionnaire given to the subjects.

RESULTS

A total of 12 patients with TRD were included in the analysis. Subjects were allowed to remain on their current medication regimens; with dosages kept the same. Benzodiazepines were held at least 12 hours before ECT. These medications included: venlafaxine, desvenlafaxine, bupropion, fluoxetine, vilazodone, levomilnacipran, duloxetine, amitriptyline, nortriptyline, paroxetine, zolpidem, dextroamphetamine, lisdexamphetamine, atomoxetine, oxcarbazepine, divaloprex, lithium, lamotrigine, quetiapine, aripiprazole, lurasidone, brexpiprazole, clonazepam, alprazolam and gabapentin.

Socio-demographic Profile

The sociodemographic profile of the sample is presented in Table 1. The mean age was 38.5 ± 18.5 years, with 83% female, 16% male.

TABLE 1

CLINICAL AND DEMOGRAPHIC INFORMATION BY GROUP

MEASURES	ECT + KETAMINE	ECT + MIDAZOLAM
	(N=7) MEAN (SD)	(N=5) MEAN (SD)
Age (years)	39 (11)	38 (15)
Hamilton Depression Rating Scale (HAMD) (17 item) Score at Baseline	23 (3)	24 (5)
Montgomery Asberg Depression Rating Scale (MADRS) at Baseline	36 (1)	34 (5)
Montreal Cognitive Assessment (MOCA) at Baseline	26 (2)	26 (2)
	N (%)	N (%)
Female	6 (85%)	4 (80%)
Caucasian	5 (71%)	4 (80%)

Treatment Response

Of the 12 subjects with TRD, 7 subjects were randomized to the ECT + ketamine arm and 5 subjects were randomized to the ECT + midazolam arm. There was no difference between the active ketamine and placebo arms in terms of change in HAMD, MADRS or Young Mania Rating ($b = 1.22$, $SE = 3.28$, $p = 0.72$). Per HAMD scores, 3 of the 7 ECT + ketamine subjects (42%) showed early response (50% decrease in HAMD scores) and remission ($HAMD < 8$) and maintained euthymia for 3 additional visits, where one ECT + midazolam patient showed early response but this effect was not sustained, therefore none of the ECT + midazolam subjects (0%) achieved early remission (Chi square P -Value = 0.0910) and they completed all 17 study visits (Figure 1).

Cognitive Testing

Per MOCA ($b = 0.98$, $SE = 1.12$, $p = 0.40$), or COWAT ($b = 3.72$, $SE = 3.71$, $p = 0.34$) scores there was no significant difference between groups. (Figure 2)

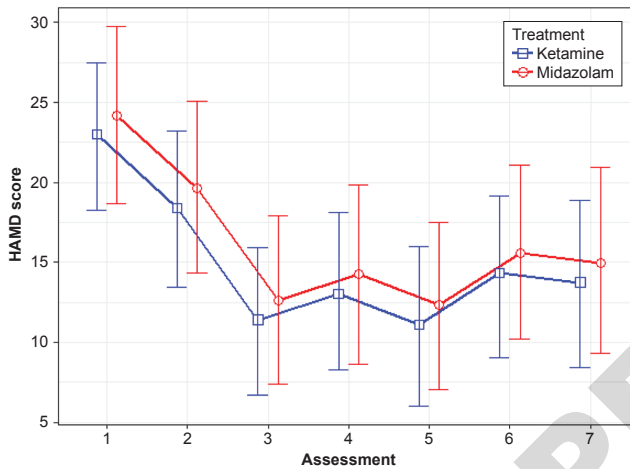
DISCUSSION

This study shows that ECT ketamine combination was not superior to ECT placebo combination in patients with TRD. To our knowledge, this is the first double-blind and placebo controlled study that combined ECT and ketamine in an interleaved fashion where patients were expected to present for the study visits every weekday for 3 weeks.

In previous studies, ketamine was used at various points of the ECT course; most studies using ketamine as an anesthetic agent or

FIGURE 1

CHANGE IN HAMD SCORE ACROSS ASSESSMENTS

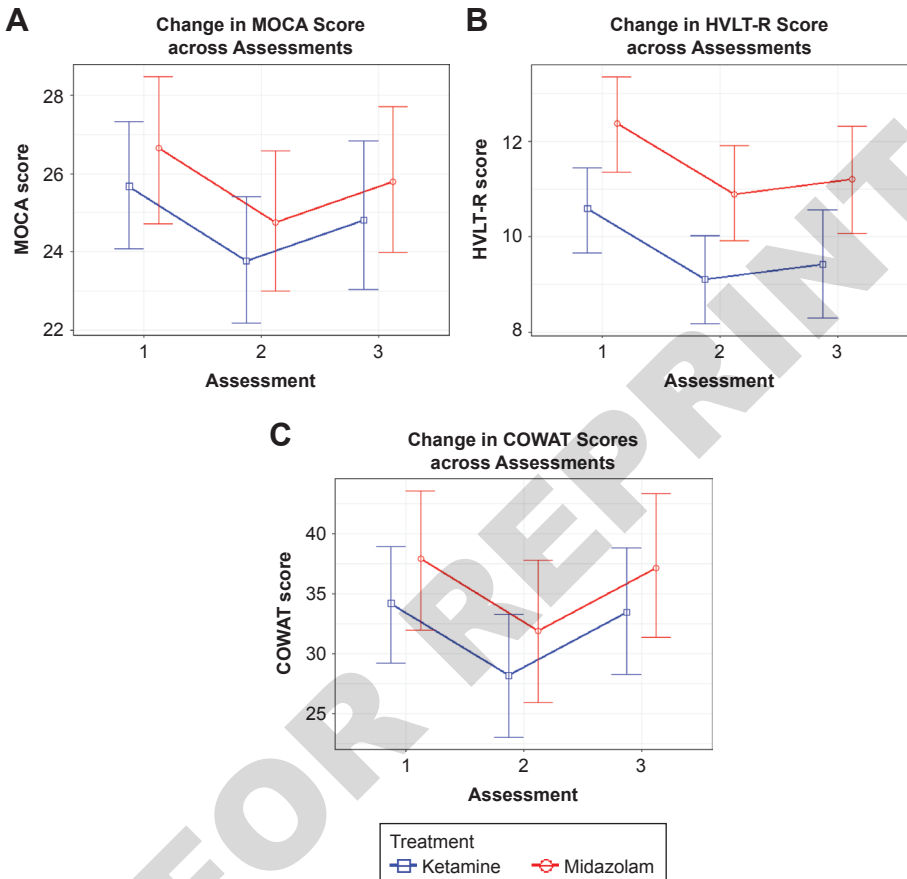


as augmentation for ECT anesthesia. Most of these studies reported negative results.^{27,28} A recent meta-analysis concluded that ketamine augmentation for ECT anesthesia did not lead to a better outcome, but accelerated the antidepressant effects of ECT.²⁹ A case report, in which a patient was given ketamine and ECT in an interleaved fashion showed a positive result, where a significant response was seen after first week (3 ECTs and 2 ketamine infusions).³⁰ Overall the results of these findings are considered to be heterogeneous and inconclusive.³¹

In our study, despite the fact that there were no statistically significant differences in response and remission rates between the two groups, one interesting finding was that 3 of 7 ECT + ketamine subjects achieved early remission where none of the 5 ECT + midazolam subjects showed early remission. This effect was not seen in the previous studies, suggesting a trend that an interleaved administration of ECT and ketamine might still have more of a synergistic effect compared to ECT and ketamine administered on the same day or compared to using ketamine as an anesthetic agent for ECT. This trend could be due to several different reasons: ECT's acute effects remaining at least 24 hours and overpowering ketamine when administered on the same day; but when administered on separate days, ECT's overpowering effect subsides and the 2 treatments act synergistically. Although not tested in this study, one other explanation for this synergistic effect could be due to ECT and ketamine having similar mechanisms of action; namely suggesting for the first time that one of the mechanisms underlying ECT's antidepressant effect could be via glutamate modulation.

FIGURE 2

CHANGE IN COGNITIVE TEST SCORES ACROSS ASSESSMENTS



Given that in this study, the ECT + midazolam combination was not inferior compared to ECT + ketamine combination, it still suggests that ECT is a very effective treatment in TRD, but this efficacy is seen later in the course of the treatment compared to ECT + ketamine combination.

CONCLUSION

Overall, the results of the study showed no difference between ketamine and placebo when added to ECT treatment. However, a trend level difference in rates of early remission was seen which suggests that addition of ketamine to ECT may lead to a faster relief of symptoms. A larger sample size is needed for statistical confirmation of ECT + ketamine being more likely to lead to early remission compared to ECT + midazolam.

LIMITATIONS

The small sample size, high female/male ratio were the main limitations in this study. Another limitation was that ketamine was given in only one dose (0.5 mg/kg). A larger study with a bigger sample size and more study arms including different ketamine dosages might be needed to drive more definite conclusions.

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