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The Rapid Antidepressant Effect of Ketamine in the Electroconvulsive Therapy Setting

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Abstract

Objectives—Studies now provide strong evidence that the NMDA receptor antagonist ketamine possesses rapidly acting antidepressant properties. This study aimed to determine if low dose ketamine could be used to expedite and augment the antidepressant effects of electroconvulsive therapy treatments in patients experiencing a severe depressive episode.

Methods—Subjects with major depressive disorder or bipolar disorder referred for ECT treatment of a major depressive episode were randomized to receive thiopental alone or thiopental plus ketamine (0.5 mg/kg) for anesthesia prior to each ECT session. Hamilton Depression Rating Scales (HDRS) were administered at baseline, and 24 – 72 h following the 1st and the 6th ECT sessions.

Results—ECT exerted a significant antidepressant effect in both groups ($F_{(2,24)} = 14.35$, $p < .001$). However, there was no significant group effect or group-by-time interaction on HDRS scores. Additionally, post-hoc analyses of the time effect on HDRS showed no significant HDRS reduction after the 1st ECT session for either group.

Conclusions—The results of this pilot study suggest that ketamine, at a dose of 0.5 mg/kg, given just prior to ECT, did not enhance the antidepressant effect of ECT. Interestingly, the results further suggest that the co-administration of ketamine with a barbiturate anesthetic and ECT may attenuate the acute antidepressant effects of NMDA antagonist.

Keywords

ECT; Ketamine; rapid; antidepressant; barbiturate

Introduction

Slightly over a decade ago, it was found that ketamine, an anesthetic agent with N-Methyl-D-aspartic acid receptor (NMDAR) antagonist properties, exerts a rapid and potent antidepressant effect in patients with severe treatment resistant depression¹. This finding

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has now been well replicated in several small pilot studies^{2–13}. The antidepressant effect exerted by ketamine in these preliminary studies is consistently evident within 4 hours of its administration, with response rates ranging between 50% and 90%, one to three days after a single injection of ketamine. This rapid antidepressant effect is in contrast to traditional monoamine-based antidepressants that take weeks to months to reach their full antidepressant effect¹⁴, with response rates in the range of 40 – 50%¹⁵. Accordingly, the newly found rapid robust antidepressant effect of ketamine has generated considerable enthusiasm in the field to integrate this valuable pharmacotherapy with other available treatment modalities in the management of severely ill patients.

Electroconvulsive therapy (ECT) is recognized as a highly effective treatment for unipolar and bipolar depression¹⁶. ECT is generally considered to have a more rapid onset of action than standard antidepressant agents, but the limited data on the onset of ECT's antidepressant action suggest that a range of 5–7 treatments (approximately 2 weeks) are required on average to obtain a significant reduction in symptom severity, varying some by position of lead placement and stimulus intensity¹⁷. Therefore, it is logical to question whether co-administration of ketamine could expedite the antidepressant response of ECT. Interestingly, ketamine has been used in ECT anesthesia for decades^{18, 19}, with preliminary evidence suggesting that ketamine anesthesia in ECT may improve seizure duration relative to other anesthetic agents that are commonly used, and to minimize side effects, particularly cognitive impairment^{20, 21}. However, there is no evidence that the direct antidepressant effects of the drug were considered as a potential benefit to the use of drug in these early studies. More recently, a prospective study comparing ketamine (.86 mg/kg) to propofol (.94 mg/kg) for ECT anesthesia showed ketamine to be associated with an earlier antidepressant response over the first 2-weeks of ECT. However, the magnitude of the antidepressant effect did not differ between the two forms of anesthesia at weeks 3 and 4²². This study showed longer seizure duration in the ketamine group during the 1st and 6th ECT session²². Another recent retrospective study noticed a decrease in the number of total ECT sessions, lower depression severity scores, and higher cognitive ratings in patients who received S-ketamine (46.7mg) anesthesia as compared to thiopental (236mg)²³.

In the current study, we sought to further investigate the potential ability of ketamine to accelerate the antidepressant effects of electroconvulsive therapy in patients suffering from a major depressive episode. Based on the doses used in the placebo controlled studies of ketamine, and the preclinical studies suggesting that low (sub-anesthetic) doses of ketamine had significantly different effects on brain physiology^{24, 25} and behavior²⁶ than anesthetic doses, we chose to specifically examine the benefit of adding a low dose of ketamine (.5 mg/kg) to a standard anesthetic dose of thiopental.

Materials and Methods

Study design

Patients aged 18–65 experiencing a major depressive episode and scheduled to receive ECT treatment, and were able to provide voluntary consent, were recruited into this study. Participants met DSM-IV criteria for a diagnosis of either major depressive disorder (MDD) or bipolar disorder (BD) currently in a major depressive episode, as determined by a structured clinical interview²⁷. All participants provided written informed consent according to the Yale University School of Medicine human investigation committee approved study protocol. Exclusion criteria included a lifetime diagnosis of primary psychotic disorder, mental retardation, dementia, or mood disorder due to general medical condition. Patients with substance dependence or serious medical conditions were also excluded. The original pilot study plan was to randomize 40 patients into two treatment groups at a ratio of 1:1. However, a midterm analysis showed no difference between

treatment groups and the study was stopped for futility. Thus, only 18 patients were enrolled into the two treatment groups.

Treatment

ECT was delivered either unilaterally or bilaterally via a SpECTrum 5000 Q (Mecta) as determined by the treating physician (RO), using the dose-titration method. In brief, seizure threshold was determined at the index treatment by gradual stimulus increase until seizure initiation was achieved. At the subsequent treatment the energy was increased by 50% for bilateral treatment and 5–6 fold for right unilateral treatment. As per our clinical protocol, energy would only be increased on subsequent treatments if there was failure to obtain adequate seizure morphology. ECT treatment was administered 3 times per week for the 2 weeks encompassing the study duration. EEG seizure duration was determined by two lead EEG and motor seizure duration was determined using the cuff method, observing foot movement.

The ketamine group ($n = 9$) received .5 mg/kg ketamine + 3.5 mg/kg thiopental I.V. push for anesthesia immediately prior to each ECT session. The control group ($n = 9$) received only thiopental (3.5 mg/kg) for anesthesia. Treatment-team members, including psychiatrists and nurses conducting the rating scales, were blinded to the treatment group –except for the anesthesiologist. Clinical assessment included Hamilton depression rating scale (HDRS₂₅)²⁸ and Beck depression inventory (BDI)²⁹. HDRS₂₅ was administered at baseline, and 24 – 72 h following the 1st and the 6th ECT sessions. BDI was administered at baseline and after the 6th ECT session. ECT measures were recorded for each session.

Statistical analysis

Prior to conducting each analysis, the distribution of outcome measures was examined using Kolmogorov-Smirnov test statistics. The Mann-Whitney U test was used for skewed distributions. Demographics and clinical measures were compared among groups using Chi square or independent t-test. General Linear Model (GLM) repeated-measures was conducted on HDRS₂₅ as the dependent variable, with time of assessment (baseline, after 1st ECT & 6th ECT) as the within-subject factor, and treatment group (Ketamine vs. control) as the between-subjects factor. Post-hoc analyses of pairwise comparisons of estimated marginal means used Bonferroni adjustment for multiple comparisons. Similar analysis was employed for BDI as the dependent variable. Average EEG and motor seizure durations across all sessions were compared among groups. Given that the duration measures were not normally distributed, Mann-Whitney U test was used to compare treatment groups (ketamine vs. control).

Results

Demographic characteristics, revealing a larger percentage of MDD subjects concomitantly using antidepressant medications in the ketamine group and larger percentage of BD subjects concomitantly using mood stabilizers in the control group but similar baseline depression severity ratings, are reported in Table 1. One patient in each group exited the study before any post-treatment follow-up. One subject in each group also exited the study prior to the 6th treatment.

Both treatment conditions were associated with symptom improvement (Table 2). GLM repeated-measures showed a strong main time effect on HDRS₂₅ ($F_{(2,24)} = 14.35, p < .001$), reflecting an antidepressant effect in both groups. Partial Eta Squared effect size was .55 (a medium sized effect). However, there was no significant difference among groups (ketamine vs. control) ($F_{(1,12)} = .09, p = .76$) or group-by-time interaction ($F_{(2,24)} = .66, p = .52$),

indicating that sub-anesthetic doses of ketamine did not enhance the antidepressant effect of ECT. Post-hoc analyses of the time effect on HDRS₂₅, using Bonferroni adjustment for multiple comparisons, showed no significant HDRS₂₅ reduction after the 1st ECT session ($p = .074$), showing no rapid antidepressant effect in both groups. The antidepressant effect in both groups only reached significance after the 6th ECT session ($p = .001$) (see Fig. 1). Similar GLM repeated-measure analysis showed main time effect on BDI ($F_{(1,12)} = 13.15$, $p = .003$). Yet, there was no treatment group (ketamine vs. control) effect ($F_{(1,12)} = .03$, $p = .85$) or treatment-by-time interaction effect ($F_{(2,24)} = 2.04$, $p = .18$).

Examining the response rate ($\geq 50\%$ reduction on HDRS₂₅) among groups, we found no responders in the ketamine group following the 1st ECT treatment. At the same time point, there was 1 (13%) responder in the control group. After the 6th ECT, we found 1 (13%) responder in the ketamine group and 3 (38%) responders in the control. Chi-Square test, conducted at both time points, showed no statistically significant difference in response rate between groups ($p > .20$). GLM analyses were repeated while including diagnosis (MDD vs. bipolar depression) and ECT lead placement (unilateral vs. bilateral). These analyses showed similar findings of significant antidepressant effect ($p < .001$), but no effect for groups ($p > .6$), diagnosis ($p > .3$), ECT lead placement ($p > .8$), or interaction ($p > .5$). Significance was not changed when medication status was included in the model (data not shown).

EEG and motor seizure durations are reported in Table 3. There is a suggestion that ketamine augmentation may be associated with an increased duration of motor seizure and a weak trend toward EEG seizure duration lengthening. No major adverse effects were observed in this cohort during the 2 weeks of ECT treatment. Minimal transient side effects reported by both groups included nausea, headaches, disorientation, and muscle pain.

Discussion

Although this by no means can be considered a definitive study, we found no evidence suggesting ketamine at .5 mg/kg administered with thiopental anesthesia for ECT facilitated a more rapid antidepressant response. There were no statistically significant or clinically meaningful differences in depression severity scores or likelihood of response between the ketamine and control groups after the first and 6th ECT treatments. In fact, the control (thiopental only) group showed a slightly greater numerical reduction in depression severity ratings at both time points. It is difficult to draw any firm conclusions regarding the differences between the two treatment groups from this small study as there were potentially important differences in the breakdown of diagnoses and concomitant medications between the two groups, in addition to the varied lead placement. However, considering the existing study protocol design for this study, we determined that it was futile to continue this preliminary study.

Perhaps the most interesting finding to come from this study was the fact that within the ketamine group, we did not observe the robust rapid antidepressant response that has been reported in several previous studies. The current study found no subjects to meet response criteria one day following ketamine administration. This is in stark contrast to the highly consistent reports of 50–90% response rates in the days immediately following a single dose of 0.5 mg/kg ketamine^{1, 2, 4, 5, 9, 30}. There are several factors that may account for this surprising result. First, it is possible that this study, selectively enrolling subjects recommended for ECT, included a more severe and treatment resistant cohort of subjects. However, considering the level of subject severity and treatment resistance reported in the previous studies^{1, 4}, and the finding that ECT non-response did not have a major impact on ketamine treatment outcome⁷, this does not seem a likely explanation. Second, it is possible

that the change in the mode of administration (given IV push instead of IV infusion) altered the antidepressant efficacy of the treatment. Again however, there is evidence from at least one open-label study³⁰ suggesting that an IV push, albeit 0.25 mg/kg, was highly effective in producing the rapid antidepressant response. Skeptics of the rapid antidepressant properties of ketamine may suggest a third option; since ketamine was co-administered with an anesthetic agent, both the researchers and the subjects were truly blinded to the treatment. However, there is evidence from Kudoh et al. study showing that ketamine co-administered with fentanyl and propofol anesthesia for orthopedic surgery still appeared to have potent rapid antidepressant-like properties³¹. A fourth potential explanation for the discrepant findings is that the ECT treatment itself blocked or attenuated the antidepressant effects of ketamine. Although studies by Okamoto and Kranaster, where ketamine was used as the sole anesthetic agent, did suggest some added effects of ketamine on mood^{22, 23}. However, intriguingly, the literature remains devoid of any report of rapid (within 1–3 days) and potent (response rate 50–90%) antidepressant effect following the use of ketamine in ECT. One case-report noticed a rapid antidepressant effect following the administration of intramuscular ketamine (1.5 mg/kg) and one ECT session in a patient with major depression³². However, ketamine was injected one hour prior to ECT in this study, raising the question if ketamine already exerted its antidepressant effect before the ECT session.

An additional possible explanation for the failure to see the rapid ketamine-induced antidepressant effect in this study is the fact that ketamine was co-administered with thiopental, a barbiturate anesthetic agent. It is conceivable that the thiopental effects interfere with ketamine's mechanism of antidepressant action. Barbiturates are believed to exert their main physiological effect by potentiating the effects of γ -Aminobutyric acid (GABA) at the GABA_A receptor through their affinity for the alpha subunit of the receptor³³. In addition to this GABAergic effect, barbiturates have also been shown to block the signaling through the AMPA subtype of glutamate receptor³⁴. Considering these effects of thiopental on GABAergic and glutamatergic neurotransmission, it is possible that it may have resulted in an attenuation of ketamine's antidepressant effects. Several recent preclinical studies have demonstrated the necessity of a "glutamate surge" and the accompanying AMPA activation in generating the antidepressant-like response of ketamine and other NMDA antagonists^{26, 35, 36}. It is hypothesized that ketamine increases glutamate release by selectively inhibiting GABAergic neurons and thus removing the inhibition on pyramidal neurons in the cortex³⁷. So either the inhibition of glutamate release via activation of GABA_A receptors by thiopental or the direct inhibition of AMPA receptors by thiopental may have antagonized the antidepressant effect of ketamine when administered concomitantly. The other two recent studies examining the use of ketamine anesthesia in the ECT setting did not co-administer an additional anesthetic with the treatment^{22, 23}. The Kudoh study, examining the effects of sub-anesthetic ketamine combined with an anesthetic cocktail, used propofol and fentanyl and not a barbiturate anesthetic³¹.

Lastly, the finding of increased motor seizure duration and possible increase in seizure duration is of some clinical interest. There has been speculation that ketamine is clinically useful in subjects with high seizure thresholds^{38, 39}. Preclinical studies have shown ketamine to be associated with increased seizure duration⁴⁰. However, the literature in humans is mixed with regards to the effect of ketamine on seizure duration⁴¹. In our study, adding a low dose (.5 mg/kg) of ketamine to thiopental we do see some evidence suggesting an effect on seizure duration. However, considering the difference in concomitant medications used by the two groups this needs to be confirmed.

In summary, although the literature provides very strong evidence of ketamine's rapid and robust antidepressant effects in severely depressed patients, these preliminary findings failed to support the hypothesis that low doses of ketamine (.5 mg/kg), in addition to thiopental

anesthesia, can expedite and enhance the rapid antidepressant effects of ECT. In fact, ECT setting appears to attenuate the rapid antidepressant effect of ketamine. These findings, that appear to be somewhat at odds with existing case reports suggesting ketamine anesthesia may hasten the ECT response, may be explained in part by the fact that ketamine was co-administered with a barbiturate anesthetic agent in this study. It is quite possible that different doses, timing and routes of ketamine administration may produce different findings. Additionally, the sole use of ketamine as the anesthetic agent or with a different class of co-administered anesthetic could also have different effects on the treatment response. Future studies investigating the potential benefits of ketamine augmentation to ECT should consider the effects of ketamine dose, timing and concomitant medications in the study design.

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Figure 1. Hamilton Depression Rating Scale Improvement Over the Treatment Period

The antidepressant effect of ECT was significant over the treatment period in both groups. However, there was no group effect (ketamine vs. control) or group-by-time interaction. Moreover, the rapid antidepressant effect, up to 90% response rate in the literature, after a single administration of subanesthetic dose of ketamine was attenuated in the ECT setting.

Table 1

Demographics and Clinical Data

	Ketamine Group (n = 8)	Control Group (n = 8)	
	Mean $\pm$ SEM	Mean $\pm$ SEM	Sig. ^a
Age	47.8 $\pm$ 5.0	46.5 $\pm$ 3.3	.83
Female (N; %)	3 (37%)	4 (50%)	.61
MDD (N; %)	7 (87%)	3 (37%)	.04
Bilateral ECT (N; %)	6 (75%)	7 (87%)	.52
Medications:			
Antidepressant ^b	6 (75%)	2 (25%)	.05
Mood stabilizer ^c	2 (25%)	6 (75%)	.05
Antipsychotic ^d	4 (50%)	3 (37%)	.61
Sedative ^e	2 (25%)	5 (62%)	.13
Other ^f	3 (37%)	4 (50%)	.61
HDRS at baseline	35.3 $\pm$ 2.5	38.3 $\pm$ 2.1	.38
BDI at baseline	28.3 $\pm$ 2.4	34.4 $\pm$ 3.0	.13

^aIndependent t-test or Chi square test (2-tailed, significance set at $p = .05$);

^bAntidepressants: Fluoxetine, Paroxetine, Citalopram, Duloxetine, Venlafaxine, Bupropion;

^cMood stabilizers: Lithium, Valproic acid, Lamotrigine;

^dAntipsychotics: Aripiprazole, Quetiapine, Risperidone;

^eSedatives: Trazodone, Lorazepam, clonazepam;

^fOthers: Benzotropine, Synthroid, Liothyronine, Methylphenidate.

Abbreviations: MDD: Major Depressive Disorder; SEM: Standard Error of Mean; ECT: Electroconvulsive Therapy; HDRS: Hamilton Depression Rating Scale; BDI: Beck Depression Inventory.

Table 2

Clinical Outcomes

	Ketamine Group (n = 8)	Control Group (n = 8)	
	Mean $\pm$ SEM	Mean $\pm$ SEM	Sig.^a
HDRS at baseline	35.3 $\pm$ 2.5	38.3 $\pm$ 2.1	.38
HDRS post 1st ECT	30.6 $\pm$ 3.0	32.1 $\pm$ 4.0	.77
HDRS post 6th ECT (n = 7)	22.9 $\pm$ 4.7	20.4 $\pm$ 4.2	.71
BDI at baseline	28.3 $\pm$ 2.4	34.4 $\pm$ 3.0	.13
BDI post 6th ECT (n = 7)	19.1 $\pm$ 4.8	14.3 $\pm$ 4.2	.46

^aIndependent t-test (2-tailed, significance set at $p = .05$);

Abbreviations: ECT: Electroconvulsive Therapy; SEM: Standard Error of Mean; HDRS: Hamilton Depression Rating Scale; BDI: Beck Depression Inventory.

Table 3

Seizure and Convulsion Durations

	Ketamine Group		Control Group		N	Sig. ^a
	Mean	± SEM	Mean	± SEM		
Seizure Duration (s)	57.3	± 5.4	43.9	± 2.7	79	.29
Convulsion Duration (s)	41.4	± 3.6	30.3	± 1.5	79	.036

^aMann-Whitney U (2-tailed); SEM: Std. Error Mean; Bold: Statistically significant *p* value (*p* .05);