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# Rapid antidepressant effects of repeated doses of ketamine compared with electroconvulsive therapy in hospitalized patients with major depressive disorder

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## ABSTRACT

Accumulating evidence suggests that *N*-methyl-D-aspartate receptor (NMDAR) antagonists (e.g. ketamine) may exert rapid antidepressant effects in MDD patients. In the present study, we evaluated the rapid antidepressant effects of ketamine compared with the electroconvulsive therapy (ECT) in hospitalized patients with MDD. In this blind, randomized study, 18 patients with DSM-IV MDD were divided into two groups which received either three intravenous infusions of ketamine hydrochloride (0.5 mg/kg over 45 min) or ECT on 3 test days (every 48 h). The primary outcome measure was the Beck Depression Inventory (BDI) and Hamilton Depression Rating Scale (HDRS), which was used to rate overall depressive symptoms at baseline, 24 h after each treatment, 72 h and one week after the last (third) ketamine or ECT. Within 24 h, depressive symptoms significantly improved in subjects receiving the first dose of ketamine compared with ECT group. Compared to baseline level, this improvement remained significant throughout the study. Depressive symptoms after the second dose ketamine was also lower than the second ECT. This study showed that ketamine is as effective as ECT in improving depressive symptoms in MDD patients and have more rapid antidepressant effects compared with the ECT.

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## 1. Introduction

Major depressive disorder (MDD) is a severe, heterogeneous, and common medical illness which is associated with enormous morbidity and public health costs. Cost of illness estimates for depression in the USA varies between \$12.4 billion per year for direct treatment costs (28% of total societal costs) and \$4 billion per year for the consequences of not treating depression (Patel, 2008). With depression set to become the second largest cause of disability worldwide by 2020, it is important to examine carefully the cost-effectiveness of any new treatment. Although over the past half century the biogenic amine models have provided meaningful links with the clinical phenomena of, and the

pharmacological treatments currently employed in, mood disorders, there is still a need to examine the contribution of other systems to the neurobiology and treatment of mood disorders (Berman et al., 1996; Delgado, 2000). This need stems from the fact that monoamine depletion paradigms, for example, failed to find a “final common pathway” for antidepressant efficacy. Current treatments for MDD are only partially effective in many cases and, in some cases, not at all effective. For instance, a large study on 3671 outpatients with MDD demonstrated that only 36% of MDD patients achieved remission following optimized trial of the serotonin selective reuptake inhibitor citalopram for up to 12 weeks (Rush et al., 2006). Furthermore, remission in half of the patients often occurs after 6 months of treatment with two antidepressant trials (Trivedi et al., 2006). Emerging from previous studies is a rapidly changing picture that may provide an entirely new set of potential therapeutic targets. Accumulating data in recent years have demonstrated that the excitatory glutamatergic/NMDA (*N*-methyl-D-aspartate) receptor signaling may play a pivotal role in the pathophysiology of MDD. This hypothesis has

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arisen from many observations by many investigators worldwide. Among NMDA receptor antagonists, ketamine has been investigated in both clinical and pre-clinical studies on mood disorders (for review see Ghasemi, 2013). Both clinical and pre-clinical data have robustly shown that ketamine could exert antidepressant effects and could be a promising drug for rapid improvement of major depression, especially in treatment-resistant MDD patients.

Electroconvulsive therapy (ECT) is recognized as a highly beneficial treatment of unipolar and bipolar depression (Kellner et al., 2012). ECT has generally a more rapid onset of action than conventional antidepressants do, 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 cause a significant reduction in symptom severity, varying some by position of lead placement and stimulus intensity (Nobler et al., 1997; Kellner et al., 2012). On the other hand, the antidepressant effect exerted by ketamine in previous preliminary studies is consistently observed within the first few hours of its administration, with response rates ranging from 50% to 90%, 1–3 days after a single injection of ketamine (Aan Het Rot et al., 2012; Ghasemi, 2013). This rapid antidepressant effect is also in contrast to traditional monoamine-based antidepressants that take weeks to months to reach their full antidepressant effect (Katz et al., 2004), with response rates between 40% and 50% (Trivedi et al., 2006). A prospective study (Okamoto et al., 2010) comparing ketamine (0.86 mg/kg) to propofol (0.94 mg/kg) for ECT anesthesia also demonstrated that ketamine is associated with an earlier antidepressant response during the first 2 weeks of ECT. Although these data has suggested that ketamine can potentiate antidepressant effects of ECT in MDD, the fact that whether ketamine is as effective as ECT in MDD needs to be further investigated. Therefore, the aim of the present study was to investigate the antidepressant effects of ketamine in comparison with ECT in hospitalized MDD patients experiencing a major depressive episode.

## 2. Materials and methods

### 2.1. Subjects

Patients aged 18–75 years 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 criteria for a diagnosis of major depressive disorder (MDD), currently in a major depressive episode, according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV), as determined by a structured clinical interview (First et al., 1995). All participants provided written informed consent according to the Tehran University of Medical Sciences' human investigation committee approved study protocol. Exclusion criteria were a lifetime diagnosis of primary psychotic disorder, manic or hypomanic episode, mental retardation, dementia, or mood disorder due to general medical condition. Patients with substance dependence or serious medical conditions were also excluded. Based on these criteria, 18 patients with DSM-IV MDD without psychotic features were enrolled in the study. Patients were randomly assigned either to the ECT group (nine patients) or the ketamine group (nine patients).

### 2.2. Treatment

In the ECT group, patients underwent three ECT sessions every 48 h. They received bilateral ECT using ThymatronDGx (Somatics INC). All ECT procedures were performed between 7:30 and 9 A.M at Roozbeh hospital. Patients were fasting for at least 8 h before ECT procedure. During each ECT procedure, patients were administered 0.5 mg atropine followed by 2–3 mg/kg thiopental intravenously (IV); succinylcholine (0.5 mg/kg) was administered as a muscle relaxant after the induction of anesthesia. The stimulus intensity was determined by a dose titration procedure (starting at 25.2 mC) and seizure threshold was identified in the first session (Haghighi et al., 2013). Then, electrical dose was determined by multiplying seizure threshold dose by 2.5 in the following sessions. Seizure duration (tonic and clonic) was recorded by isolation of one leg by inflation of cuff over 240 mmHg to assess quality of seizure. If seizure duration were less than 15 s (aborted seizure),

electrical dose would be increased by 50%. Patients' ventilation was supported using 100% oxygen by a bag and mask until resumption of patients' breath. Electrocardiogram, arterial oxygen saturation (pulse oximetry), noninvasive blood pressure and heart rate of the patients were monitored continuously during the procedure.

The ketamine group ( $n=9$ ) and ECT group ( $n=9$ ) received three infusions of ketamine hydrochloride (0.5 mg/kg, IV, over 45 min) and ECT on 3 test days (every 48 h), respectively. Treatment team members, including physicians and psychologists conducting the rating scales, were blinded to the treatment group except for the anesthesiologist (A.Y.). Clinical assessment was performed using the Hamilton Depression Rating Scale (HDRS<sub>25</sub>) and the Beck Depression Inventory (BDI). The HDRS<sub>25</sub> and BDI was administered to rate overall depressive symptoms at baseline, 24 h after each treatment, 72 h and one week after the last (third) ketamine or ECT session.

### 2.3. Self report of depressive symptoms: Beck Depression Inventory (BDI)

Patients completed the BDI (Beck, 1961) to self-report depressive symptoms. BDI is a 21-question multiple-choice self-report inventory which is composed of items relating to symptoms of depression (e.g. hopelessness and irritability), cognitions (e.g. guilt or feelings of being punished), as well as physical symptoms (e.g. fatigue, weight loss, and lack of interest in sex). When the test is scored, a value of 0–3 is assigned for each answer and then the total score is compared to a key to determine the depression's severity. Higher total scores indicate more severe depressive symptoms.

### 2.4. Experts' ratings of depressive symptoms: Hamilton Depression Rating Scale-25 (HDRS<sub>25</sub>)

Independent physicians and psychologists assessed patients' depression severity with the HDRS (Hamilton, 1960). The 25-item questionnaire evaluates symptoms related to depression (e.g. low mood, suicidality, irritability, tension, loss of appetite, loss of interests, and somatic symptoms). When the test is scored, a value of 0–5 is assigned for each answer, with higher total scores reflecting more marked depressive symptoms.

### 2.5. Statistical analysis

A mixed-design analysis of variance model was employed to test for differences between groups for six repeated measures. Evaluation session was a within subjects factor and treatment group was a between-subjects factor; the interaction between treatment group and evaluation time was included in the model. The violation of equality of covariance matrices and violation of sphericity assumption was verified. Due to the violation of Mauchly's test for sphericity, significance levels and partial Eta squared effect size of each factor and their interaction was estimated using Greenhouse–Geisser correction. Once the effect of treatment group was established the independent *t*-test was used to mark out the session by session difference in depression scores with Cohen's *d*. All analyses used two-tailed significance criteria of  $P < 0.05$  and were performed with IBM SPSS 19.

## 3. Results

### 3.1. Patients

Eighteen patients diagnosed with major depression were randomized in two groups. Demographic features and baseline depression scores, as well as medication used during and before the current major depressive episode, are summarized in Tables 1 and 2. Patients' age was ranged between 20 and 74 years with a mean of 37.6 years (S.D.=15.05). Ten patients in both groups were female (56%). Patients received their first target treatment an average of 12.94 (S.D.=10.2) days after entering the hospital. Nine (50%) patients were randomized in ketamine group and other 9 (50%) received the ECT. Comparison of demographic features and baseline depression scores did not show a significant difference between two groups.

### 3.2. Efficacy

After Greenhouse–Geisser correction the linear mixed model showed a significant improvement in depression scores evaluated by BDI ( $F_{5,80}=50.56$ ,  $P < 0.001$ ) and HDRS ( $F_{5,80}=73.7$ ,  $P < 0.001$ )

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