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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.

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 ThymatroneDGx (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 oximetery), 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 ($HDRS_{25}$) and the Beck Depression Inventory (BDI). The $HDRS_{25}$ 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 ($HDRS_{25}$)

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 ($F_{5,80}=73.7$, $P<0.001$)

Table 1
Demographic and illness characteristics for patients receiving ketamine and ECT.

Demographics	ECT group ($n=9$)		Ketamine group ($n=9$)		x^2	P
	N	%	*N*	%		
Gender (male)	4	44.4	4	44.4	0	1
Marital status					0.23	0.62
Single	2	22.2	2	22.2		
Married	6	66.7	5	55.6		
Divorced	0	0	2	22.2		
Widowed	1	11.1	0	0		
Additional DSM-IV diagnoses						
Anxiety disorder (OCD, GAD)	2	22.2	3	33.3	0.27	0.59
Addiction	1	11.1	0	0	1.06	0.3
Bipolar disorder	1	11.1	0	0	1.06	0.3
Personality disorder	3	33.3	1	11.1	0.32	0.57
	Mean	S.D.	Mean	S.D.	*t*	*P*
Age (years)	40	16.41	35.22	13.63	0.67	0.51
Education (years)	8	4.33	10.33	3.31	1.28	0.21
Age of onset (years)	30.78	17.51	28.11	9.67	0.39	0.69
Length of current episode before admission (weeks)	9.22	10.97	8.77	8.91	0.09	0.92
Time in hospital before study start (days)	13.44	10.76	12.44	9.64	0.2	0.83
Total number of hospitalizations	2.44	1.59	1.67	1.32	1.12	0.27
Number of suicidal attempts	1.33	1.66	0.77	1.48	0.74	0.46
Clinical scale ratings at baseline						
BDI score	42.44	9.53	34.66	10.7	1.63	0.12
HDRS score	35.88	6.47	30.22	5.78	1.96	0.07

BDI: Beck Depression Inventory; GAD: generalized anxiety disorder; HDRS: Hamilton Depression Rating Scale; OCD: obsessive compulsive disorder.

over time. The comparison of two treatment groups shows a significant difference for both BDI scores ($F_{1,78}=6.67$, $P<0.02$) and HDRS scores ($F_{1,78}=12.2$, $P<0.01$) throughout all six sessions. However, after correction, the interaction between time and treatment group were only significant for HDRS scores ($F_{5,80}=4.80$, $P<0.02$) while in the case of BDI results are slightly higher than significance level ($F_{5,80}=2.74$, $P<0.075$). which can be explained by the slight different BDI scores at the baseline in two groups. Figs. 1 and 2 summarize the results provided by mixed model comparison.

Post hoc session by session comparison using *t* tests indicated significantly fewer BDI and HDRS scores in patients who received ketamine versus those who received ECT at the first treatment, the second treatment and 72 h post-treatment. The effect sizes were moderate to large at the first treatment, the second treatment and 72 h post-treatment. The biggest effect size was observed at the first ketamine infusion (Table 3).The biggest non-significant difference between the two treatment groups was at treatment session 3, indicating lower HDRS scores in the ketamine group.

From within group point of view both BDI and HDRS scores were significantly lower than baseline from session one through one week post-treatment for both groups. A single infusion of ketamine reduced scores of the BDI by an average of 14.44 points (S.E.M.=2.36, $P<0.001$), as well as scores of the HDRS by an average of 13.33 points (S.E.M.=2.68, $P<0.001$). The first infusion of Ketamine led to 42% reduction in depressive symptoms comparing to baseline, as well as reduction of more than half of depressive symptoms in the case of 44% of participants.

In the same way depression scores reduced after the first ECT, however results show a lower depression reduction compared with ketamine group; BDI scores reduced after the first ECT by an average of 5.59 points (S.E.M.=1.65, $P<0.01$), as well as scores of the HDRS by an average of 4.44 points (S.E.M.=1.12, $P<0.005$). Compared to baseline, 12% of depressive symptoms were reduced after the first ECT. Depressive symptoms were lowered by half for 11% of participants. See Tables 3 and 4.

Table 2
Medication use during current major depressive episode and lifetime (before admission) in patients receiving ketamine and ECT.

Medication	ECT group ($n=9$)				Ketamine group ($n=9$)			
	Current		Lifetime		Current		Lifetime	
	N	%	*N*	%	*N*	%	*N*	%
Lithium	0	0	0	0	1	11.1	1	11.1
Antidepressants								
SSRIs	7	77.8	5	55.5	5	55.5	4	44.4
TCAs	4	44.4	2	22.2	2	22.2	1	11.1
Trazodone	1	11.1	0	0	2	22.2	0	0
Antipsychotics								
Olanzapine	2	22.2	0	0	1	11.1	0	0
Risperidone	2	22.2	2	22.2	0	0	1	11.1
Anticonvulsants								
Lamotrigine	1	11.1	1	11.1	0	0	0	0
Valproate	1	11.1	0	0	0	0	0	0
Carbamazepine	1	11.1	0	0	1	11.1	1	11.1
Benzodiazepines	4	44.4	5	55.5	7	77.8	2	22.2

Both ketamine treatment and ECT were well tolerated in all patients. Overall, there was no significant change in hemodynamic parameters including heart rate and blood pressure in both groups. There was only increase in systolic blood pressure as well as heart rate in three patients after the second and the third dose of ketamine which was temporary and this rise was not clinically significant. In the ECT group, the hemodynamic parameters were not significantly altered.

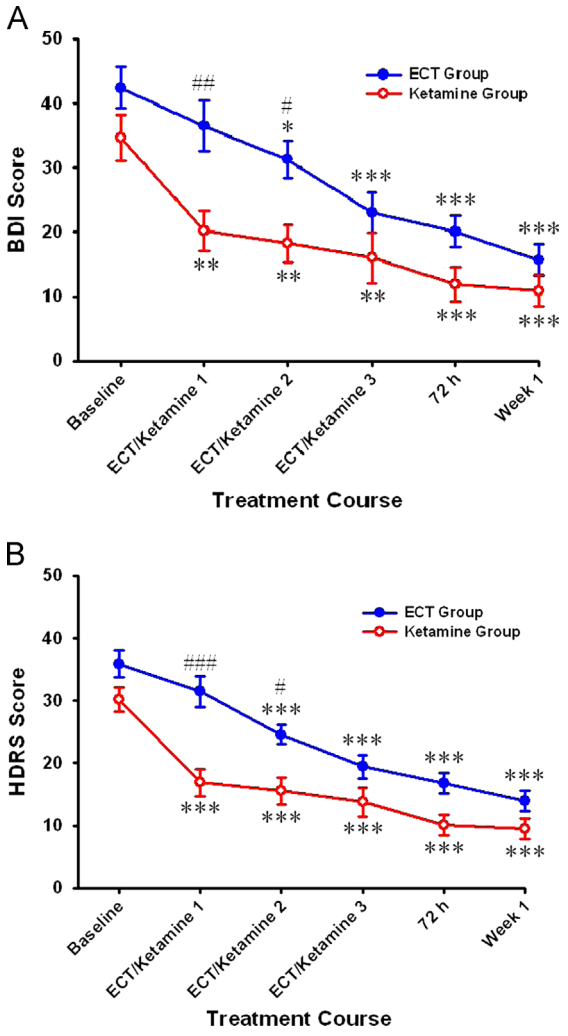

Fig. 1. BDI and HDRS scores at baseline, 24 h after the first, the second and the third ECT or ketamine injection, 72 h and one week after the last (third) ECT or ketamine injection in MDD patients. $^{*}P < 0.05$ and $^{***}P < 0.001$ compared with the baseline score in the same group. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, and $^{\#\#\#}P < 0.001$ compared with the corresponding group in the ketamine group. Each group consisted of nine patients.

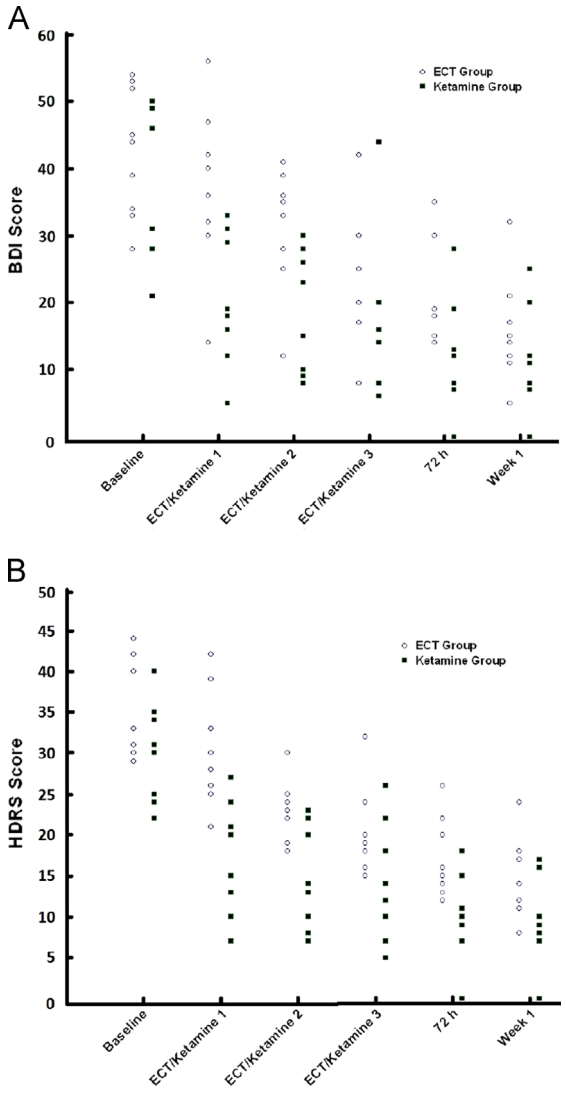

Fig. 2. Dot plot representation of BDI and HDRS scores at baseline, 24 h after the first, the second and the third ECT or ketamine injection, 72 h and one week after the last (third) ECT or ketamine injection in MDD patients.

4. Discussion

In the present study we found that repeated treatment with low doses of ketamine (0.5 mg/kg, three times) as well as ECT can exert rapid antidepressant effects in patients with MDD. The antidepressant effects of ketamine also remained 72 h and 1 week after the last (third) injection of ketamine as measured by BDI and HDRS. Further analysis interestingly indicated significantly less depressive symptoms in patients who received ketamine versus those who received ECT at the first treatment, the second treatment and 72 h post-treatment. These data suggest that antidepressant effects of ketamine are more rapid and effective than ECT in the early stages of treatment.

Ketamine is an NMDA receptor antagonist with slow open-channel blocking/unblocking kinetics, and a specific type of channel closure, called “trapping block” (Machado-Vieira et al., 2009a; Ghasemi and Schachter, 2011). Although the first preclinical evidence of antidepressant effects of NMDA receptor antagonists was reported by Trullas and Skolnick in 1990 (Trullas and Skolnick, 1990), a decade later the first evidence of clinically rapid antidepressant effects of ketamine was obtained by a group of investigators in the inpatient research unit setting at Yale University School of Medicine (Berman et al., 2000). They found significant improvement in depressive symptoms within 72 h after ketamine infusion (0.5 mg/kg, IV, over 40 min) in eight treatment-resistant MDD patients. Ketamine decreased $HRSD_{25}$ scores within 4 h. Further reductions in $HRSD_{25}$ scores were observed at 24, 48 and 72 h post-infusion, and persisted in some patients beyond 72 h. Half of the patients showed a 50% or greater reduction in $HRSD_{25}$ scores at 72 h post-infusion. Depression severity returned to baseline levels several days to 1 week following ketamine infusion (Berman et al., 2000). Ketamine appeared to directly improve the core symptoms of depression which include sad mood, helplessness, worthlessness and suicidality, rather than inducing a nonspecific mood-elevating effect (Berman et al., 2000; Mathew et al., 2012). The second study in 2006 was a larger randomized double-blind placebo-controlled crossover study on 18 inpatients by an investigative team based at the U.S. NIMH Intramural Research Program (Zarate et al., 2006). A single dose of ketamine (0.5 mg/kg over 40 min) rapidly and significantly improved depressive symptoms in treatment-resistant MDD inpatients within 110 minutes and this effect remained significant for one week. More than 70% of patients met the criteria for response (50% improvement), 29% met remission criteria at 24 h after

Table 3
BDI and HDRS scores at baseline, 24 h after the first, the second and the third ECT or ketamine injection, 72 h and one week after the last (third) ECT or ketamine injection in MDD patients. Each group consisted of nine patients.

Treatment course	ECT group ($n=9$)		Ketamine group ($n=9$)		T	P	Cohen's d	95% CI	
	Mean	S.D.	Mean	S.D.					
BDI score									
Baseline	42.44	9.53	34.66	10.7	1.63	0.123	0.814	1.19	0.14
First treatment	36.5	11.84	20.22	9.23	3.26	0.005	1.627	2.06	0.90
Second treatment	31.3	8.79	18.22	8.63	3.19	0.006	1.593	2.02	0.87
Third treatment	23	9.39	16	11.79	1.39	0.182	0.697	1.06	0.03
72 h post-treatment	20.11	7.37	11.88	8.03	2.26	0.038	1.133	1.52	0.44
One week post-treatment	15.66	7.51	10.88	7.49	1.35	0.196	0.676	1.04	0.01
HDRS score									
Baseline	35.88	6.47	30.22	5.78	1.96	0.068	0.978	1.36	0.30
First treatment	31.44	7.26	16.88	6.58	4.45	0.000	2.229	2.72	1.44
Second treatment	24.55	4.64	15.55	6.54	3.37	0.004	1.683	2.12	0.95
Third treatment	19.44	5.25	13.77	6.98	1.9	0.074	0.974	1.35	0.29
72 h post-treatment	16.77	4.81	10.11	5.01	2.88	0.011	1.438	1.85	0.73
One week post-treatment	14	4.9	9.55	4.98	1.91	0.074	0.955	1.34	0.28

Table 4
Percentage of reduction in HDRS and BDI scores after each treatment, and proportion of patients in each group with 50% reduction in scores comparing to baseline.

Treatment course	ECT group		Ketamine group	
	Percentage of reduction in depressive symptoms after each treatment	Percentage of patients with more than 50% reduction in depressive symptoms compared to baseline	Percentage of reduction in depressive symptoms after each treatment	Percentage of patients with more than 50% reduction in depressive symptoms compared to baseline
BDI score				
First treatment	11.06	11.11	42.69	44.44
Second treatment	12.25	11.11	1.74	55.56
Third treatment	26.58	44.44	9.15	77.78
72 h post-treatment	17.04	44.44	16.69	77.78
One week post-treatment	25.76	77.78	6.59	77.78
HDRS score				
First treatment	14.30	11.11	41.97	77.78
Second treatment	20.68	22.22	5.51	77.78
Third treatment	20.76	66.67	3.37	88.89
72 h post-treatment	13.07	88.89	17.40	100.00
One week post-treatment	19.25	88.89	5.66	100.00

infusion, and 35% showed a sustained response after one week; two of these maintained response at least two weeks (Zarate et al., 2006). Our data also demonstrated that first dose of ketamine could significantly exert rapid antidepressant effects as measured by both BDI and HDRS 24 h post-infusion. This effect of ketamine has been similarly observed in another cohort involving 26 treatment-resistant MDD patients (Phelps et al., 2009). Open-label ketamine treatment (0.5 mg/kg, IV, single dose over 40 min) improved depressive symptoms within 230 min (Phelps et al., 2009). Two other studies on 26 (Price et al., 2009) and 23 (Machado-Vieira et al., 2009b) patients with treatment-resistant MDD also demonstrated that single dose ketamine is capable of reducing depressive symptoms shortly at 40 min post-infusion. Other studies have consistently reported that ketamine is beneficial in treatment-resistant MDD patients (Denk et al., 2011; Ibrahim et al., 2011; Murrough et al., 2011), MDD patients with concurrent pain syndrome (Correll and Futter, 2006), depressed patients in pre- and post-operative states (Kudoh et al., 2002; Goforth and Holsinger, 2007), and in treatment-resistant MDD comorbid with alcohol dependence and pain syndrome (Liebrenz et al., 2007).

We also found that repeated-dose ketamine caused a significant reduction in depressive symptoms and the improvement in depressive symptoms remained even one week after the last (third) injection of ketamine. This rapid antidepressant effect is in contrast to traditional monoamine-based antidepressants that take weeks to months to exert their full antidepressant effect (Katz et al., 2004), with response rates between 40% and 50% (Trivedi et al., 2006). Some investigators have suggested repeated-dose ketamine as a potential antidepressant continuation strategy for patients who show initial response to ketamine infusion. For instance a group of researchers in Mount Sinai School of Medicine used repeated-dose open-label ketamine (6 infusions over 12 days) in 10 medication-free treatment-resistant MDD patients (Aan Het Rot et al., 2010). On day one, patients received a single dose of ketamine (0.5 mg/kg, IV over 40 min) in an inpatient setting with continuous vital-sign monitoring. If patients showed more that 50% decrease in depressive symptoms on the next day, they received five additional infusions on an outpatient basis 3 times per week. Following the sixth infusion, follow-up visits were conducted twice weekly for 4 weeks or until relapse. Ninety percent (nine) of patients met the response criterion after the first infusion, and all of these patients continued their response throughout the 2-week period. There was an 85% mean reduction in depressive symptoms following six infusions. The mean relapse time was 19 days after the final ketamine infusion (Aan Het Rot et al., 2010). Further investigation showed that the time until relapse is varying between 6 days to greater than 3 months (Aan Het Rot et al., 2010; Murrough et al., 2011). A trial on a patient with treatment-resistant MDD and dysthymic disorder for 18 years also

showed that intramuscular (IM) injection of 6 doses of ketamine (1 mg/kg) at intervals of 7–8 days caused a significant improvement in depressive symptoms at 1 h post-injection which continued for 6–7 days (Zanicotti et al., 2012). In another study, a treatment-refractory MDD patient was treated with 6 doses of ketamine (0.5 mg/kg, IV, days 1, 3, 5, 8, 11 and 13) and his depressive symptoms were improved significantly within 13 days and persisted for 3 months (Murrough et al., 2011). These data together with our data suggest that repeated doses of ketamine could also be effective in improving depressive symptoms in depressed patients.

It is well established that ECT is a highly effective treatment for both unipolar and bipolar depression (Dierckx et al., 2012; Kellner et al., 2012). ECT can generally improve depressive symptoms more rapidly than conventional antidepressants. However, 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 significantly or perhaps completely reduce symptom severity (Nobler et al., 1997; Kellner et al., 2012). In the present study, we compared the antidepressant effects of ketamine to ECT in MDD patients who were scheduled for ECT. Our data showed that although both ECT and ketamine are capable of reducing depressive symptoms in both groups, ketamine has more rapid onset of action and more effectiveness in improvement of symptoms. Our results demonstrated significantly fewer BDI and HDRS scores in patients who received ketamine versus those who received ECT at the first treatment, the second treatment and 72 h post-treatment. The biggest effect size was observed at the first ketamine infusion. There are scarce data regarding the comparison between ECT and ketamine treatment in previous studies. These studies mostly evaluated whether ketamine used as an anesthetic agent or at low doses before ECT is able to enhance antidepressant effects of ECT. For instance, a prospective study (Okamoto et al., 2010) comparing ketamine (0.86 mg/kg) to propofol (0.94 mg/kg) for ECT anesthesia reported that ketamine is associated with an earlier antidepressant response during the first 2 weeks of ECT. Other study on MDD patients undergoing orthopedic surgery showed that using ketamine (1 mg/kg combined with propofol and fentanyl) for anesthesia during surgery caused a significant improvement in the depressed mood, suicidal tendencies, somatic anxiety, and hypochondriasis in these patients at 24 h post-infusion compared with those who received only propofol and fentanyl (Kudoh et al., 2002). A case report study also revealed that ketamine (0.5 mg/kg) used for anesthesia in ECT (3 sessions) in a patient with treatment-resistant MDD and 20-year history of schizoaffective disorder improved depressive symptoms immediately and at 48 h post-infusion (Ostroff et al., 2005). Another case report demonstrated that higher dose of ketamine (1.5 mg, IM) as part of a conscious sedation protocol 1 h before ECT in patient with recurrent MDD and psychotic features led to an immediate improvement in depressive symptoms (less psychomotor agitation, improved interaction with peers, regained spontaneous appetite, and improved sleep patterns) at 8 h post-ECT, continuing for the next 2 days (Goforth and Holsinger, 2007). In a more recent randomized, double-blind, controlled study on 48 patients with treatment-resistant MDD patients, it was shown that single-dose ketamine (0.8 mg/kg, IV) as anesthetic before ECT significantly improved depressive symptoms in ketamine alone or ketamine plus propofol group compared with propofol alone group over 7 days (Wang et al., 2012). These results suggest that ketamine is able to enhance the therapeutic effects of ECT on depressive symptoms in MDD patients. Accordingly, our present data also suggest that ketamine is as effective as ECT in depressive symptoms in MDD patients and has even more rapid onset of antidepressant action compared to ECT. Therefore, using ketamine alone might be a novel approach for those MDD patients who are subject for ECT. However, this assumption needs to be further evaluated by further studies using a larger number of patients.

In summary, our randomized, blinded study showed that low doses of ketamine (0.5 mg/kg) are capable of reducing depressive symptoms in a group of MDD patients without psychotic features who were scheduled for ECT. We also showed that compared to ECT, ketamine has more rapid onset of antidepressant effects as well as more effectiveness in decreasing depression in this group of patients. It is noteworthy that there are some limitations in the current study which needs to be considered. We used the titration method for ECT, which might result in a non-effective seizure in the first ECT treatment (Tiller and Ingram, 2006). Moreover, we used thiopental as anesthetic, which has considerable anticonvulsant properties (Prabhakar et al., 2013), and might also results in slower onset of action (Hoyer et al., 2013). Due to the unavailability of the ECT apparatus equipped with electroencephalography (EEG), the investigators were unable to record seizure durations by EEG. Moreover, in the current pilot study we included a small number of patients; therefore, more studies using a higher number of participants are needed to clarify the efficacy of ketamine treatment in MDD patients. Considering the fact that IV administration of ketamine might have some unwanted effects on hemodynamic and cognitive function (Aan Het Rot et al., 2012), some recent studies have shown that other routes of ketamine administration such as intranasal treatment (Papolos et al., 2013) or oral treatment (Irwin et al., 2013; Lara et al., 2013) could be well tolerated and be effective in treatment of mood disorders. Therefore, they could be a useful and easier way for long term ketamine administration in MDD patients.

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