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Short communication

Continuation phase intravenous ketamine in adults with treatment-resistant depression

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ABSTRACT

Background: Little is known about the antidepressive effects of repeated intravenous ketamine infusions beyond the acute phase of treatment in patients with refractory depression.
Methods: Twelve subjects with treatment-resistant non-psychotic unipolar or bipolar major depression and suicidal ideation were given repeated (up to 6) thrice-weekly acute-phase intravenous infusions of ketamine (0.5 mg/kg, administered over 100 min). Those who remitted during acute-phase treatment received continuation-phase treatment that consisted of 4 weekly ketamine infusions, followed by 4 weeks of post-continuation phase follow-up (during which no further ketamine infusions were administered). Clinical measures were assessed at baseline, at 24 h following each infusion, at the last acute-phase observation, and during continuation and post-continuation follow-up (acute phase remitters only).
Results: Of the 12 enrollees, 5 (41.7%) remitted and 7 (58.3%) responded to ketamine treatment during the acute-phase. All five subjects who remitted during the acute-phase experienced further depressive symptom improvement during continuation-phase treatment. Four subjects lost remission status during the post-continuation phase, but all were still classified as positive treatment responders at the end of the post-continuation phase. Adverse effects were generally mild and transient during acute- and continuation-phase treatment; however, one subject developed behavioral outbursts and suicide threats during follow-up while hospitalized, and one subject died by suicide several weeks after the end of follow-up.
Limitations: This was an uncontrolled feasibility study with a small sample size.
Conclusions: The continuation-phase administration of ketamine at weekly intervals to patients with treatment-resistant depression who remitted during acute-phase ketamine treatment can extend the duration of depressive symptom remission. The antidepressive effect of ketamine persisted for several weeks after the end of continuation-phase treatment. Our results highlight the need for close monitoring of subjects who are at high baseline risk for suicide but do not respond clinically to ketamine.
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1. Introduction

Multiple controlled trials have demonstrated the short-term effectiveness of both single and repeated administration of sub-anesthetic doses of intravenous (i.v.) and intranasal ketamine, a potent non-competitive glutamatergic N-methyl-D-aspartate (NMDA) antagonist, for treating the symptoms of non-psychotic treatment-resistant unipolar and bipolar major depression (McGirr et al., 2015; Newport et al., 2015). In these trials, subjects who benefitted from ketamine experienced rapid (within hours) onset of clinical antidepressive response lasting 3–14 days on average, with generally benign and transient adverse effects.

The field has now focused its attention on translating ketamine clinical trial protocols to routine practice, with a focus on repeated administrations of ketamine to sustain initial therapeutic benefit over longer-term treatment (Bobo et al., 2016). Repeated acute-phase infusions of ketamine provided over 12–14 days have been associated with larger reductions in depressive symptoms than single infusions for up to 14 days (Coyle and Laws, 2015). However, relapse rates in these studies were high—generally occurring within 18–19 days (aan het Rot et al., 2010; Murrough et al., 2012). There is a paucity of studies of the antidepressive effects and safety of repeated i.v. ketamine infusions beyond the acute-phase of treatment.

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We thus conducted an open label trial of i.v. ketamine in 12 adults with treatment-resistant unipolar or bipolar major depression, followed by 4 weeks of continuation i.v. ketamine treatment for subjects who achieved depressive symptom remission during the acute-phase.

2. Methods

2.1. Participants

The study protocol was approved by the Mayo Clinic Institutional Review Board. Adults (aged 18–64 years) meeting DSM-IV-TR criteria for non-psychotic, treatment-resistant major depressive disorder (MDD) or bipolar I or II disorder (BP) who were psychiatrically hospitalized for acute suicidal ideation were enrolled between December 30, 2014 and May 18, 2016. The subjects in this study are unique from those of a previously published report by our group (Rasmussen et al., 2013). MDD or BP diagnoses were established by clinical interview and confirmed using the Structured Clinical Interview for DSM-IV (SCID). Treatment resistance was defined as failure to respond to at least two therapeutic trials of antidepressants or mood stabilizers (for patients with bipolar disorders) that were of adequate duration and dose, or electroconvulsive therapy during the current depressive episode. The number and adequacy of previous therapeutic trials was systematically assessed at the time of study enrollment using the Antidepressant Treatment History Form (ATHF) (Sackeim, 2001). Eligible subjects had a 9-item Patient Health Questionnaire (PHQ-9) suicide item (item 9) score of ≥ 1 at the screening visit. Exclusionary criteria included psychotic symptoms, duration of the current depressive episode > 2 years, current alcohol or non-nicotine substance use disorder (unless in remission for ≥ 12 months), history of developmental delay or intellectual disorder, pregnancy, unstable medical condition, and involuntary psychiatric hospitalization. The determination of current disqualifying substance use disorders was made on the basis of clinical assessment, supplemented by a negative urine drug screen. All participants provided written informed consent.

2.2. Study design

This was a single-arm, open-label trial conducted in two phases. During the acute-phase, i.v. ketamine was administered thrice-weekly for up to 2 weeks. Those who achieved depressive symptom remission (Montgomery Åsberg Depression Rating Scale (MÅDRS) (Montgomery and Åsberg, 1979) total score ≤ 9 measured 24 h after any acute-phase infusion) received continuation-phase treatment that consisted of once-weekly i.v. ketamine infusions for 4 additional weeks (Hawley et al., 2002). Remission could occur after any of the 6 acute-phase infusions, at which point the next infusion was the first (of four) continuation-phase infusions. Individuals who remitted during acute-phase and completed continuation-phase treatment had 4 additional weekly post-continuation follow-up visits. Those who responded to i.v. ketamine ($\geq 50\%$ reduction from baseline in MÅDRS total score) but did not remit during acute-phase were not eligible for continuation-phase treatment. Suicidal ideation was assessed clinically throughout the trial, supplemented by scores on the MÅDRS suicide item (item 10). The PHQ-9 was used as an assessment instrument at the screening visit only.

2.3. Ketamine administration

Ketamine (0.5 mg/kg) was administered i.v. over 100 min for all acute- and continuation-phase infusions. During the infusions, heart rate, ECG, and pulse oximetry were continuously monitored. Blood pressure was measured at 15 min intervals. Monitoring of vital signs continued in this manner until 60 min after the end of infusion. Initial acute ketamine infusions were provided in the hospital, and continuation-phase infusions were generally provided as outpatients in a dedicated Clinical Research Unit.

2.4. Outcome measures

Depressive symptoms were measured using the MÅDRS prior to each infusion, at the end of each infusion (100 min), at 24 h post-infusion, and at all 4 post-continuation phase follow-up visits. Additional effectiveness measures were assessed at the same time points and included the Clinical Global Impression severity (CGI-S) and change (CGI-C) subscales (Guy, 1976) and MÅDRS factor scores (sadness [Factor 1], negative thoughts [Factor 2], detachment [Factor 3], and neurovegetative symptoms [Factor 4]) (Williamson et al., 2006). Withdrawal from the study was based on worsening depressive symptoms (CGI-S rating of much or very much worse, or at the discretion of the clinical investigator).

Treatment-emergent manic symptoms were assessed using the Young Mania Rating Scale (YMRS) (Young et al., 1978). Adverse effects were also assessed in 15 min intervals by direct questioning during all infusions and for up to 60 min post-infusion. Dissociative and psychotic (hallucinatory) effects were assessed clinically by spontaneous report and direct questioning. For example, spontaneous reports of feeling as though one were floating, disconnected, or "spacey" (but not lightheaded) were classified as representing dissociation. Subjects were also asked directly whether they experienced any of these sensations. CGI-S ratings were completed by study clinicians. All other clinical ratings were completed by trained research staff. Baseline scores for all measures were taken before the first acute-phase infusion.

2.5. Concomitant treatments

All subjects continued to receive hospital or outpatient care as usual during their participation in this study, including changes to pharmacotherapy when necessary and psychosocial interventions. Based on preliminary data suggesting benzodiazepine use may attenuate ketamine response, administration of benzodiazepines at ≥ 4 mg/day lorazepam equivalents was not allowed (Frye et al., 2015). No benzodiazepine doses were given on the morning of ketamine administration. Treatment with electroconvulsive therapy (ECT), transcranial magnetic stimulation, or deep brain stimulation was not allowed.

2.6. Statistical procedures

Statistical analyses included all subjects who received at least one acute-phase ketamine infusion. Change in baseline to endpoint values (24 h after the last infusion received during acute-phase treatment) for continuous efficacy measures were assessed using paired *t*-tests at a 2-tailed α level of 0.05. *T*-tests were used to compare mean baseline and mean percent change (baseline to last observed value during acute-phase) in efficacy measures between groups defined by remission status (remitters vs. non-remitters). Descriptive statistics were used to summarize demographic and other discrete variables, including rates of response and remission. All analyses were performed using STATA Version 14 statistical software (STATA Corp., College Station, TX, USA).

3. Results

3.1. Subject demographic and clinical characteristics

All 12 enrolled subjects received at least one acute-phase ketamine infusion. Subjects were predominantly middle-aged (mean

age, 45.8 ± 8 years), female (n=11, 91.7%), and Caucasian (n=11, 91.7%). Nine (75.0%) had confirmed diagnoses of MDD; all others had diagnoses of bipolar I (n=1) or II (n=2) depression. Subjects had failed to respond to 3 or more treatments during the current depressive episode, including four who responded poorly to ECT.

3.2. Subject retention

The majority of enrolled subjects (7/12, 58.3%) completed acute-phase treatment. Of the 5 who were unable to complete acute-phase treatment, two were withdrawn due to adverse effects, one elected to stop acute treatment due to lack of benefit, and two were withdrawn due to clinical worsening (one subject experienced a treatment-emergent behavioral outburst with suicidal threat, and one attempted suicide) and absence of positive response, as discussed further below.

3.3. Clinical outcome

Five (41.7%) subjects achieved depressive symptom remission and 7 (58.3%) were positive responders in the acute-phase. The majority who remitted (4/5, 80.0%) did so after the first acute infusion. The remaining subject remitted after the third acute infusion. There were no significant differences in MÅDRS total or MÅDRS factor scores at baseline between subjects who eventually remitted in acute-phase and those who did not remit.

The main effects of ketamine on depressive symptoms during acute and continuation phases of treatment, and during post-continuation phase follow-up, are summarized in Fig. 1. Significant reduction (improvement) in MÅDRS total scores occurred between baseline and the end of the first acute infusion in the entire sample, and in both remitters and non-remitters (data not shown). However, only remitters had significant improvement in MÅDRS total scores 24 h after the first infusion, and at the last acute phase observation. For remitters, further improvement in depressive symptoms was observed during 4 weeks of continuation-phase treatment. All 5 subjects retained positive treatment response at the end of post-continuation phase follow-up; however, only one of 5 subjects remained in a remitted status.

Additional effects of ketamine on MÅDRS total scores and other effect measures during acute phase treatment are presented in Table 1. There was a mean 41.5% reduction in MÅDRS total scores between baseline and the last acute phase observation in the entire sample. Significantly greater reduction in MÅDRS total scores (baseline to last acute-phase observation) occurred in remitters than non-remitters. Similar results were observed for MÅDRS factors and CGI-S scores. Scores on the MÅDRS suicide item (item 10) decreased significantly between baseline and the last acute phase observation in the entire sample and for remitters, but not for non-remitters. The change in MÅDRS suicide item scores from baseline to last acute phase observation was numerically greater for remitters than non-remitters at the level of statistical trend (p=0.12).

3.4. Adverse effects

Most common adverse effects during acute-phase treatment were dissociation (n=9), dizziness (n=7), numbness or tingling in the extremities (n=7), sleepiness or sedation (n=6), tearfulness/emotionality (n=4), and facial numbness (n=3). No subjects experienced visual or other types of hallucinations. In nearly all cases, these adverse effects resolved within two hours following the end of infusions. No new adverse effects were observed during continuation-phase treatment. There were no significant increases in YMRS scores during or following acute or continuation phase infusions.

There were statistically significant but transient increases in systolic and diastolic blood pressure during nearly all acute phase infusions. Peak systolic blood pressure (SBP) readings were significantly

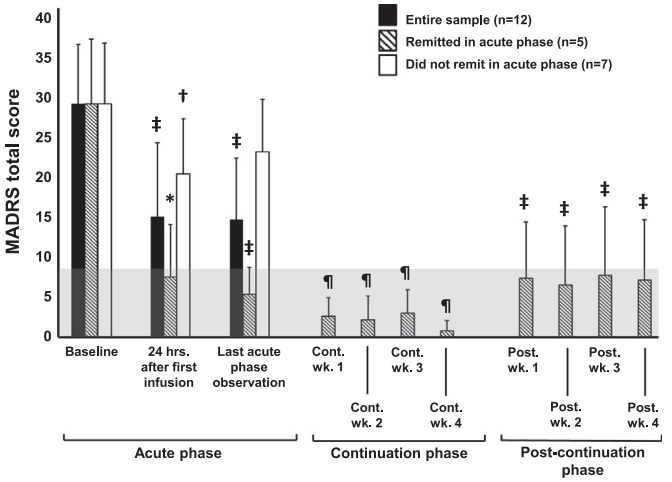

Fig. 1. Mean scores on the Montgomery Åsberg Depression Rating Scale (MÅDRS) during acute and continuation phase treatment, and post-continuation follow-up. Mean MÅDRS scores are shown for the entire sample (solid black bars), for subjects who remitted during acute phase treatment (stripe-patterned bars), and for those who did not remit during acute phase treatment (solid white bars). Remission was defined as a MÅDRS total score ≤9 measured 24 h after ketamine infusion (gray colored zone). Only subjects who remitted after any acute phase treatment received continuation phase treatment and post-continuation phase follow up. All 5 acute phase remitters retained remission status during continuation phase treatment. Although mean MÅDRS total scores were ≤9, only one of 5 acute phase remitters retained remission status during post-continuation phase follow up. Key: †p=0.06; *p<0.05; ‡p≤0.01; ¶p≤0.001.

elevated from baseline during the first (130.6 ± 17.4 mmHg vs. 114.9 ± 18.3 mmHg, p=0.0001), second (124.3 ± 11.2 mmHg vs. 108.8 ± 13.3 mmHg, p=0.009), and third acute phase infusions (130.9 ± 26.9 mmHg vs. 110.4 ± 15.0 mmHg, p=0.02). Corresponding peak diastolic blood pressure (DBP) readings were also significantly increased from baseline during the first (79.7 ± 7.5 mmHg vs. 70.9 ± 7.1 mmHg, p=0.005) and the third acute phase infusions (75.9 ± 10.7 mmHg vs. 66.0 ± 4.2 mmHg, p=0.02). Similar increases in SBP and DBP occurred during continuation phase treatment among the 5 subjects who remitted during the acute phase. One patient experienced transient elevation of blood pressure during the acute phase that resolved within 2 h post-infusion. There were no significant increases in heart rate or decreases in oxygen saturation levels during the acute phase (all treated subjects) or the continuation phase (subjects who remitted during the acute phase).

Two patients who were not benefitting acutely from ketamine were withdrawn from the study due to clinical worsening, per protocol. The first subject, who had a past history of attempted suicide, was withdrawn after five acute-phase infusions following a behavioral outburst and suicide threats precipitated by external stressors during hospitalization. The second subject, who had a history of recurring suicidal ideation despite multiple pharmacotherapeutic trials and ECT, experienced only transient antidepressive benefit and was withdrawn after four acute-phase infusions following an attempted medication overdose that occurred several days post-hospitalization. This was the subject's first known lifetime suicide attempt. Neither event was judged as being directly related to ketamine treatment, although both subjects expressed disappointment regarding the lack of sustained antidepressive effects. The second patient died by suicide ~10 weeks after being withdrawn from the study.

4. Discussion

To our knowledge, this study is among the first to demonstrate the effectiveness of continuation-phase administration of i.v. ketamine infusions with treatment-resistant unipolar or bipolar

Table 1
Depressive symptom, suicide-related, and global clinical measures at baseline and during the acute phase of intravenous ketamine therapy.

Outcome measures	Entire cohort (n=12)	Remission[a] (n=5)	Non-remission (n=7)
	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.
MÅDRS total score at:			
Baseline	29.4 ± 7.5	29.4 ± 8.2	29.4 ± 7.7
Last acute phase observation	15.9 ± 10.6***	5.4 ± 3.4**	23.4 ± 6.3
MÅDRS total score, % change from baseline at:			
Last acute phase observation	−41.5 ± 40.3	−79.1 ± 13.0†††	−14.6 ± 11.0
MÅDRS Factor 1[b] score at:			
Baseline	7.4 ± 2.0	7.4 ± 2.6	7.4 ± 1.7
Last acute phase observation	3.5 ± 2.3***	1.2 ± 0.5***	5.1 ± 0.5*
MÅDRS Factor 1 score, % change from baseline at:			
Last acute phase observation	−50.3 ± 35.7	−83.6 ± 15.7†††	−26.5 ± 24.2
MÅDRS Factor 2[b] score at:			
Baseline	6.0 ± 1.5	6.2 ± 1.6	5.9 ± 1.6
Last acute phase observation	3.4 ± 1.7***	1.8 ± 1.5*	4.6 ± 0.5
MÅDRS Factor 2 score, % change from baseline at:			
Last acute phase observation	−37.0 ± 36.5	−65.4 ± 31.4††	−16.7 ± 25.2
MÅDRS Factor 3[b] score at:			
Baseline	9.5 ± 3.1	9.8 ± 2.7	9.3 ± 3.5
Last acute phase observation	4.9 ± 3.5***	1.4 ± 1.3***	7.4 ± 1.8
MÅDRS Factor 3 score, % change from baseline at:			
Last acute phase observation	−40.2 ± 48.5	−84.3 ± 14.8††	−8.9 ± 37.3
MÅDRS Factor 4[b] score at:			
Baseline	6.5 ± 3.0	6.0 ± 3.8	6.9 ± 2.6
Last acute phase observation	3.8 ± 3.6*	1.0 ± 1.2*	5.9 ± 3.4
MÅDRS Factor 4 score, % change from baseline at:			
Last acute phase observation	−36.0 ± 58.0	−84.3 ± 20.4†††	−8.4 ± 54.4
MÅDRS suicide (item 10) score at:			
Baseline	2.9 ± 1.1	3.2 ± 1.1	2.7 ± 1.1
Last acute phase observation	1.7 ± 0.8**	1.2 ± 0.8*	2.2 ± 0.4
MÅDRS suicide (item 10) score, % change from baseline at:			
Last acute phase observation	−26.7 ± 45.4	−50.0 ± 46.8†††	−7.2 ± 37.1
CGI-S score at:			
Baseline	5.6 ± 0.5	5.4 ± 0.5	5.7 ± 0.5
Last acute phase observation	3.9 ± 1.7***	2.6 ± 0.9***	4.9 ± 1.6
CGI-S score, % change from baseline at:			
Last acute phase observation	−29.4 ± 30.8	−50.7 ± 20.3	−14.3 ± 28.7

Key: CGI-S=Clinical Global Impression-severity subscale; MÅDRS=Montgomery Åsberg Depression Rating Scale.

[a] Remission was defined as a MÅDRS total score ≤9 measured 24 h after any acute phase infusion.

[b] MÅDRS factor 1 (sadness) consisted of MÅDRS items 1 and 2; factor 2 (negative thoughts) consisted of MÅDRS items 9 and 10; factor 3 (detachment) consisted of MÅDRS items 6–8; and factor 4 (neurovegetative symptoms) consisted of MÅDRS items 3–5. Compared with baseline value.

* $p \leq 0.08$.
** $p < 0.05$.
*** $p \leq 0.01$. Remitters compared with non-remitters.
† $p < 0.05$.
†† $p \leq 0.01$.
††† $p \leq 0.001$.

depressed patients who remitted during acute treatment with ketamine. Five subjects who remitted during acute-phase experienced further depressive symptom improvement during once-weekly continuation-phase treatment. One subject remained in remitted status throughout 4 weeks of post-continuation phase follow-up. Adverse effects were generally mild and transient during acute- and continuation-phase treatment. Transient increases in SBP and DBP in this study were similar to those reported in previous short-term clinical trials of i.v. ketamine infused at faster rates (generally over 40 min), and intranasal ketamine, for treatment-resistant depression (Bobo et al., 2016).

The most critical limitation of ketamine as antidepressive treatment is the brief duration of its beneficial effect (Bobo et al., 2016). Prior studies showed the majority of patients who responded well to a single-dose of ketamine relapsed within 2–3 weeks (Berman et al., 2000; Diazgranados et al., 2010; Zarate et al., 2006, 2012). Previous research has shown repeated acute-phase ketamine infusions were associated with sustained antidepressive benefit while administered for up to 2 weeks; however, relapses occurred after 18–19 days following the last ketamine administration (aan het Rot et al., 2010; Murrough et al., 2013), and 55–89% of patients treated acutely with repeated ketamine infusions may relapse within one month following final infusion (aan het Rot et al., 2010; Rasmussen et al., 2013; Shiroma et al., 2014).

In our study, one subject developed behavioral outbursts and suicide threats during follow-up while hospitalized. Another subject died by suicide several weeks after the end of follow-up. Whether the severe behavioral outcomes observed in the two subjects under discussion here would have been expected for

other inpatients and those who were discharged had they not received ketamine is difficult to discern. The subjects in this trial were all hospitalized owing to severe depression and acute suicidal ideation, and thus constituted a sample of depressed individuals at perhaps higher-than-usual risk of adverse behavioral outcomes. Conversely, others have reported the onset of dysphoria, increased anxiety, and suicidal ideation in two ketamine-treated individuals with refractory obsessive-compulsive disorder who were described as having minimal depressive symptoms at the start of infusion (Niciu et al., 2013). Two serious treatment-emergent adverse events including treatment-emergent anxiety and a suicide attempt that occurred 4 weeks after the last ketamine dose were also reported in a recently published randomized trial of repeated acute phase ketamine infusion therapy for treatment-resistant unipolar major depression (Singh et al., 2016). Our group recently reported a case of ketamine over-use and clinical deterioration under ketamine treatment for depression when provided off-label in non-research settings (Schak et al., 2016). At minimum, our report further highlights the need for very close clinical monitoring and follow-up of ketamine-treated depressed patients who are at high risk for suicide, particularly those who do not achieve significant benefit.

Our results suggest that a brief continuation-phase consisting of once-weekly administration of i.v. ketamine can be used to extend the duration of depressive symptom remission in patients with treatment-resistant depression who respond well to acute treatment with i.v. ketamine. We also observed sustained antidepressive benefit during 4 weeks following the end of the continuation-phase, when no additional ketamine infusions were provided. This suggests the time window between ketamine infusions could be extended incrementally beyond administration every 7 days in patients who continue to tolerate and benefit from ketamine beyond its immediate, acute-phase effects. This may permit identification of an optimal frequency of ketamine infusions for patients who require ongoing, post-acute phase ketamine treatment—a clinical hypothesis in need of systematic investigation.

Our findings are limited by lack of a placebo or other control group and small sample size. Although our response (58%) and remission (42%) rates are comparable to those reported by others (Murrough, 2012), it is unknown whether the relatively slow rate of ketamine infusion in our study (over 100 min) may have limited its acute antidepressive effects. Further, we did not test the acute effects of ketamine at doses higher than 0.5 mg/kg. Medication therapy other than ketamine could be adjusted at any time during the trial, thus raising the possibility that clinical improvements may have occurred as a result of treatment-as-usual, although the very rapid onset of therapeutic effect among the subjects who experienced depressive symptom response and remission argues against this. We were unable to conduct secondary analyses of ketamine effects within subgroups defined by sex or race owing to very low numbers of male and non-Caucasian participants. And finally, several subjects were unable to complete all acute-phase treatments owing to lack of sustained benefit or adverse effects.

5. Conclusions

Intravenous administration of continuation-phase ketamine at weekly intervals to patients with treatment-resistant unipolar or bipolar major depression who remitted during acute-phase ketamine treatment (given up to thrice-weekly) can extend the duration of depressive symptom remission. The antidepressive effect of ketamine may persist several weeks after the end of continuation-phase treatment. Our results also highlight the need for close monitoring of subjects who are at high baseline risk for suicide but do not respond clinically to ketamine.

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