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Research report

Augmentation of response and remission to serial intravenous subanesthetic ketamine in treatment resistant depression

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ABSTRACT

Background: Ketamine has been showing high efficacy and rapid antidepressant effect. However, studies of ketamine infusion wash subjects out from prior antidepressants, which may be impractical in routine practice. In this study, we determined antidepressant response and remission to six consecutive ketamine infusions while maintaining stable doses of antidepressant regimen. We also examined the trajectory of response and remission, and the time to relapse among responders.
Methods: TRD subjects had at least 2-month period of stable dose of antidepressants. Subjects completed six IV infusions of 0.5 mg/kg ketamine over 40 min on a Monday–Wednesday–Friday schedule during a 12-day period participants meeting response criteria were monitored for relapse for 4 weeks.
Results: Fourteen subjects were enrolled. Out of twelve subjects who completed all six infusions, eleven (91.6%) achieved response criterion while eight (66.6%) remitted. After the first infusion, only three and one out of twelve subjects responded and remitted, respectively. Four achieved response and six remitted after 3 or more infusions. Five out of eleven subjects remain in response status throughout the 4 weeks of follow-up. The mean time for six subjects who relapsed was 16 days.
Limitations: Small sample and lack of a placebo group limits the interpretation of efficacy.
Conclusions: Safety and efficacy of repeated ketamine infusions were attained without medication-free state in patients with TRD. Repeated infusions achieved superior antidepressant outcomes as compared to a single infusion with different trajectories of response and remission. Future studies are needed to elucidate neural circuits involved in treatment response to ketamine.

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1. Introduction

The efficacy of current pharmacological agents for depression is disappointing. The largest (4041 patients at 41 clinical sites) and longest (data collected over seven years) study ever done to evaluate depression treatment, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Trivedi et al., 2006), showed that approximately only 30% of patients achieved remission after first-line antidepressant citalopram. A second large-scale study, the Combining Medications to Enhance Depression Outcomes (CO-MED) trial (Rush et al., 2011), compared two antidepressant combinations with serotonin selective reuptake inhibitor monotherapy at 12 weeks and 7 months. Similar to STAR*D, remission rates were modest (37.7–38.9%).

In addition to low response rate, the long delay of traditional antidepressants in the onset of therapeutic action (up to 12 weeks) increases the burden of illness, morbidity, and risk of suicidal behavior (Jick et al., 2004). Current antidepressants exert their primary biochemical effect by targeting monoamine substrates. The delay in the therapeutic actions of existing pharmacologic agents is due to the fact that they initially act on substrates that are considerably upstream of targets that are ultimately responsible for the antidepressant effects. Neurotrophic signaling cascades and the glutamatergic system are expected to be more closely related to adaptive changes in critical neuronal networks responsible for sustainable long-term therapeutic action of antidepressants. More recently, Ketamine, a noncompetitive, high-affinity antagonist of the N-methyl-D-aspartate (NMDA) type glutamate receptor used for induction and maintenance of anesthesia (Green and Li, 2000), has been investigated for its high efficacy and rapid antidepressant effect.

Since Berman and colleagues reported the first finding of a rapid antidepressant response to a single infusion of ketamine as

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compared to saline in nine depressed patients (Berman et al., 2000), multiple case reports, case series, and several clinical trials including placebo-controlled studies (Zarate et al., 2006; Diazgranados et al., 2010; Zarate et al., 2012) have supported the rapid antidepressant effect of a single ketamine infusion in unipolar or bipolar depression. However, follow-up periods have been variable with common return of depression within a day to a week and occasional patient showing several weeks of remission following the single infusion. The strategy of repeated ketamine infusion to maintain antidepressant response has recently been explored.

Murrough et al. (2013b) conducted series of six thrice weekly ketamine infusions (0.5 mg/kg over 40 min) found an overall response rate (as defined by an at least 50% reduction in depression scores by study end) of 70.8%, which was higher than 50–71% reported with single-infusion studies in unipolar depression (Berman et al., 2000; Zarate et al., 2006). Similarly, Rasmussen et al. (2013) had a response rate of 80% using multiple infusions although at a slower rate of administration (0.5 mg/kg over 100 min).

Most studies of ketamine infusion wash subjects out from prior antidepressants, which may be impractical in clinical settings and even unethical especially among patients with TRD. Other studies allow modification of concurrent antidepressant dosages during infusion confounding the effect of ketamine on depression. In this preliminary report, we aim to determine whether antidepressant response and remission can be increased by completing six consecutive infusions as compared to a single infusion. For this purpose, we maintain stable doses of antidepressant regimen including other psychotropic medications used as augmenting agents. By the administration of multiple infusions, the study also examined the trajectory of treatment response, particularly important for those subjects that do not respond after a single infusion. Finally, we also aimed to estimate time to relapse among responders after completion of the six infusions.

2. Methods and material

2.1. Participants

Adult subjects participated in an open-label study of repeat ketamine infusion conducted over 12 days at the Special Diagnostic and Treatment Unit (SDTU) of the Minneapolis VA Medical Center followed by a 4-week follow-up period. Subjects were recruited by direct referral from clinicians in the Mental Health and Primary Care Clinics. Medical records were reviewed prior to a brief phone interview with patients. Those who qualified were invited to a personal interview to determine final eligibility. Baseline assessments were ascertained within 1 week of first ketamine infusion. The Minneapolis VA Medical Center Institutional Review Board approved the study, and written informed consent was obtained from all subjects before participation.

2.1.1. Inclusion criteria

- Men and women aged 18 to 70 years.
- Have recurrent Major Depressive Disorder (MDD) without psychotic features confirmed by depression subset of the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996).
- Have 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) score greater than or equal to 14 at screen.
- Current major depressive episode resistant to treatment, defined as failure to achieve remission (elimination of symptoms and restoration of pre-morbid psychosocial functioning) from at least 2 antidepressant trials of different pharmacological classes. Systematic evaluation of previous antidepressant trials was assessed by using the Antidepressant Treatment History Form (Sackeim, 2001).
- If present, current pharmacological antidepressant dosages including augmenting agents must be stable for at least 2 months prior to beginning of the study.

2.1.2. Exclusion criteria

- Inability to speak English.
- Inability or unwillingness to provide written informed consent.
- Mini Mental State Examination (MMSE) (Folstein et al., 1975) scores ≤ 26.
- Current or lifetime diagnosis of post-traumatic stress disorder, acute stress disorder, psychosis-related disorder, bipolar disorder I or II disorder, substance-induced disorder, any mood disorder due to a general medical condition or any Axis I disorder other than MDD that was judged to be the primary presenting problem.
- Diagnosis of Parkinson's disease, dementia of any type, multiple sclerosis, seizures or other CNS related disorders.
- History of traumatic brain injury.
- Comorbid substance use, abuse or dependence within 6 months of assessment plus negative urine toxicology screen test.
- Clinically unstable medical illness including but not limited to history of or current myocardial ischemia or arrhythmias, severe pulmonary secretions, history of or current closed angle glaucoma, congestive heart failure or angina, significant renal or hepatic impairment, scheduled elective surgery or other procedures requiring general anesthesia during the study, uncontrolled hypertension.
- Current use of barbiturates or narcotic medications.
- Non-benzodiazepine hypnotics at doses higher than zolpidem 1 mg qhs or equivalent for insomnia.
- History of antidepressant- or substance-induced hypomania.
- History of first degree relative(s) with an Axis I psychotic disorder.
- For women: pregnancy (confirmed by baseline lab test), the initiation of female hormonal treatments within 3 months of screening, or inability or unwillingness to use a medically accepted contraceptive method for the duration of the study.
- Current active suicidal ideation judged to cause imminent danger.

2.2. Rating scales and procedures

Participants completed six IV infusions of ketamine on a Monday–Wednesday–Friday schedule over a 12-day period. Patients who met response criterion by the last dose of ketamine were followed weekly for 4 consecutive weeks or until relapse was observed. During this follow-up period, patients continued with similar dosages from pre-study antidepressant regimen. Response was defined as $\geq 50\%$ improvement from baseline depression score as measured by the Montgomery–Åsberg Depression Rating Scale (Montgomery and Asberg, 1979) (MADRS). Remission was established by a MADRS score ≤ 9. Relapse was defined as $< 50\%$ of baseline MADRS score at that follow-up visit.

On the day of infusion, subjects arrived in the morning after an overnight fast. An indwelling catheter was placed in the nondominant arm for ketamine administration. Digital pulse oximetry, respiratory rate, heart rate and blood pressure was recorded every 10 min for 1 h beginning 10 min before infusion. Based on the dose, rate of infusion, and endpoint/purpose of the study, the ketamine infusions did not fall into the category of “moderate sedation” and thus no cardiac monitoring was required at our institution. Before each infusion, MADRS score and self-rated