Rapid Antidepressant Response with Ketamine: Is it the Solution to Resistant Depression?

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ABSTRACT

Background: Treatment-resistant depression (TRD) is a relatively common condition, challenging the clinician. There is an urgent need to develop pharmacological treatments for TRD that exert rapid and sustained antidepressant effects. Ketamine induces a rapid antidepressant effect. Aims: In India, very few studies have corroborated such findings, and the present study aimed to assess the effectiveness and sustainability of antidepressant effects of ketamine in subjects with TRD. Materials and Methods: The present study was a single-center, prospective, 4-week, open-label, single-arm pilot study. Twenty-two subjects with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition major depression (treatment resistant) were recruited. After a 2-week drug-free period, subjects were given a single intravenous infusion of ketamine hydrochloride (0.5 mg/kg) and were rated at baseline and at 40, 80, 110, and 230 min and 1, 2, 3, 4, 7, and 14 days postinfusion. The main outcome measure was changes in scores on the 17-item Hamilton Depression Rating Scale (HDRS). Data were analyzed by using Friedman’s analysis of variance and a post hoc test. Results: The ketamine infusion was effective in reducing the HDRS scores, and the change remained significant from minute 80 to day 3 postinfusion at each time point. The change was not significant at any time after day 3. Conclusion: The real strength of this study rests in documenting the rapid, albeit short-lived, antidepressant effect of ketamine in TRD.

Key words: Glutamate, ill-sustained, ketamine, treatment-resistant depression

INTRODUCTION

The World Health Organization estimated that 5–10% of the population at any given time is suffering from identifiable depression needing psychiatric or psychosocial intervention and that there has been an increase in the burden associated with major depressive disorder (MDD).[1] Treatment-resistant depression (TRD) is a relatively common condition presenting with substantial challenges to both the clinician and the researcher.[2] Since the observation that antidepressant imipramine was clinically effective in treating MDD, many other antidepressants have been developed; these are largely similar to imipramine in their mechanism of action, but are more selective. For example, selective serotonin reuptake inhibitors are safer and better tolerated than are tricyclic antidepressants, but they have not been unequivocally shown to offer advantages in terms of efficacy or time of onset of action. However, recent studies clearly demonstrated that antidepressants are only of limited effectiveness for many patients. The largest open-label study sequenced treatment alternatives to relieve depression (STAR*D) study that evaluates standard therapies for MDD found less than one-third of the patients receiving standard antidepressants experienced remission after up to 4 months of treatment.[3]

Unfortunately, these medications take several weeks to
achieve their full effects, and in the mean time, patients continue to suffer from their symptoms and risk self-harm as well as harm to their personal and professional lives. This lag period in the onset of action of several weeks of traditional antidepressants is recognized as a major limitation, resulting in considerable morbidity and high risk of suicidal behavior especially in the first 9 days after initiating the antidepressant treatment.[4] Moreover, remission in half of the patients often required 6 months of treatment and two antidepressant trials.[3] Novel pharmacological approaches that have rapid onset of antidepressant effects within hours or even a few days and that are sustained would thus have an enormous impact on public health. The ‘initiation and adaptation’ model for understanding the delayed therapeutic actions of antidepressants has been an important line of research; this paradigm posits that 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.[6] Numerous clinical studies have supported a critical role for the glutamatergic system in the pathophysiology of MDD. It has become increasingly clear that there is an urgent need to develop pharmacological treatments for MDD that exert rapid and sustained antidepressant effects within hours or even a few days. In this context, the finding that the N-methyl-d-aspartate (NMDA) antagonist ketamine induces a rapid antidepressant response within hours has led to exciting new research into cellular mechanisms that affect rapid antidepressant action.[7]

Thus, it appears that agents targeting the glutamatergic system may be key to developing a new generation of improved treatments for this devastating illness. Ketamine (dl-2-(o-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride) is a noncompetitive NMDA antagonist and a derivative of phencyclidine.[8] Ketamine is a chiral compound and a dissociative anesthetic. Ketamine is water and lipid soluble and can be easily administered through diverse routes with ample distribution in the body. Ketamine metabolism is regulated by hepatic microsomal enzymes. One initial study found improvement in treatment-resistant depressive symptoms within 72 h after ketamine infusion in seven subjects with MDD.[9] In India till date very few studies have corroborated such findings, and the present study aimed to assess the efficacy and sustainability of antidepressant effects of ketamine in subjects with TRD.

MATERIALS AND METHODS

The present study was a single-center, prospective, 4-week, open-label, single-arm pilot study to assess the clinical utility and efficacy of antidepressant effects of single subanesthetic infusion of ketamine. Twenty-two patients (aged 18–65 years) participated in this study between March 2011 and November 2011. Participants fulfilled the criteria for Diagnostic and Statistical Manual of Mental Disorders—Text Revision (DSM-IV-TR) for MDD (treatment resistant). Treatment resistance was defined as two or more failed, adequate antidepressant trials in the current episode as determined by the Antidepressant Treatment History Form.[10] DSM-IV-TR diagnoses of MDD were established by the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I/P).[11] Subjects were free of psychotropic medication for 2 weeks before infusion (4 weeks for fluoxetine); were free of substance abuse/dependence for 6 months; denied lifetime use of ketamine and phencyclidine; had no history of psychotic disorder, mania, or hypomania; and had no clinically unstable medical or neurological conditions. All subjects were in good physical health as determined by medical history, physical examination, blood laboratory results, electrocardiogram, chest radiography, and urinalysis and toxicology findings. Subjects had a negative urine toxicology screen and were judged clinically not to be a serious suicide risk. Subjects received a complete description of the study, and written informed consent was subsequently obtained. The study was approved by the institutional ethics committee and was carried out in a psychiatry critical care unit of a large teaching hospital having major drainage from rural districts and nearby urban areas. The patients were admitted to hospital and received a single infusion racemic ketamine hydrochloride (0.5 mg/kg diluted in 0.9% saline, administered over 40 min) by an intravenous pump by an anesthesiologist; the patients were kept under continuous cardiorespiratory monitoring. They were rated 60 min prior to the infusion (baseline) and at 40, 80, 110 and 230 min as well as at 1, 2, 3, 4, 7 and 14 days postinfusion. Rating scales included the 17-item Hamilton Rating Scale for Depression (HDRS),[12] which was the primary outcome measure, and Brief Psychiatric Rating Scale (BPRS; a positive-symptom subscale), which was the secondary outcome measure.[13] Clinical response was defined as a 30% or greater decrease in the HDRS score from baseline, and remission was defined as an HDRS score of 6 or lower. With respect to standardized scales, a score of 6 or less on the 17-item HDRS is often used to define a remission.[14,15] All items on each scale were used. There were no dropouts from the study.

RESULTS

The data were described by using GraphPad Prism version 5 (GraphPad Software Inc, San Diego, CA). Significant effects were examined with simple effect tests. Within the group analysis, the change in
HDRS and BPRS scores over time was compared with baseline scores by using Friedman’s analysis of variance and a post hoc Dunn’s test was applied. The proportion of responders and remitters were evaluated at each time point. Significance was evaluated at \( P<0.05 \).

Table 1 describes the demographic and clinical characteristics of the subjects participating in the study. The overall sample \((n=22)\) had a mean±SD age of 50.23±7.9 years. The sample had 12 women and 10 men, with a mean body weight of 63.18 kg; 31.8% had a lifetime diagnosis of substance abuse or dependence. The mean±SD length of illness was 24.68±11.4 years, and the mean±SD of current depressive episode was 26.27±22.64 months. Four patients had previously received electroconvulsive therapy. All subjects had adequate antidepressant trials for the current major depressive episode.

To study the effect of ketamine on severity of depression (HDRS scores), Friedman’s analysis of variance was applied as the data were not normally distributed. The ketamine infusion was effective in reducing the HDRS scores, and the main effect of time measurement was significant \((F=151.8; \, P<0.001)\). Mean±SD HDRS scores declined by 7 points from baseline \((22.55±5.2)\) to 80-min postinfusion \((15.23±2.67)\) \((P<0.01)\). The change remained significant from minute 80 to day 3 postinfusion at each time point. The maximum change was detected at 230 min \((10.77±2.18; \, P<0.001)\), with more than 50% change over baseline. The change was not significant at any time after day 3, with scores approaching baseline by day 7 \((20.94±6.93; \, P>0.05)\). Figure 1 depicts the change in mean HDRS scores over time.

Figure 2 shows the change in BPRS (a positive-symptom subscale) scores over time. Post hoc results reveal that the change was significant only at 40-min postinfusion compared with baseline scores \((P<0.001)\) and was not statistically significant any time after that.

None of the subjects met the criteria for remission at any time point. Figure 3 shows the proportion of responders at each time point. Eleven subjects \((50\%)\) met response criteria 110-min postinfusion and 77% subjects fulfilled response criteria 1 day after infusion.

| Table 1: Sociodemographic and clinical characteristics of the patients \((n=22)\) |
|-----------------|---------|---------|
| **Characteristic** | **Mean** | **SD**   |
| Age (years)      | 50.23   | 7.946   |
| Monthly income (Rs.) | 7480   | 8662   |
| Length of illness (years) | 24.68  | 11.4   |
| Current depressive episode (months) | 26.27  | 22.64  |
| Number of previous episodes | 6.5    | 4.195  |
| Body weight (kg.) | 63.18   | 9.545   |

Only 13% maintained response up to day 7, with one subject maintained response till 2 weeks, showing that maximum responders to ketamine was on day 1. Adverse effects such as elevated blood pressure, euphoria, headache, increased thirst, and dizziness occurring with ketamine administration ceased within 40 min [Figure 2]. No serious adverse events occurred during the study.
DISCUSSION

The most important finding of this open-label study conducted in Indian subjects with a diagnosis of resistant depression was that a single subanesthetic infusion of NMDA antagonist ketamine was effective in attenuating depression rating scores on the HDRS. This study found that ketamine induced a rapid and dramatic antidepressant response, which was statistically significant from minute 80 to day 3 postinfusion but was relatively ill-sustained, with score change not being statistically significant from day 4 onward as compared with baseline scores. Such a rapid and robust response with a single administration has seldom been reported with any other drug or somatic treatment (i.e., sleep deprivation, thyrotropin-releasing hormone, antidepressant, dexamethasone, or electroconvulsive therapy) in TRD.\[16-19\] In reviews and meta-analysis of antidepressant trials in MDD, response rates at 8 weeks were 63% for selective serotonin reuptake inhibitors and 65% for venlafaxine while the present study found more than 68% response only 230 minutes postinfusion.\[20,21\]

By comparing our results with the findings of Zarate et al.,\[22\] we confirmed the rapid antidepressant effect of ketamine, the longer follow-up period; the larger sample size of this study allowed us to obtain information regarding time of onset, course of response, and degree of improvement. As compared with the previous study, our study detected an earlier onset of antidepressant response (80 min vs 110 min), significant change in HDRS scores from baseline sustained for a shorter period (day 3 vs day 7), and a longer follow-up of the present study (day 14 vs day 7), which enhanced the strength of this study. We were able to characterize the magnitude of response and remission over 2 weeks, with response on day 1 being 77% and no remitters with 71% responders and 29% remitters at the same time point as mentioned by Zarate et al. While comparing our results with a significant study (Phelps et al.\[23\]), we confirmed the brisk amelioration of HDRS scores at 80 min but none of our subjects met the remission criteria at 230 min (0% vs 26%).

Preclinical studies postulated that ketamine’s mechanism of action is initially mediated by NMDA antagonism but subsequently involves enhanced throughput of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA). Recent studies suggest that ketamine probably acts by disinhibiting GABAergic inputs and thereby increasing the firing rate of glutamatergic neurons, increasing the presynaptic release of glutamate, and resulting in increased extracellular levels of glutamate. This increased glutamate release preferentially favors AMPA receptors over NMDA receptors, because the latter are blocked by ketamine; the net effect of ketamine’s antidepressant effect on a cellular level is thus an increased glutamatergic throughput of AMPA relative to NMDA.\[24,25\]

The real strength of this study rests in documenting the rapid, albeit short-lived, antidepressant effect of ketamine in an Indian subpopulation with TRD, highlighting the aspect that improvement associated with ketamine infusion reflects a lessening of core symptoms of depression and is disconnected from ketamine-induced euphoria and psychotomimetic symptoms [Figure 2] and that ketamine exerts its effects remarkably, considering its short half-life,\[26\] which might be useful clinically.

However, several limitations do exist and the results of this preliminary study should be interpreted cautiously; as the sample size was small, there was no placebo arm. The results might not be generalizable to all populations as all patients do not respond to ketamine the same way. Blood levels of ketamine or its metabolites were not collected; differences in drug metabolism could have contributed in part to the findings.

Although the findings of this study support the notion that directly targeting NMDA receptor complex acutely attenuates the depressive symptoms, which have high clinical relevance, further in-depth relapse prevention strategies\[27\] or newer therapeutic protocols for sustained antidepressant effects need to be explored.

CONCLUSION

Rapid, robust antidepressant effects with a single intravenous dose of ketamine; which has onset within minutes but significantly for a short time span.

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