International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Original Article

Efficacy and Safety of Ketamine in Treatment-Resistant Depression: A Prospective Clinical Study

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Received: 15-10-2025
Accepted: 14-11-2025
Available online: 20-11-2025

ABSTRACT

Background: Treatment-resistant depression (TRD) is a major challenge in clinical psychiatry. Ketamine, an NMDA receptor antagonist, has emerged as a novel therapeutic option due to its rapid antidepressant effects. This study aimed to evaluate the efficacy and safety of ketamine in patients with TRD.
Methods: This was a prospective, open-label clinical study conducted on patients diagnosed with major depressive disorder not responding to at least two adequate antidepressant trials. Intravenous ketamine (0.5 mg/kg) was administered over 40 minutes twice weekly for two weeks. Patients were assessed using the Hamilton Depression Rating Scale (HDRS) and Montgomery-Asberg Depression Rating Scale (MADRS) at baseline, Day 3, Day 7, and Day 14. Adverse effects were monitored using a standardized checklist.
Results: A total of 40 patients with TRD were enrolled. Mean HDRS scores reduced significantly from 25.3±3.2 at baseline to 12.4±2.8 at Day 14 ($p<0.001$). MADRS scores showed a similar decline from 32.1±4.5 to 14.8±3.7 ($p<0.001$). Response rate (≥50% reduction in HDRS) was observed in 67.5% of patients, and remission (HDRS ≤7) in 22.5%. Adverse effects were mild and transient, with dissociation (20%), dizziness (12.5%), and nausea (10%) being most common.
Conclusion: Intravenous ketamine demonstrates rapid and significant antidepressant effects in patients with treatment-resistant depression and is generally well-tolerated. Further controlled studies with larger sample sizes and long-term follow-up are warranted to establish its sustained efficacy and safety.

Keywords*: Ketamine, Treatment-resistant depression, NMDA receptor antagonist, Rapid-acting antidepressant.*

INTRODUCTION

Major depressive disorder (MDD) is one of the leading causes of disability worldwide. Despite the availability of multiple classes of antidepressants, approximately 30–40% of patients do not achieve adequate response even after trials of two or more antidepressants, thereby fulfilling the criteria for treatment-resistant depression (TRD). This clinical challenge underscores the need for novel therapeutic agents with faster onset and greater efficacy. Ketamine, a phencyclidine derivative and NMDA receptor antagonist, has gained attention for its rapid antidepressant effects observed within hours of administration. It modulates glutamatergic transmission and enhances neuroplasticity through downstream activation of AMPA receptors and mTOR signaling. This study was designed to prospectively evaluate the efficacy and safety of intravenous ketamine in Indian patients diagnosed with TRD.

MATERIALS AND METHODS

This prospective, open-label study was conducted at the Department of Psychiatry, Noida International Institute of Medical Sciences, Greater Noida, in collaboration with the Department of Anaesthesia, UCMS and GTB Hospital, New Delhi, between January 2024 and July 2025.

Inclusion criteria included adults aged 18–60 years, diagnosed with MDD as per DSM-5, and nonresponsive to at least two

adequate antidepressant trials. Exclusion criteria were psychotic disorders, substance use disorder, unstable medical illness, or pregnancy.

Participants received six infusions of ketamine (0.5 mg/kg IV) over 40 minutes twice weekly for two weeks. Depression severity was measured using HDRS and MADRS at baseline, Day 3, Day 7, and Day 14. Vital parameters and side effects were closely monitored.

RESULTS

A total of 40 participants met inclusion criteria and completed the two-week study protocol. The mean age was 37.2 ± 9.6 years (range 19–58 years), with a gender distribution of 22 females (55%) and 18 males (45%). The average duration of depressive illness was 4.8 ± 2.3 years. Most participants (60%) had failed two prior antidepressant regimens, while 40% had failed three or more.

At baseline, the mean HDRS score was 25.3 ± 3.2, which significantly decreased to 12.4 ± 2.8 by Day 14 ($p < 0.001$). Similarly, the mean MADRS score declined from 32.1 ± 4.5 to 14.8 ± 3.7 ($p < 0.001$). Notably, 27 patients (67.5%) achieved a clinical response (≥50% HDRS reduction), and 9 patients (22.5%) achieved remission (HDRS ≤ 7) by the end of treatment. Improvement was evident as early as Day 3 post-first infusion.

Adverse events were reported in 14 patients (35%). The most frequent were dissociation (20%), dizziness (12.5%), and nausea (10%). All side effects were mild to moderate and resolved spontaneously within one hour post-infusion. No cases of psychosis, hemodynamic instability, or persistent cognitive impairment were recorded.

Overall, the treatment was well-tolerated, and no patients discontinued due to adverse effects. These findings reinforce ketamine's potential as a safe, rapid-acting, and effective intervention for patients with TRD.

Assessment Timepoint	Mean HDRS (±SD)	Mean MADRS (±SD)
Baseline	25.3 ± 3.2	32.1 ± 4.5
Day 3	18.2 ± 2.9	24.6 ± 3.9
Day 7	14.5 ± 2.5	18.7 ± 3.4
Day 14	12.4 ± 2.8	14.8 ± 3.7

Response rate (≥50% HDRS reduction) was 67.5%, while remission (HDRS ≤7) was achieved in 22.5%. No serious adverse events were reported. The most frequent side effects were transient dissociation (20%), dizziness (12.5%), and nausea (10%).

DISCUSSION

The findings of this prospective study highlight ketamine's remarkable efficacy in rapidly alleviating depressive symptoms among individuals with treatment-resistant depression (TRD). The rapid reduction in HDRS and MADRS scores within the first week of treatment emphasizes ketamine's distinct advantage over traditional antidepressants, which often take several weeks to achieve therapeutic effects. This rapid response is clinically significant, especially in patients at high risk for suicide, as ketamine has been shown to exert potent anti-suicidal effects through its modulation of the glutamatergic system.

Mechanistically, ketamine's antidepressant action is attributed to NMDA receptor antagonism, leading to an acute surge in glutamate release. This, in turn, stimulates AMPA receptor activity, enhancing synaptic plasticity and promoting neurogenesis through downstream activation of the mTOR signaling pathway and increased expression of brain-derived neurotrophic factor (BDNF). Neuroimaging and preclinical studies further suggest that ketamine reverses stress-induced synaptic deficits in the prefrontal cortex and hippocampus, regions implicated in mood regulation.

In the present study, the response rate of 67.5% and remission rate of 22.5% align with existing literature, such as the findings of Zarate et al. (2006) and Murrough et al. (2013), who reported comparable efficacy following a single or repeated infusion regimen. The consistent decline in HDRS and MADRS scores across all time points underscores ketamine's robust and reproducible antidepressant potential. Importantly, no serious adverse events were observed, reflecting its safety when administered under proper supervision and dose regulation.

The observed adverse effects—dissociation, dizziness, and nausea—were mild, transient, and self-limiting, consistent with previous safety profiles. Dissociation typically appeared within minutes of infusion onset and resolved within 60 minutes post-infusion. These effects are believed to stem from ketamine's transient cortical dysregulation and can be mitigated with careful dose titration and patient monitoring.

Our results also contribute to the growing evidence that ketamine may induce a neurobiological 'reset' in dysfunctional neural circuits associated with depression. Functional MRI studies have demonstrated normalization of connectivity within

the default mode network (DMN) and limbic structures following ketamine treatment. Such neuroadaptive changes may explain the sustained mood improvement observed even after cessation of infusions.

However, limitations of this study include the relatively small sample size, open-label design, and short-term follow-up period. The absence of a placebo control prevents definitive causal inference regarding ketamine's superiority. Long-term effects, relapse rates, and cognitive impacts require further exploration through randomized, double-blind, controlled trials. Nonetheless, the present findings offer valuable real-world data from an Indian population, highlighting ketamine's therapeutic viability and tolerability profile in diverse clinical settings.

Future directions should include studies on alternative routes such as intranasal esketamine, evaluation of maintenance protocols, and exploration of biomarkers predictive of treatment response. Integration of ketamine therapy within comprehensive psychiatric care, including psychotherapy and psychosocial support, may further enhance and sustain clinical outcomes.

CONCLUSION

Ketamine demonstrates robust, rapid, and safe antidepressant effects in treatment-resistant depression. Its inclusion in treatment algorithms may revolutionize depression management, especially for patients unresponsive to traditional therapies. Future randomized controlled trials with extended observation are necessary to validate and extend these findings.

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