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Middle East Current Psychiatry (2024) 31:31
https://doi.org/10.1186/s43045-024-00420-x

Middle East Current Psychiatry

RESEARCH Open Access

A prospective open-label study to evaluate the effectiveness of intravenous ketamine as an adjunct in treating severe depression

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Abstract

Background Ketamine, an emerging pharmacotherapeutic agent for depression, has demonstrated rapid and substantial improvement in mood and suicidal ideation, particularly in severe cases. While previous studies have established its efficacy, the current study aims to delve into the effectiveness of intravenous ketamine in treating severe depression.

Methods An open-label prospective study enrolled 49 consecutive patients with severe depression. Baseline assessments using the Hamilton Depression Rating Scale (HAMD), Montgomery-Asberg Depression Rating Scale (MADRS), and Modified Scale for Suicidal Ideation (MSSI) were conducted. Intravenous (IV) ketamine, administered at 0.5 mg/kg in 100-ml normal saline over 40 min, was given during sessions spaced on alternate days. Each patient received at least five sessions alongside their regular antidepressants. Close monitoring occurred during the infusion, and disease rating scale scores were recorded. Data was analyzed; employed paired Student *t*-test and graphical were used for visual clarity.

Results Following the initiation of IV ketamine, a significant reduction in scores was observed from baseline. Response rates were achieved in over half of the patients by the third session and in nearly all by the end of fifth session. Remission rates were attained in nearly half of the patients by the fourth session and in almost all by the fifth session.

Conclusions IV ketamine could be considered as an adjunct to antidepressants in treating severe depression especially among those with suicidal ideations to obtain rapid improvement. However, the need for long-term studies is emphasized to determine the duration of its effect.

Keywords Depression, Depressive disorder, Ketamine, Therapeutics, Investigational therapies

Introduction

Depression is one of the common mental health conditions, affecting nearly 15% of adults and contributing to 2.58 lakh suicidal deaths in India. In 2015 alone, it accounted for 7.5% of all years lived with disability [1]. The treatment of depression assumes paramount significance in alleviating the burden, and various therapeutic options have been delineated, each demonstrating varying rates of response or remission. Notable among these are distinct groups of antidepressants, electroconvulsive therapy (ECT), and psychosocial

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interventions. Within the realm of psychosocial interventions, those supported by good evidence include cognitive behavior therapy, interpersonal therapy, and supportive therapy, among others. Additionally, emerging or experimental modalities such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) have gained attention. When clinical improvement falls short and is categorized as non- or partial response, the recourse to combination treatments becomes imperative [2].

Among these emerging modalities, ketamine surfaces as a pharmacotherapeutic agent under exploration. The efficacy of intravenous (IV) ketamine is undergoing scrutiny for the treatment of depression under various conditions, including combination, dose, and administration route [3, 4]. Given the mounting evidence supporting the role of glutamate in depression through N-methyl-D-aspartate (NMDA) receptors, coupled with the established role of serotonin receptors, ketamine, fundamentally an anesthetic agent, modulates NMDA receptors by non-competitively blocking the voltage-dependent NMDA receptors. At low doses, it exhibits antidepressant effects, while at higher doses, it functions as an anesthetic agent [5]. A meta-analysis [4] reveals rapid and substantial mood improvement and reduction in suicidal ideations with ketamine administration.

Efficacy, gauged by an intervention's ability to produce desired results or changes under ideal conditions while controlling numerous variables, differs from effectiveness, which assess whether an intervention yields beneficial effects in real-world clinical settings [6]. Notably, existing evidence on ketamine predominantly pertains to its efficacy. Given the established efficacy of low-dose ketamine in depression, our study aims to explore its effectiveness in real-world settings. Consecutively, the current study was designed to investigate the effectiveness of IV ketamine in the naturalistic clinical settings, with the aim of translating the findings into clinical application.

Methods

Aims and objectives

The primary objective of this study was to assess the effectiveness of IV ketamine as an adjunct in the treating depression, both with and without suicidal ideation. The secondary objective aimed to determine the number of sessions required to achieve a treatment response and remission. In the context of this study, a treatment response in depression was defined as a 50% reduction in the depression scores, while remission was determined based on a specific rating scale.

Study details

Sociodemographic details

It included details such as age, gender, psychiatric diagnosis, and the number of IV ketamine sessions received. Additionally, it documented investigations conducted and vital signs monitored throughout the sessions. Demographic and illness-related variables, which a prior study [7] did not associate with the response rate, were excluded.

Depression rating scales

Depression severity was evaluated using the Montgomery-Asberg Depression Rating Scale (MADRS) [8] and Hamilton Rating Scale for Depression 17 item (HAMD) [9]. These clinically rated scales, commonly employed in antidepressant efficacy trials, were chosen for their perspective in assessing depression symptomatology. The cutoff values for MADRS were "severe depression" with score above 35, "moderate depression" with score of 20 to 34, and "mild depression" with score of 7 to 19. Similarly for HAMD, the cutoff values were "very severe depression" with score of 23 and above, "severe depression" with score of 19 to 22, "moderate depression" with score of 14 to 18, and "mild depression" with score of 8 to 13 [10]. As per the rating scale, remission is defined as a score ≤ 9 for MADRS and ≤ 7 for HAMD [11].

Suicide rating scale

Suicidal ideation was objectively measured using Modified Scale for Suicidal Ideation (MSSI) [12], comprising 18 items. Severity categorization included "low suicidal ideation" for scores between 0 and 8, "mild-moderate suicidal ideation" for scores between 9 and 20, and "severe suicidal ideation" for scores of 21 or above.

Methodology

The study commenced after obtaining ethics approval from institution ethic committee (IEC). Conducted as an academic clinical trial, it aimed to test the effectiveness of IV ketamine in depression treatment and was not registered with Clinical Trial Register of India (CTRI). Structured as an open-label prospective study, patients and researchers were aware of the intervention, with patients maintaining their pre-inclusion antidepressant medication regimen. Among the antidepressant medications, most were on selective serotonin reuptake inhibitors (like escitalopram and sertraline) and/or selective norepinephrine reuptake inhibitors (like desvenlafaxine). None of the patients received ECT and did not qualify for treatment-resistant depression at the time of entry into

the study. Study spanned from January 2023 to September 2023 conducted in Department of Psychiatry at a tertiary teaching hospital, and patients with a diagnosis of depressive disorder (including single episode depressive disorder, recurrent depressive disorder, bipolar affective disorder, and obsessive-compulsive disorder with depression) provided written consent before inclusion.

Inclusion and exclusion criteria

Patients with severe depression without psychotic symptoms, as per International Classification of Disorders 11 (ICD-11) [13], were included based on disease severity rating scale (*MADRS* > 35 and *HAMD* > 22), even if the depression was a comorbid condition. Severe depression with psychotic symptoms was excluded as there is evidence for ketamine increasing the psychotic symptoms [14]. Those patients with past or present history of cardiac conditions (other than well-controlled hypertension), neurological conditions (such as cerebrovascular stroke, transient ischemic attacks), ophthalmic conditions, psychotic features (even depression with psychosis), respiratory conditions, thyroid abnormalities, and abnormalities detected in the initial blood investigations/chest X-ray/electrocardiogram (ECG) were excluded. If any abnormalities were detected during the evaluation, appropriate clinical management was undertaken for the betterment of the patient.

Procedure

The initial assessment included a range of blood investigations such as complete blood picture, liver function tests, renal function tests, thyroid function tests, serum electrolytes, electrocardiogram (ECG), and chest X-ray to rule out any organic pathology. Disease severity rating scales were scheduled before the first IV ketamine session (as a baseline measure) and the rest after session (recorded as session 2 up to 5). Assessments were strategically scheduled to avoid post-procedural drowsiness. Vital signs, including blood pressure (BP), pulse rate (PR), respiratory rate (RR), and oxygen saturation (SpO2), were closely monitored during and after the procedure.

Dosage and route of ketamine

The administration mode, infusion rate, dose, and session duration were determined based on previous studies [15–18]. IV ketamine, administered as a drip mixed in 100-ml normal saline over 45 min every alternate day for at least five sessions, utilized a subanesthetic dose of 0.5 mg per kg body weight. Number of sessions was planned pragmatically based on the depression rating scores, those who attained the remission scores foregoing further sessions. IV ketamine was preferred over intranasal esketamine due to availability and logistical considerations.

Flowchart of the study

Statistical analysis

Patient data was recorded in a Microsoft Excel sheet and subjected to analyzed using R language [19] with R studio as integrated development environment (IDE). Sociodemographic details were succinctly presented using frequencies and percentages. Disease severity scale scores, encompassing both depression and suicide assessments, underwent analysis to determine the mean difference between sessions, utilizing the paired Student *t*-test. Additionally, mean values of the disease severity scale scores were visually represented using box and whisker plot.

Results

Sociodemographic details of the participants

The mean age of the participants was 30 years, with a standard deviation of 6.7 years, ranging from a minimum of 20 years to a maximum of 46 years. Females comprised of 57.1% of the sample, with the predominant diagnosis being major depressive disorder (71.4%), followed by comorbid depression (20.4%). A substantial majority of participants underwent a minimum of 5 sessions (57.1%) of IV ketamine. Vital signs (BP, PR, RR, and SpO2) remained within normal ranges during and after sessions. Patients remained stable except for drowsiness after the session which lasted for approximately an hour, during which time patients were closely monitored.

Response of the depression to intravenous ketamine (Table 1, Figs. 1 and 2)

A significant reduction in depression scores was observed from the baseline following the initiation of IV ketamine. Significant reduction in mean values was noted with each subsequent session. Response, defined as a 50% decrease in depression rating scores, was achieved in more than half (57% in MADRS and 73% in HAMD) of patients by the third session and in nearly all (95% in both MADRS and HAMD) by the fifth session. Remission, defined as score less than 9 and 7 according to MADRS and HAMD, respectively, was attained in nearly half of the patients by the fourth session (49% according to MADRS and 55% according to HAMD) and almost all patient by the fifth session (95% according to both MADRS and HAMD).

Response of suicidal ideation to intravenous ketamine (Table 1, Fig. 3)

A significant reduction in suicidal ideation scores was observed from the baseline following the initiation of IV ketamine. By third session, three-fourths (77%) have

Table 1 Comparison of depression and suicide scores during intravenous ketamine sessions

Sl. no.	Rating scale	Baseline	Session 2		Session 3		Session 4		Session 5	
		Mean (SD)	Mean (SD)	*p*-value	Mean (SD)	*p*-value	Mean (SD)	*p*-value	Mean (SD)	*p*-value
1	MADRS	43.1 (8)	29.6 (13.1)	< 0.001	19.4 (13)	< 0.001	10 (10.5)	< 0.001	3.5 (7.3)	< 0.001
2	HAMD	32.8 (9.8)	21.1 (9.6)	< 0.001	12.7 (9.1)	< 0.001	6.7 (7.4)	< 0.001	3.6 (6.7)	< 0.001
3	MSSI	25.9 (8.6)	14.3 (10.7)	< 0.001	6.3 (8.7)	< 0.001	2.3 (6.3)	< 0.001	0 (0)	< 0.001

MADRS Montgomery-Asberg Depression Rating Scale: *HAMD* Hamilton Rating Scale for Depression: *MSSI* Modified Scale for Suicidal Ideation: test used, Wilcox sign-rank test; *p*-value < 0.001 is highly significant

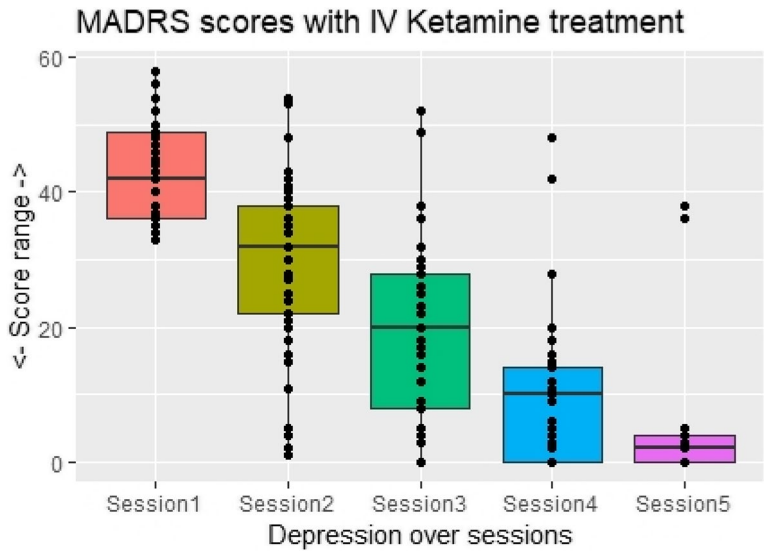

Fig. 1 MADRS scores over IV ketamine treatment

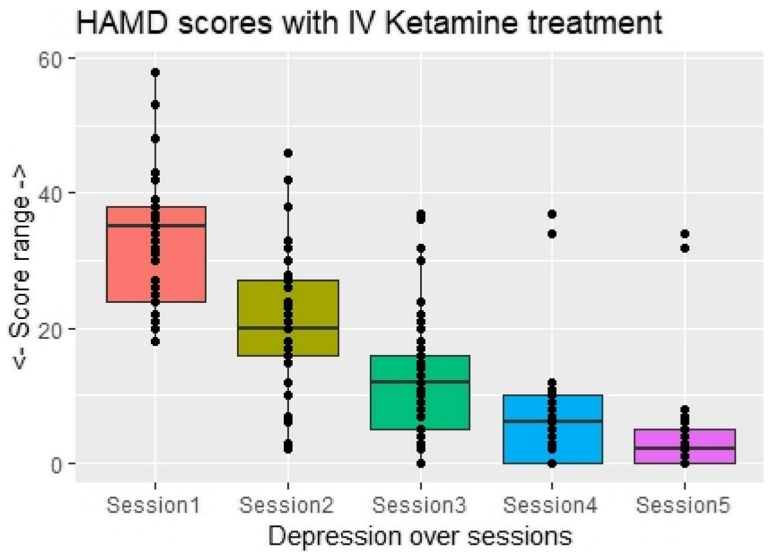

Fig. 2 HAMD scores over IV ketamine treatment

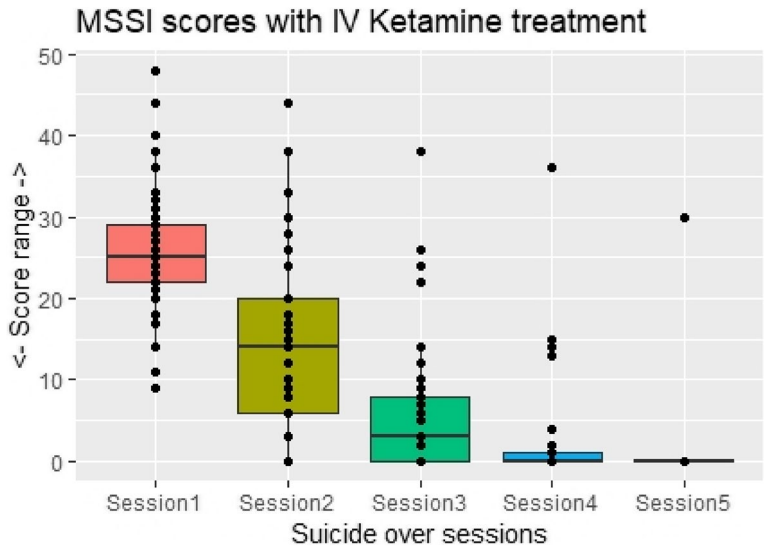

Fig. 3 MSSI scores over IV ketamine treatment

reported reduction in MSSI scores to mild category. Subsequently, values reduced to zero in almost all patients by the fifth session.

Discussion

The sequenced treatment alternatives to relieve depression (STAR*D) trial [20], which investigated the effectiveness of antidepressants through four treatment steps, reported a cumulative remission rate of 67% after using up to four different antidepressants. However, recent reanalysis by Pigott H. E. et al. [21] suggests a lower rate of 35%. Similar response rates (66.6%) were observed in a randomized control trial (RCT) [22] with antidepressant treatment over 6 months. Another RCT [23] examining response rates with a second augmentative agent found rates of 31.8% and 26.9% even with two different augmenting agents. The variability in response rates, even with augmentation of pharmacotherapeutic agents, underscores the necessity for combining different modalities of treatment.

Combination treatments, such as psychotherapy, ECT, and various pharmacotherapic agents, are often required for severe depression management [2]. However, even with combination of different modalities, the response rates are less. A meta-analysis [24] comparing psychotherapies reported a response rate of 41%, and only one-third attained remission status, emphasizing the importance of combining different treatment approaches. Even ECT, considered an effective add-on for resistant depression, yields response and remission of 54% and 31%, respectively [25]. Previous studies [26–28] on ECT as add-on with one or more adequate medication trials found response rates ranging from 50 to 60%. Ongoing research explores newer modalities like repetitive transcranial magnetic stimulation (rTMS) [29] and transcranial direct current stimulation (tDCS) [30] to enhance treatment outcomes.

Ketamine has gained attention as a pharmacotherapeutic approach to augment depression treatment, aiming faster response and reduced suicidality. Berman R. et al. [18] administered two sessions of IV ketamine separated by at least 1 week to four patients who were not on any medications and observed post infusion response (50% reduction in scores) within 3 days, which maintained for 1 to 2 weeks. They felt that the improvement resulted in lessening of core depressive symptoms which could not be attributed to ketamine-induced euphoria. A double-blind placebo controlled study added IV ketamine to treatment-resistant depression (TRD), found 0.5 mg/kg and 1 mg/kg doses to possess good antidepressant efficacy with no significant adverse effects compared to placebo but also noted that clinical meaningful therapeutic benefit did not last after 5 days, and with 1 mg/kg, it lasted for 15 to 30 days [31]. Similarly, another study compared IV ketamine with placebo and reported that there was a drastic decline in depression severity and suicidal severity within 6 h of infusion [32]. The current study aligns with previous findings, demonstrating significant improvement in depressive symptoms and suicidal ideation. The response and remission were observed in almost all the patients by the end of fifth IV ketamine session.

The study due to the design cannot shed light on the long-term maintenance. Previous studies [33, 34] have found that the effect of IV ketamine is short lasting

(median of 2 to 4 weeks), and various strategies are also being tested to prolong its efficacy. Despite the proven efficacy and effectiveness of faster response in severe depression, ketamine is considered an investigative agent [35], and routine clinical use may take time. We believe some factors contributing to this are as follows: first, ketamine has been established and used extensively primarily as an anesthetic agent, only off late it has not been popularized for its use in mental health conditions, and it is more popular for causing psychiatric manifestations/behavioral abnormalities; second, psychiatrists do not have knowledge and hands-on experience in using ketamine and may be the lag in using; third, ketamine poses abuse potential and hence placed in schedule H drug list which makes it difficult to procure; fourth, it requires a close observation of the patient during the administration, and hence, a dedicated team is a requisite; and finally, the molecule has been in market for a long time, and hence, it may not be perceived as a profitable business to promote.

Conclusions

There is a need to work on establishing standard operating procedures (SOP) for integrating ketamine into regular mental healthcare setting in India. While the short-term efficacy of ketamine in short-term treatment of depression is established, further exploration is needed for long-term efficacy, with a focus on testing maintenance sessions and determining optimal spacing durations. Although there are studies trying to understand the neurobiological changes with ketamine use, more needs to be done in this arena.

Limitations

The study's limitations include small sample size, continuation of regular antidepressant medications alongside IV ketamine, which was not factored into result interpretation, as the focus was on studying IV ketamine's effectiveness in a natural setting. Additionally, pragmatic session design, with the suspension of IV ketamine (continued on regular antidepressants) upon achieving remission status, may have an impact on the results.

Abbreviations

HAMD	Hamilton Depression Rating Scale
MADRS	Montgomery-Asberg Depression Rating Scale
MSSI	Modified Scale for Suicidal Ideation
ECT	Electroconvulsive therapy
ECG	Electrocardiogram
IV	Intravenous
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
rTMS	Repetitive transcranial magnetic stimulation
tDCS	Transcranial direct current stimulation
NMDA	N-methyl-D-aspartate
CTRI	Clinical Trial Registry of India
ICD-11	International Classification of Disorders 11
RCT	Randomized clinical trial
IDE	Integrated development environment
BP	Blood pressure
PR	Pulse rate
RR	Respiratory rate
SpO2	Oxygen saturation
TRD	Treatment-resistant depression

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43045-024-00420-x.

Supplementary material 1.

Acknowledgements

Not applicable

Authors' contributions

PKTV was involved in designing the study, administering intravenous ketamine, and reviewed the manuscript; DB was involved in doing relevant literature review, designing the study, and manuscript reviewing; RKD was involved in data analysis, statistical analysis, and manuscript writing; and AP and AG were involved in data acquisition.

Funding

The current study did not get funding from any institution or body.

Availability of data and materials

The dataset generated and analyzed during the current study are available in the "Figshare" repository, accessed at 10.6084/m9.figshare.25051592.

Declarations

Ethics approval and consent to participate

Institute ethics committee approval has been obtained before starting the study (IEC letter no.: NRIAS/IEC/253/2015), and informed written consent has been obtained from each patient before including in the study.

Consent for publication

Not applicable

Competing interests

P. K. T. V. administered IV ketamine is qualified in both psychiatry and anesthesia. The other authors declare that they have no competing interests.

Received: 26 January 2024 Accepted: 11 March 2024
Published online: 23 April 2024

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