International Journal of Research in Medical Sciences
Rasool U et al. Int J Res Med Sci. 2023 Feb;11(2):535-543
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20230029

Original Research Article

Effect of ketamine infusion in treatment resistant depression and in depressive patients with active suicidal ideations: a study from North India

Ubaid Rasool[1], Neelofer Jan[1], Marya Zahoor[1]*, Fazle Roub[1], Yasir Hassan Rather[1], Arshad Hussain[1], Rukhsana Najeeb[2]

[1]Department of Psychiatry (IMHANS-K), GMC Srinagar, Kashmir, Jammu and Kashmir, India
[2]Department of Anaesthesiology, GMC Srinagar, Kashmir, Jammu and Kashmir, India

Received: 26 December 2022
Revised: 09 January 2023
Accepted: 11 January 2023

***Correspondence:**
Dr. Marya Zahoor,
E-mail: maryazahoor@gmail.com

ABSTRACT

Background: Treatment resistant depression can be a life-threatening condition as it leads to an increase of suicide attempts by two to three folds. It has been estimated that nearly 1 million people die due to suicide every year, and more than two-third of these cases occur when the person is undergoing a major depressive episode. Ketamine is an NMDA receptor antagonist, an anesthetic agent that is short acting and has recently been used as an antidepressant and anti-suicidal agent. It has been seen that a single intravenous infusion of ketamine at a lower dose. i.e., subanesthetic dose of 0.5 mg/kg over a period of 40 minutes produces antidepressant effect which lasts for about a week and various studies have proved that repeated infusions of ketamine can prolong the duration of the antidepressant response.
Methods: It was an observational/descriptive study done in the ketamine clinic/ECT suite of institute of mental health and neurosciences Kashmir (an associate hospital of government medical college Srinagar) which runs once a week. In this study, patients satisfying the criteria of TRD and depressive patients with active suicidal ideations, visiting the ketamine clinic who had given a valid informed consent for ketamine infusion enrolled and observed for ketamine efficacy by using specific scales. The study done over a period of 18 months from January 2020 till July 2021.
Results: The response rate of ketamine in our study for treatment resistant depression was 70.27%. The response rate of ketamine for suicidality in our study was 63.16%. Our study showed a rapid onset of action for ketamine, two hours after ketamine infusion.
Conclusions: A significant fraction of patients suffering from major depressive disorder do not respond to antidepressants and have a poor psychosocial functioning and an increased risk of suicide attempts making their condition life threatening. These patients therefore require special attention to address their underlying condition as well as suicidality to improve their outcome. In this context we studied the role of intravenous ketamine infusion in these patients in improving the psychosocial outcome as well as preventing the suicidal ideation.

Keywords: Depression, Suicide, Ketamine

INTRODUCTION

Major depressive disorder (MDD) is a chronic disorder which is characterized by a varying course over a period of time where some patients have fluctuating levels of symptomatology, and some remain fully symptomatic over time and experience significant impairment in psychosocial and occupational functioning.[1] MDD is a heterogenous disorder, and it has been seen that nearly 30% of the patients suffering with MDD do not achieve

remission with commonly used antidepressant medications. Various large scale clinical trials like sequenced treatment alternatives to relieve depression (STAR*D study), have found the cumulative remission rate after 4 trials of conventially used antidepressants to be 67%, with 10%-20% of patients failing to achieve remission after 4 trials of sequenced treatment approaches.[2] Such patients who do not achieve remission fall in the category of treatment resistance. Treatment resistant depression (TRD) is generally defined as failure to respond to at least two different classes of antidepressants for an adequate duration of 4-6 weeks with full compliance.[3] Patients who belong to the group of TRD have poor prognosis in comparison to those who respond to antidepressant medications. Various risk factors associated with TRD comprise of any psychiatric comorbidity like anxiety and personality disorders, early onset, frequent hospitalizations, episode severity, melancholic features and non response to first treatment. Such patients also experience frequent relapses and have a poor psychosocial functioning and quality of life. Also, TRD can be a life-threatening condition as it leads to an increase of suicide attempts by two to three folds as compared to those who are treatment responsive.[4] Thus, TRD requires special attention as this condition can have worst outcome in form of poor psychosocial functioning and suicide.

Suicide is a psychiatric emergency. Experiencing suicidal ideations is very common in patients with MDD who do not achieve remission. It has been estimated that nearly 1 million people die due to suicide every year, and more than two-third of these cases occur when the person is undergoing a major depressive episode.[5] Suicidal behavior can occur because of multiple factors varying from any sudden distressful event or as a result of an ongoing mental illness such as depression and schizophrenia.[6] One of the important factors related to suicidal behavior is the time between decision making and executing the plan of suicide. It has been found that nearly 74% of the suicide attempts are made during this time period. Presently various therapeutic interventions available for reducing suicidal risk include conventional antidepressants, lithium and ECT along with dialectal behavior therapy (DBT) and cognitive behavioral therapy (CBT) for bipolar affective disorder and MDD as well as clozapine, an antipsychotic for schizophrenia. All these interventions take time to show effect to change the course of suicidal behavior and are helpful in long-term suicidal prevention.[7] Thus, in a clinical scenario a timely and rapidly acting therapeutic intervention is required to reduce the risk of suicidal attempt when the person is in the process between decision making as well as action taking.

Ketamine is an NMDA receptor antagonist, an anesthetic agent that is short acting and has recently been used as an antidepressant and anti-suicidal agent. Ketamine has different effects at different doses.[8] It has been seen that a single intravenous infusion of Ketamine at a lower dose. i.e., subanesthetic dose of 0.5 mg/kg over a period of 40 minutes produces antidepressant effect which lasts for about a week and various studies have proved that repeated infusions of ketamine can prolong the duration of the antidepressant response.[9] Several studies have also supported the role of single ketamine infusion in reducing the suicidal ideations for at least seven days and the role of repeated infusions in sustaining the anti-suicidal effect.[5]

Ketamine was synthesized by Calvin Lee Stevens PhD, Professor of organic chemistry at Wayne university.[10] It is an N-methyl-d-aspartate (NMDA) receptor antagonist. Normally a GABA interneuron is present between two glutamate neurons which inhibits the release of glutamate from the postsynaptic neuron i.e., the second glutamate neuron. When ketamine (NMDA receptor antagonist) acts on a GABA interneuron, the GABA interneuron is inactivated, and it does not release GABA which normally would inhibit the release of glutamate from the post synaptic glutamate neuron. Thus, the release of glutamate is increased. This increase in glutamatergic activity stimulates AMP and m-GluR receptors which activates ERK/AKT signal transduction cascade which further triggers m-tor (mammalian target of rapamycin) pathway and brain derived neurotrophic factor (BDNF) that causes the expression of synaptic proteins leading to an increased density of dendritic spines.[11,12] It is this increase in dendritic spines that causes the rapid onset of antidepressant effect. Other mechanisms of action of ketamine involve its effect on cholinergic system, monoaminergic system and its affinity for opioid receptors as well. Ketamine can be administered by numerous routes including intravenous, subcutaneous, intranasal, oral, sublingual, and intramuscular. Recently in 2019 FDA approved intranasal es-ketamine for treating depression.[13] Two features of the antidepressant response to ketamine make it striking: first, it can manifest itself within minutes or hours; second, its effect has mostly been shown to take place in patients with treatment resistant depression and since it can provide immediate relief, it removes the impetus to engage in suicidal acts as well. The response rate of ketamine has generally been 50% in placebo-controlled trials.[14]

Many studies have been done internationally on the effect of ketamine in terms of treatment resistant depression and suicide but only a few studies are available from India and no study has been done in Kashmir so far. Thus, this study aims to analyze the effect of ketamine in patients with treatment resistant depression and in reducing suicidal ideations in depressive patients with active suicidality among Kashmiri population.

METHODS

Study type

This was a descriptive observational study.

Study place

The study was done in the ketamine clinic/ECT suite of institute of mental health and neurosciences Kashmir (an associate hospital of government medical college Srinagar) which runs in collaboration with the department of anesthesia, GMC Srinagar once a week.

Study period

The study was done over a period of 18 months from January 2020 till July 2021.

Selection criteria

Two types of patients were taken up for this study- Subjects who fulfilled the criteria of treatment resistant depression TRD (i.e., a failure to respond to at least two different classes of antidepressants for a period longer than 4 weeks at the maximum recommended dose) and depressive patients with active suicidal ideations.

Inclusion criteria

Patients fulfilling the criteria of TRD and depressive patients with active suicidal ideations, who belonged to the age group of 18-60 years and who gave informed written consent were included in the study.

Exclusion criteria

Subjects below the age of 18 and above 60, patients with history suggestive of contraindications to use of ketamine i.e myocardial infarction within the last three months, unstable angina or uncontrolled cardiac failure, severe vascular disease, cerebral vascular disorders, raised intracranial pressure, pheochromocytoma, or penetrating eye injury and subjects with any other organic brain disease were excluded from the study.

Study method and instrument used

The nature of the study was explained to the patients in detail and in an understandable and unambiguous language and they were given freedom of choice to accept or refuse the participation. The patients were enrolled after they had given a proper consent by filling a proper consent form which was provided to them.

The subjects selected based on above-mentioned criteria were assessed for the severity of depression and suicidality by applying montgomery asberg depression rating scale (MADRS) and Hamilton depression rating scale (HAM-D) at baseline. After the application of the scales the subjects were administered ketamine infusion as per the hospital standards (0.5 mg/kg over a period of 40 mins). Subjects were observed throughout the infusion and for 2 hours post-infusion. MADRS and HAM-D was applied again at 2hrs and 24 hours after the infusion. The subjects underwent further sessions depending upon the severity of their symptoms, with a maximum of 6 sessions with one session per week. Scales were applied in same way as in the first session. MADRS (1-6) and HAMD (1-6) have been used in the study to represent the scores before the six consecutive ketamine cycles administered to the patients, while MADRS (7) and HAMD (7) represent the scores after 24 hours of administration of sixth dose of ketamine. The side effects if any were also noted and managed accordingly.

MADRS is a 10-item version scale which is most sensitive to change. It is more focused on psychological aspects of depression.[15]

HAM-D is a 17-item version scale which is more focused towards the biological aspects of depression.[15]

Thus, the above-mentioned scales were to assess change in psychological and biological features of depression.

The effect on suicidal ideations was assessed using the suicide item of both MADRS and HAM-D.

Statistical analysis was done using SPSS 26 version.

Ethical approval was obtained from the institutional ethical committee of GMC Srinagar.

RESULTS

A total of 37 patients were included in the study. Mean age of the patients was 39.59±9.97 years. In our study, 2.7% of patients belonged to the age group of 0-20 years, 45.95% of patients were in the age group of 21-40 years. 51.35% patients were in the age group of 41-60. The 51.35% of the patients were females and 48.65% were males. Male: female ratio was 0.94:1. In our study, 70.25% of patients belonged to rural background and the remaining 29.73% were from urban background. 72.97% patients were married and 27.03% were unmarried. Majority of patients in our study (27.3%) were illiterates followed by 21.62% who had completed higher secondary school, 18.92% had completed middle school education, 8.11%% up to high school, 18.92% were graduates and only patient was a postgraduate and one had studied only up to primary school. 43.24% of the patients in our study belonged to lower class, followed by 29.73% patients who belonged to upper-lower class. 21.62%% patients belonged to lower middle class and 5.41% belonged to upper-middle class. None of the patient was from upper class. Majority of our cases were unemployed (37.24%) followed by employed (21.62%), 18.92% were farmers, 10.81% were students and same percentage of cases were skilled workers. Maximum no of the patients were cases of MDD (54.05%), 35.14% were cases of BPAD whereas 10.81% had other psychiatric illness with depression as a comorbidity. 48.65% of patients visiting the ketamine clinic were resistant to oral medication and only 2 had active

suicidality only, while both resistance to oral medication as well as active suicidality was seen in 45.95% patients.

Out of the 37 patients included in the study one patient dropped out after receiving only a single ketamine infusion, while the remaining 36 patients received 6 cycles of ketamine infusion each. Remission which was defined as MADRS score of less than 10 and HAMD score of less than 7 was observed in 43.24% of patients while response which was defined as greater than 50% reductions from baseline in MADRS and HAMD scores was seen in 27.03% patients. 29.73% patients did not show any response (Table 1).

Table 1: Distribution of cases as per response to ketamine.

Response to ketamine	N	Percentage (%)
No response	11	29.73
Response	10	27.03
Remission	16	43.24

Overall response rate of ketamine infusion for treatment resistant depression in study came out to be 70.27%.

A total of 19 patients in the study had suicidal ideations which persisted in seven (36.84%) patients at the end of six ketamine infusions while it was absent in the remaining 12 (63.16%) patients. Thus, the response rate of ketamine for suicidality in our study came out to be 63.16% (Table 2). In majority of the patients, suicidal ideations were absent after administration of second or third infusion (Table 3) Giddiness was the most common side effect seen in 67.5% patients followed by headache seen in 35.1% patients. Dissociation was seen in 18.9% cases whereas nausea/vomiting was experienced by 13.5% of patients and anxiety was experienced by 24.3% of cases (Table 4).

Table 2: Distribution of cases as per effect of ketamine on suicidal ideations at the end of 6 cycles of infusion, (n=19).

Suicidal ideations at the end of 6 cycles	N	Percentage (%)
Still present	7	36.84
absent	12	63.16

Table 3: Distribution of cases as per number of infusions after which suicidal ideations were not seen.

No. of infusions after which suicidal ideations were not present	N	Percentage (%)
First infusion	1	8.33
Second infusion	5	41.67
Third infusion	5	41.67
Forth infusion	1	8.33

Table 4: Distribution of cases as per side effects.

Side effects	N	Percentage (%)
Headache	13	35.1
Giddiness	25	67.5
Dissociation	7	18.9
Nausea/ vomiting	5	13.5
Anxiety	9	24.3

The results in our study showed a rapid onset of action for ketamine with a significant improvement in the mean MADRS and HAMD scores as early as two hours after ketamine infusion. The maximum effect although was seen at 24 hours which then sustained for a week as shown in Tables 5 and 6. The difference between the mean MADRS and HAMD scores at different time intervals came out to be statistically significant.

We observed reductions in mean values of MADRS scores, with each consecutive dose of ketamine infusion in both the categories of patients with treatment resistance depression and active suicidality (Table 7). The maximum reduction in mean MADRS score was after first dose of ketamine from 26.36 to 21.06. The mean MADRS score after six infusions was 11.58 (Table 7) The reductions were statistically significant ($p \leq 0.05$) and quadratic (with progressive decline in degree of reduction with each consecutive cycle of ketamine). Although there is difference in the mean MADRS scores of the patients with active suicidality and treatment resistant depression, the decrease in scores with consecutive cycles of ketamine is quadratic in both the groups and the difference between the two groups is not statistically significant. On conducting the pairwise comparisons of mean MADRS score, of each ketamine cycle with mean scores of the remaining cycles for both categories of patients with treatment resistance and active suicidality, the mean difference was statistically significant ($p \leq 0.05$) every time as shown in the table depicting a significant change in mean MADRS score with all other cycles of ketamine infusion (Table 8).

We also observed reductions in mean values of HAMD score with each consecutive dose of ketamine infusion in both the categories of patients with treatment resistance depression and active suicidality (Table 9). The maximum reduction in mean HAMD score also was after the first dose of ketamine from 19.14 to 15.64. The mean HAMD score after six infusions was 7.89 (Table 9). The reductions were statistically significant ($p \leq 0.05$) and quadratic (with progressive decline in degree of reduction with each consecutive cycle of ketamine). Although there is difference in the mean HAMD score of the patients with active suicidality and treatment resistant depression, the decrease in scores with consecutive cycles of ketamine is quadratic in both the groups and the difference between the two groups is not statistically significant. On conducting the pairwise comparisons of mean HAMD score of each ketamine cycle with mean

scores of the remaining cycles for both categories of patients with treatment resistance and active suicidality, the mean difference was statistically significant ($p \leq 0.05$) every time as shown in the Table depicting a significant change in mean HAMD score with all other cycles of ketamine infusion (Table 10).

Table 5: Mean MADRS scores of all patients at different intervals of time during each ketamine cycle.

Time (Hours)	MADRS1	MADRS2	MADRS3	MADRS4	MADRS5	MADRS6
0	23.73	21.06	17.86	15.69	13.89	12.69
2	23.35	19.44	16.72	15.28	13.14	12.25
24	21.38	18.25	15.81	14.26	12.39	11.58

Table 6: Mean HAM-D scores of all patients at different intervals of time during each ketamine cycle.

Time (Hours)	HAMD1	HAMD 2	HAMD 3	HAMD 4	HAMD 5	HAMD 6
0 hours	19.14	15.64	13.22	11.50	10.17	8.53
2 hours	16.38	14.22	11.94	10.81	9.452	8.17
24 hours	15.38	13.50	11.44	10.36	8.78	7.89

Table 7: depicting mean MADRS scores of all patients before administration of first dose of each cycle (1-6) in both groups of the patients with resistance to oral medication and active suicidality.

Variables		Mean	SD	N
MADRS_1	Resistance to oral medication	23.67	5.314	18
	Active suicidality	29.06	6.890	18
	Total	26.36	6.651	36
MADRS_2	Resistance to oral medication	18.83	2.792	18
	Active suicidality	23.28	7.591	18
	Total	21.06	6.071	36
MADRS_3	Resistance to oral medication	15.67	2.521	18
	Active suicidality	20.06	8.551	18
	Total	17.86	6.599	36
MADRS_4	Resistance to oral medication	13.61	3.883	18
	Active suicidality	17.78	9.072	18
	Total	15.69	7.195	36
MADRS_5	Resistance to oral medication	11.11	4.028	18
	Active suicidality	16.67	9.804	18
	Total	13.89	7.906	36
MADRS_6	Resistance to oral medication	9.61	3.550	18
	Active suicidality	15.78	10.138	18
	Total	12.69	8.113	36
MADRS_6_24*	Resistance to oral medication	8.33	3.272	18
	Active suicidality	14.83	10.433	18
	Total	11.58	8.303	36

*Mean MADRS scores of all the patients with resistance to oral medication and active suicidality at 24 hrs. after the last cycle

Table 8: showing p values on pairwise comparison of mean MADRS score of each ketamine cycle (1-6) with mean MADRS scores of all other ketamine cycles (1-6).

Ketamine cycles	1	2	3	4	5	6
1	X	0.000	0.000	0.000	0.000	0.000
2	0.000	X	0.000	0.000	0.000	0.000
3	0.000	0.000	X	0.010	0.000	0.000
4	0.000	0.000	.010	X	0.001	0.000
5	0.000	0.000	0.000	0.001	X	0.002
6	0.000	0.000	0.000	0.000	0.002	X

Table 9: depicting mean HAMD scores of all patients before administration of first dose of each cycle (1-6) in both groups of the patients with resistance to oral medication and active suicidality.

Variables		Mean	SD	N
HAMD_1	Resistance to oral medication	17.61	3.775	18
	Active suicidality	20.67	4.498	18
	Total	19.14	4.376	36
HAMD_2	Resistance to oral medication	14.50	3.899	18
	Active suicidality	16.78	5.012	18
	Total	15.64	4.574	36
HAMD_3	Resistance to oral medication	11.94	3.506	18
	Active suicidality	14.50	5.437	18
	Total	13.22	4.691	36
HAMD_4	Resistance to oral medication	10.33	3.565	18
	Active suicidality	12.67	5.801	18
	Total	11.50	4.890	36
HAMD_5	Resistance to oral medication	8.61	3.973	18
	Active suicidality	11.72	6.824	18
	Total	10.17	5.725	36
HAMD_6	Resistance to oral medication	6.78	3.246	18
	Active suicidality	10.28	6.858	18
	Total	8.53	5.578	36
HAMD_6_24h*	Resistance to oral medication	5.83	3.258	18
	Active suicidality	9.94	7.067	18
	Total	7.89	5.810	36

*Mean HAMD scores of all the patients with resistance to oral medication and active suicidality at 24 hrs. after the last cycle.

Table 10: showing p values on pairwise comparison of mean HAM-D score of each ketamine cycle (1-6) with mean HAM-D scores of all other ketamine cycles (1-6).

Ketamine cycles	1	2	3	4	5	6
1	X	0.000	0.000	0.000	0.000	0.000
2	0.000	X	0.000	0.000	0.000	0.000
3	0.000	0.000	X	0.006	0.000	0.000
4	0.000	0.000	0.006	X	0.012	0.000
5	0.000	0.000	0.000	0.012	X	0.000
6	0.000	0.000	0.000	0.000	0.000	X

DISCUSSION

There are several therapeutic interventions available to reduce the risk of suicide in severe psychiatric disorders, notably lithium and clozapine. These agents although being effective get downplayed in clinical practice due to their slow onset of action promoting use of electroconvulsive therapy for suicidal ideation in severe depression. It has been seen that single intravenous infusion of Ketamine at a lower dose. i.e., subanesthetic dose of 0.5 mg/kg over a period of 40 minutes produces antidepressant effect within minutes to hours which lasts for about a week and various studies have proved that repeated infusions of ketamine can prolong the duration of the antidepressant response.[9] Our study found a rapid and profound effect of intravenous ketamine infusions in significantly decreasing the suicidal ideation in patients of severe treatment resistant depression. This highlights its ability to be used as a quick intervention for suicidal ideation in acutely depressed patients, until conventional agents with a delayed onset of action come into play.

The patients included in our study had treatment resistant depression, suicidal ideation, or both. All the patients were administered six cycles of intravenous ketamine infusion. They were evaluated using MADRS scale and HAMD scale before each cycle of ketamine infusion, and the scales were reapplied at two and 24 hours following the administration of each cycle of ketamine.

As the patients included in our study represent a particular geographical region, the demographics in our study vary across various other studies which have studied the role of ketamine in treatment resistant depression. The mean age of patients in our study was 39.59±9.87 years which corresponded closely to that reported by Singh et al in their randomized controlled trial, while Shiroma et al documented a mean age of 54.4 which was much greater than that of our study.[9,16] Although, social stressors tend to place younger individuals at an increased risk of depressive disorders, but the finding of majority of our patients belonging to age group of 40-60 years and mean age of patients being

around 40 years can be explained by the fact that since our study is based on treatment resistant depression, by the age of 40 years, depressive patients have usually undergone other failed therapeutic interventions before being labelled as treatment resistant cases. Our study had almost similar number of male and female patients with a male: female ratio of 0.94:1 which was similar to that of Philips et al while Diamond et al reported a greater number of male patients in their study with a ratio of 1.3:1.[5,17] Majority of the patients in the study conducted by Shiroma et al were married (68%).[9] Our study also reported a greater percentage of married patients (72.97%). This finding can be explained by the fact that the mean age of patients in our study is around 39 years and most of the people in our part of the society are married by this age. Also, married people are usually overburdened by the social and financial responsibilities which strains a marriage constantly and can manifest in form of psychological or physical distress.[18] The study conducted by Shiroma et al documented 64 % of patients who were unemployed, but our study documented a decreased percentage of 37.84% of the patients being unemployed and majority of the patients had some source of income.[9] Since this study was conducted in a tertiary care hospital which receives patients from different walks of life, many patients in our study have one or other source of income. Also, occupational environment can be a source of escalating stress in form of job insecurity or increase workload which often leads to burnout among the employees.[19] Murrough et al documented only 34% of the patients in their study to be educated.[20] In contrast in our study majority of patients (27.03%) were illiterate while all others received education up to primary school or more. Similar results were documented by Ahmad et al in their study on sociodemographic profile of depressive patients in Kashmir.[21] One of the reasons of this finding could be the fact that education provides better and timely access to resources and better ability to deal with life situations, consequently uneducated people are more prone to face difficult life situations and often are late in recognizing their condition and seeking timely management of depression.

Various studies and randomized controlled trials have shown the efficacy of ketamine in treatment resistant depression and suicidality.[14,22] In our study too treatment resistant depression was the major cause for which ketamine was administered (n=18), while in 2 patients it was administered for active suicidality only and 17 patients had treatment resistant depression compounded with active suicidality. The diagnosis of slightly more than half of the patients in our study was MDD (54.04%), followed by BPAD (35.14%), while 10.81% of the patients in our study had other psychiatric illnesses where depression was a comorbidity. Diamond et al on the other hand reported MDD in 78% of their patients, while BPAD was seen in 22% of the patients.[17]

Our study found a rapid and profound effect of ketamine on both treatment resistant depression and suicidal ideation as reflected by response rates of 70.27% and 63.16% respectively, using the MADRS and HAMD scores. Lener et al have also documented a response rate of ketamine for TRD to be equivalent to 65-70 % which is in congruence with the response rate found in our study.[23] While most studies studying the effect of ketamine on treatment resistant depression have found it to be effective, differences do exist across various studies regarding the degree of its effect. Also, the studies vary in the number of doses administered and the schedule of dosage followed. Zarate et al in his RCT comparing ketamine with a placebo found a significant improvement in depression in patients taking ketamine and the difference continued to remain significant the following week, with 35% of the subjects maintaining response for the next week.[24] Mandal et al too in their study which involved administration of six doses of ketamine over a period of 2 weeks observed significant improvement in depression, anxiety, and the severity of illness which persisted for one month following the last dose of ketamine.[8] All the patients included in our study had a significant response to the first dose of ketamine infusion. The study conducted by Zhang et al also report the largest improvement (>50%) in patients of TRD after the first ketamine infusion.[25] While Mandal et al found a significant effect after one hour of ketamine infusion, we documented the same at two hours (Table 3) following ketamine infusion when compared with the baseline.[8] The peak effect in our study was seen at 24 hours post infusion and sustained for a week, which is in concurrence with the findings of Zarate et al.[24] Although the first dose of ketamine produced the most profound effect, we observed statistically significant differences in MADRS and HAMD scores after consecutive administration of each of the total six ketamine doses (Tables 7-10). This emphasizes the necessity and efficacy of repeated infusions for a sustained response. These results when plotted graphically revealed a quadratic relationship between consecutive ketamine infusions and both MADRS and HAMD scores. Similar observations were documented by Rot et al while employing MADRS and QIDS-SR_{16} scores.[26] The response rate of ketamine for suicidal ideations in our study was 63.16%. this is in congruence with study conducted by Jennifer Phillips et al. one of the findings in our study is that out of the two patients who only had suicidal ideations without depression, ketamine proved to be effective for both as both of them did not report any suicidal ideation after repeated ketamine infusion.[5] Similar finding suggesting the role of ketamine in reducing suicidal ideations irrespective of depression and anxiety is also supported by Bellard et al in their study on improvement in suicidal ideations after ketamine infusion, however more studies are required to document the role of ketamine in reducing suicidality independent of depression and anxiety.[27] The sustained results seen in our study point towards other possible mechanisms of action for ketamine in addition to NMDA antagonism which stimulates AMP and m-GluR receptors that activates ERK/AKT signal transduction cascade which further triggers m-tor (mammalian target

of rapamycin) pathway and brain derived neurotrophic factor (BDNF) that causes the expression of synaptic proteins leading to an increased density of dendritic spines.[11,12] Although same would better be illustrated with further functional and molecular studies on the subject.

The side effects seen in our study were transient and included mainly headache and giddiness, while dissociation was seen only in seven patients (Table 4). The weekly infusions of ketamine over a period of six weeks seem to be well tolerated without any serious side effects. The safety of multiple intravenous infusions of ketamine, have also been confirmed by various previous studies. Diamond et al had also reported one case of BPAD who developed hypomanic symptoms after three infusions, however no such switch of polarity was observed in any of the BPAD patients in our study.[17] These findings suggest that the improvement in anxiety scores by ketamine infusions is not by ketamine associated dissociation or euphoria, but due to the profound effect it exerts on core depressive symptomology making it useful in clinical practice.

Limitations

Our study did not involve the follow up of patients after 6 weeks, so the role of ketamine infusion for sustained remission cannot be commented on. Various authors have also raised concerns regarding long term side effects like cognitive decline and hemorrhagic cystitis These side effects are usually seen on usage of ketamine on long term basis, as in recreational drug abusers. As our study did not involve long term follow up of patients the occurrence of these side effects cannot be ruled out in our study, but to study the cognitive deficits in patients would ideally involve employing neuropsychological tests at various intervals.[28]

CONCLUSION

A significant fraction of patients suffering from MDD do not respond to antidepressants and fall into the category of treatment resistant depression. Such patients have a poor psychosocial functioning and an increased risk of suicide attempts making their condition life threatening. These patients therefore require special attention to address their underlying condition as well as suicidality to improve their outcome. In this context we studied the role of intravenous ketamine infusion in these patients in improving the psychosocial outcome as well as preventing the suicidal ideation. Our study suggests that ketamine has a rapid and profound effect on both treatment resistant depression and suicidal ideation. It is well tolerated in multiple dosages with transient and mostly mild side effects. This highlights its ability to be used as a quick intervention for patients with treatment resistant depression and suicidal ideation, until conventional agents with a delayed onset of action come into play.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Greer TL, Kurian BT, Trivedi MH. Defining and measuring functional recovery from depression. CNS Drugs. 2010;24(4):267-84.
2. Voineskos D, Daskalakis ZJ, Blumberger DM. Management of Treatment-Resistant Depression: Challenges and Strategies. Neuropsychiatr Dis Treat. 2020;16:221-34.
3. Trevino K, McClintock SM, McDonald Fischer N, Vora A, Husain MM. Defining treatment-resistant depression: a comprehensive review of the literature. Ann Clin Psychiatr. 2014;26(3):222-32.
4. Kraus C, Kadriu B, Lanzenberger R. Prognosis and improved outcomes in major depression: a review. Transl Psychiatr. 2019;9:127.
5. Phillips JL, Norris S, Talbot J, Hatchard T, Ortiz A, Birmingham M et al. Single and repeated ketamine infusions for reduction of suicidal ideation in treatment-resistant depression. Neuro-psychopharmacology. 2020;45(4):606-12.
6. Carboni Ezio, Carta A R, Carboni Elena, Novelli A. Repurposing Ketamine in Depression and Related Disorders: Can This Enigmatic Drug Achieve Success? Front Nuerosci. 2021;30.
7. Thakurta RG, Das R, Bhattacharya AK, Saha D, Sen S, Singh OP, Bisui B. Rapid response with ketamine on suicidal cognition in resistant depression. Indian J Psychol Med. 2012;34(2):170-5.
8. Mandal S, Sinha VK, Goyal N. Efficacy of ketamine therapy in the treatment of depression. Indian J Psychiatr. 2019;61(5):480-5.
9. Shiroma PR, Thuras P, Wels J. A randomized, double-blind, active placebo-controlled study of efficacy, safety, and durability of repeated vs single subanesthetic ketamine for treatment-resistant depression. Transl Psychiatr. 2020;10:206.
10. Chang Lee C, Rajagopalan S, Mathew SJ. History of Ketamine use and its clinical indications. In; Mathew SJ, Zarate Jr CA., editors. Ketamine for treatment resistant depression- the first decade of progress. Switzerland; Springer Nature. 2016;3.
11. Fourcade EW, Lapidus KAB. The basic and clinical pharmacology of Ketamine. In; Mathew SJ, Zarate Jr CA., editors. Ketamine for treatment resistant depression- the first decade of progress. Switzerland; Springer Nature. 2016;17
12. Stahl SM. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Application. 4th ed. Cambridge, UK; New York: Cambridge University Press. 2011.
13. Breseghello CV, Da Costa LP, Luiz LA. Subcutaneous Ketamine in Depression: A Systematic Review. Front Psychiatr. 2021;12.

14. Blier P, Blier J. Ketamine: Clinical Studies in Treatment-Resistant Depressive Disorders. In; Mathew SJ, Zarate Jr CA., editors. Ketamine for treatment resistant depression- the first decade of progress. Switzerland; Springer Nature. 2016;31
15. Lee B, Mark AB. Handbook of clinical rating scales and assessment in psychiatry and mental health. 1st ed. Boston USA, Springer. 2010;8-13.
16. Singh JB, Maggie F. A Double-Blind, Randomized, Placebo-Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients with Treatment-Resistant Depression. Am J Psychiatr. 2016;173(8):816-26.
17. Diamond PR, Farmery AD, Atkinson S, Haldar J, Williams N, Cowen PJ et al. Ketamine infusions for treatment resistant depression: a series of 28 patients treated weekly or twice weekly in an ECT clinic. J Psychopharmacol. 2014;28(6):536-44.
18. Choi H, Marks NF. Marital Conflict, Depressive Symptoms, and Functional Impairment. J Marriage Fam. 2008;70(2):377-90.
19. Woo JM, Postolache TT. The impact of work environment on mood disorders and suicide: Evidence and implications. Int J Disabil Hum Dev. 2008;7(2):185-200.
20. Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, Aan het Rot M, Collins KA et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol Psychiatr. 2013;74(4):250-6.
21. Ajaz A, Sajid MW, Abdul WK. Socio-demographic and clinical profile of patients with major depressive disorder attending psychiatric OPD. JMSCR. 2020;8(5):197-205.
22. Bellard ED, Price RB. Ketamine and suicide risk. In; Mathew SJ, Zarate Jr CA, editors. Ketamine for treatment resistant depression- the first decade of progress. Switzerland; Springer Nature. 2016;46
23. Lener MS, Kadriu B, Zarate CA Jr. Ketamine and Beyond: Investigations into the Potential of Glutamatergic Agents to Treat Depression. Drugs. 2017;77(4):381-401.
24. Zarate CA, Singh JB, Carlson PJ. A Randomized Trial of an N-methyl-D-aspartate Antagonist in Treatment-Resistant Major Depression. Arch Gen Psychiatr. 2006;63(8):856-64.
25. Ji-Chun Z, Su-xia L, Hashimoto K. R (−)-ketamine shows greater potency and longer lasting antidepressant effects than S (+)-ketamine. Pharmacol Biochem Behav. 2014;116:137-41.
26. Rota MH, Collins KA. Mathewa Safety and Efficacy of Repeated-Dose Intravenous Ketamine for Treatment-Resistant Depression. Biol Psychiatr. 2010;67(2):139-45.
27. Ballard ED, Ionescu DF, Vande Voort JL, Niciu MJ, Richards EM, Luckenbaugh DA et al. Improvement in suicidal ideation after ketamine infusion: relationship to reductions in depression and anxiety. J Psychiatr Res. 2014;58:161-6.
28. Schwartz J, Murrough JW, Iosifescu DV. Ketamine for treatment-resistant depression: recent developments and clinical applications. Evid Based Mental Health. 2016;19(2):35-8.

Cite this article as: Rasool U, Jan N, Zahoor M, Roub F, Rather YH, Hussain et al. Effect of ketamine infusion in treatment resistant depression and in depressive patients with active suicidal ideations: a study from North India. Int J Res Med Sci 2023;11:535-43.