International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

# A Randomised Study to Evaluate and Compare the Safety of Intravenous vs Intramuscular Ketamine in Major Depressive Disorder with Suicidal Ideations

**Dr. Akanksha[1], Dr. Ved Prakash Gupta[2], Dr. Mohd. Asif Seraj[3], Dr. Deoshree Akhouri[4]**

[1]Senior Resident, Department of Psychiatry, JNMCH, AMU, Aligarh, India
[2]Consultant Psychiatrist, Shubh Superspeciality Centre, Aligarh, India
[3]Junior Resident, Department of Psychiatry, JNMCH, AMU, Aligarh, India
[4]Consultant Psychologist, Department of Psychiatry, JNMCH, AMU, Aligarh, India

**ABSTRACT**

**Background:** Depression is a common psychiatric illness that can be very disabling. In severe instances, it can result in suicide. Being an emergency, ketamine has showed rapid response in terminating suicidality and reducing depressive symptoms.

**Objectives:** The aim of the study was to evaluate and compare the safety of intravenous and intramuscular ketamine in major depressive disorder.

**Method:** The present study was conducted in the MDD patients with suicidal ideations who were recruited from psychiatry OPD/IPD during the period November 2021 to October 2022. Ketamine was given at a dose of 0.5mg/kg as a single intravenous infusion in 100 ml NS for a period of 40 minutes or a single intramuscular injection on gluteal muscle and safety of ketamine was assessed on semi-structured proforma.

**Results:** In both groups, most common side effect was anxiety. Other side effects noted were *nausea/vomiting, sedation/drowsiness, dizziness, heaviness of head, lightness of body, emotional abreaction, derealisation/depersonalisation, blurred vision, tachycardia, raised blood pressure and elevated mood*. All side effects were transient and improved on its own within 24 hours. None of the participants withdrew because of the adverse effects of ketamine. So, ketamine can be a safer alternative when given by im route.

**Keywords:** Depression, suicide, ketamine, intravenous ketamine, intramuscular ketamine

Major depressive disorder (MDD), commonly referred to as clinical depression, is a mental disorder marked by at least two weeks of persistent low mood, poor self-esteem, and loss of interest or pleasure in usually pleasurable activities. Depression is a common psychiatric illness that can be very disabling. It can significantly lower social and occupational functioning, lowering quality of life.

Depression is associated with more than half of all suicide attempts, and patients with untreated depressive

disorder have a 20% lifetime risk of suicide (Gotlib et al., 2002). Suicide is a global public health issue. Suicide is the second leading cause of death in the second and third decades of life. Suicide rates differ between sexes and across lifetimes, and methods vary by country. (Bachmann S., 2018).

Anti-depressants commonly used today either boost monoamine transmission or stop degradation. Although they immediately enhance neurotransmitter transmission, the clinical antidepressant benefits of these drugs may take a few weeks to manifest. (Krishnan and Nestler 2008). Also, suicide is a psychiatric emergency. Though all these pharmacological and psychological methods are effective in one or other way but they do not lead to rapid termination of suicidal ideations. Ketamine is a drug that is being studied for it's action in rapid reduction of suicidal ideations.

Ketamine works by blocking the N-methyl-D-aspartate (NMDA) receptor on postsynaptic glutamate binding protein. Its effectiveness may be explained by the fact that anomalies in glutamatergic signalling have been linked to major depressive disorder and suicide. The rapid onset of action of ketamine, together with an acute antidepressant effect, seems to have the potential to lessen suicidal ideation as well, even though the neurological basis for the association between depression and suicide is not fully understood (Rajkumar et al., 2015).

Ketamine has been demonstrated to be safe and well tolerated in sub-anaesthetic doses. As an antidepressant, a sub-anaesthetic dose of 0.5mg/kg appears to be the most feasible and tolerable. Less than this dose has minimal antidepressant benefit, whereas doses above 0.5 mg/kg have significant adverse effects and can be very sedating (Fava et al., 2018).

The most common general side effects in the first four hours after the infusion were drowsiness, poor coordination, dizziness, blurred vision, and a strange or unreal feeling. It is widely accepted that adverse effects from sub-anaesthetic ketamine doses peak within the first two hours of infusion and resolve within 4-24 hours. There have been no cases where the effects have lasted longer than this. Dissociation is a common side effect of ketamine infusions and is the most commonly reported psychotomimetic side effect at subanaesthetic doses (Short et al. 2018). Psychotic symptoms such as hallucinations or bizarre behaviour can occur.

Ketamine's activation of the sympathetic nervous system causes an increase in blood pressure and heart rate (Tweed, Minuck, and Mymin 1972). A bolus injection of IV ketamine followed by a maintenance dosage infusion or a continual slow infusion can cause acute deficits in working, episodic, and semantic memory. (Curran HV et al., 2001)

The majority of studies looking into ketamine's safety as an antidepressant and antisuicidal have used the intravenous route. The other routes including intramuscular have been scarcely studied. While intravenous route is cumbersome, relatively costly and requires close observation during 40 min infusion, intramuscular route may eliminate these disadvantages. There is no study as per our knowledge comparing specifically the safety of intramuscular and intravenous route in depression with suicidality with a single dose of ketamine. So, this study was done with the aim to evaluate the safety of intramuscular vs intravenous ketamine in Major Depressive Disorder with suicidal ideations.

**Material and methods**

This study was randomised, hospital based, comparative, parallel group interventional study between November 2021 to October 2022. This study was approved by the Institutional Ethics Committee, JNMCH, AMU, Aligarh, UP, India (Ref No.- IECJNMC/407). Appropriate written informed consent was taken from the patient before giving ketamine injection/infusion.

**Sampling Technique**

Random purposive sampling was used to collect the data for study.

**Inclusion criteria:**

1. Subjects aged 18-60 years of both male and female gender.
2. Subjects who gave informed consent for this study.
3. Subjects who met the DSM-5 criteria for Major Depressive Disorder.
4. Subjects who scored 14 or more (moderate to severe) on Hamilton Depression Rating Scale.
5. Subjects who had suicidal ideations.

**Exclusion criteria:**

1. Subjects aged below 18 years and above 60 years.
2. Subjects who did not give informed consent for study.
3. Subjects who had any contraindication to administration of ketamine.
4. Subjects who had any other psychiatric or physical comorbidity.
5. Subjects with HAM-D score of less than 14 and having no suicidal ideation.

**Study procedure**

Total 110 patients of depression with suicidal ideations were recruited from Psychiatry OPD/IPD after making the diagnosis of Major Depressive Disorder as per DSM-5. They were assessed on a semi structured proforma which included socio-demographic details, brief clinical history, physical examination and mental status examination. Depression was assessed using Hamilton Depression Rating Scale (HAM-D) and suicidal ideations were assessed using Modified Scale for Suicidal Ideation (MSSI). Patient evaluation, randomisation, intervention and scale application was done by senior resident of psychiatry under consultant supervision.

After assessment and based on inclusion and exclusion criteria, around 80 patients were randomised into 2 groups (Group 1 and Group 2) using chit method. Group 1 was given intravenous infusion of ketamine, 0.5mg/kg of body weight in 100 ml normal saline slowly over a duration of 40 minutes and Group 2 was given intramuscular ketamine in the dose of 0.5 mg/kg of body weight in the gluteal region.

Vitals like pulse rate, blood pressure (BP), respiratory rate, saturation (SpO2) were assessed just before starting the procedure and on an hourly basis for 4 hours after giving ketamine injection in both groups. Adverse effects were monitored during the whole procedure and till 24 hours on semi structured ketamine safety proforma.

**Statistical Analyses**

The data obtained from this study was analyzed with the help of Statistical Package for Social Sciences (Version 26.0.), using statistical tools listed below. Frequency distribution was calculated for socio-demographic and clinical profile of depression patients with suicidal ideations. Group differences between safety of intravenous and intramuscular groups were analyzed using the Chi square test.

**Results**

This study included 110 subjects of Major Depressive Disorder having suicidal ideations. Thirty patients were excluded and 80 were randomised into 2 groups using chit method. Forty-one patients were given

given intravenous infusion of ketamine and 39 subjects were given ketamine through intramuscular route.

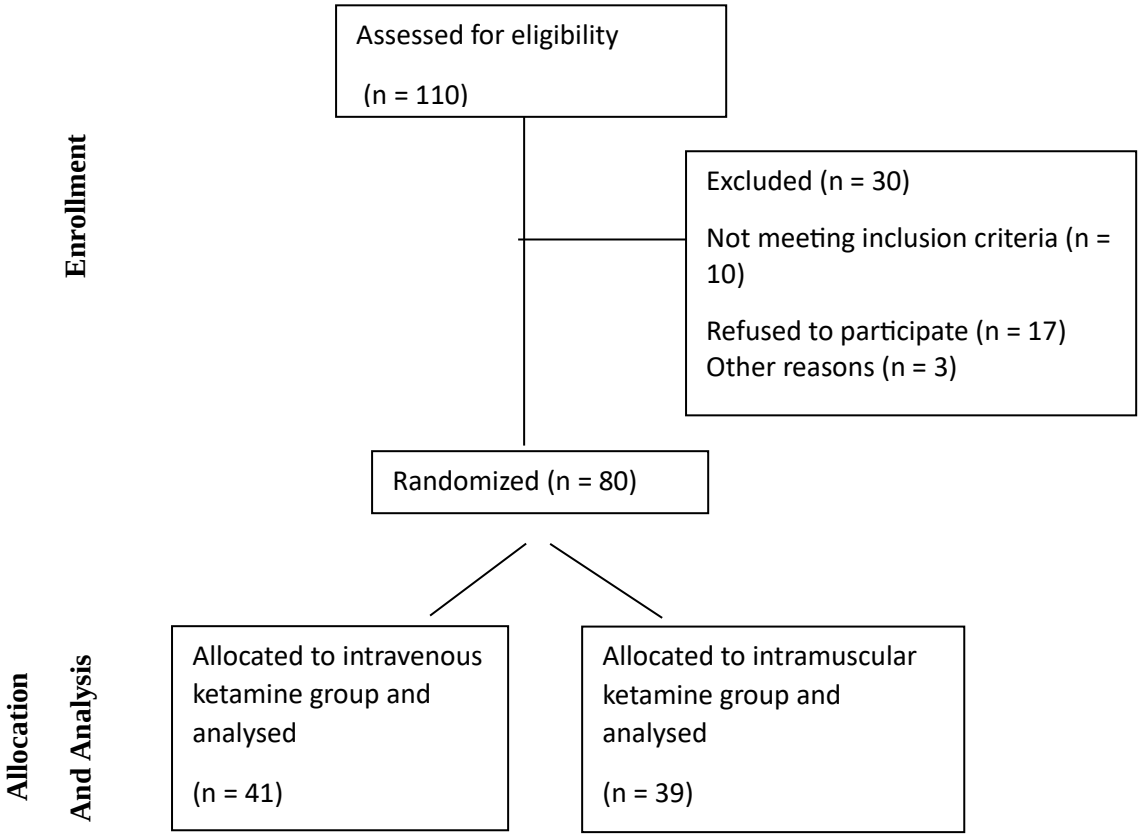


***Table 1*** depicts socio-demographic profile of individuals. Most of the patients in both the groups were in the 18-30 age group, males and married, with the mean age in intravenous group to be 34.63 ± 9.86 while it was 34.31 ± 11.77 in intramuscular group. IV group consisted of 31.7% illiterates while IM group had 23.1% illiterates with rest being literate till post- graduation. Most of the patients were employed in both groups with only 2 and 5 patients unemployed in IV and IM group respectively. Majority in both the groups were residing in urban area, following Islam religion, living in nuclear families, had some precipitating event, with few having past and family history suggestive of any psychiatric illness.

**Table 1: Socio-Demographic profile of patients in both intravenous and intramuscular groups**

| Socio-Demographic Variables | Mode 0f Injection | | Total | p-Value |
|---|---|---|---|---|
| | Intravenous N (%) | Intramuscular N (%) | N (%) | |
| **Age group** | | | | |
| 18-30 | 17 (41.5) | 16 (41.0) | 33 (41.3) | 0.848 |
| 31-40 | 13 (13.7) | 12 (30.8) | 25 (31.3) | |
| 41-50 | 8 (19.5) | 6 (15.4) | 14 (17.5) | |
| 51-60 | 3 (7.3) | 5 (12.8) | 8 (10.8) | |
| Mean ± sd | 34.63 ± 9.86 | 34.31 ± 11.77 | 34.48 ± 10.76 | |
| **Gender** | | | | |
| Male | 26 (63.4) | 23 (59.0) | 49 (61.3) | 0.684 |

| | | | | |
|---|---|---|---|---|
| Female | 15 (36.6) | 16 (41.0) | 31 (38.8) | |
| **Marital status** | | | | |
| Single | 15 (36.6) | 13 (33.3) | 28 (35.0) | 0.761 |
| Married | 26 (63.4) | 26 (66.7) | 52 (65.0) | |
| **Education** | | | | |
| Illiterate | 13 (31.7) | 9 (23.1) | 22 (27.5) | |
| Primary | 2 (4.9) | 4 (10.3) | 6 (7.5) | |
| Middle | 4 (9.8) | 3 (7.7) | 7 (8.8) | |
| Secondary | 2 (4.9) | 9 (23.1) | 11 (13.8) | 0.315 |
| Senior secondary | 5 (12.2) | 3 (7.7) | 8 (10.0) | |
| Graduate | 11 (26.8) | 8 (20.5) | 19 (23.8) | |
| Post graduate | 4 (9.8) | 3 (7.7) | 7 (8.8) | |
| **Occupation** | | | | |
| Student | 10 (24.4) | 9 (23.1) | 19 (23.8) | |
| Labourer | 3 (7.3) | 4 (10.3) | 7 (8.8) | |
| Housewife | 6 (14.6) | 10 (25.6) | 16 (20.0) | 0.439 |
| Farmer | 8 (19.5) | 4 (10.3) | 12 (15.0) | |
| Business | 6 (14.6) | 2 (5.1) | 8 (10.0) | |
| Professional | 6 (14.6) | 5 (12.8) | 11 (13.8) | |
| Unemployed | 2 (4.9) | 5 (12.8) | 7 (8.8) | |
| **Religion** | | | | |
| Hindu | 19 (46.3) | 15 (38.5) | 34 (42.5) | 0.476 |
| Muslim | 22 (53.7) | 24 (61.5) | 46 (57.5) | |
| **Residence** | | | | |
| Urban | 21 (51.2) | 24 (61.5) | 45 (56.3) | 0.352 |
| Rural | 20 (48.8) | 15 (38.5) | 35 (43.8) | |
| **Family type** | | | | |
| Nuclear | 23 (56.1) | 21 (53.8) | 44 (55.0) | |
| Joint | 13 (31.7) | 13 (33.3) | 26 (32.5) | 0.980 |
| Extended | 5 (12.2) | 5 (12.8) | 10 (12.5) | |
| **Precipitating factor** | | | | |
| Present | 21 (51.2) | 24 (61.5) | 45 (56.3) | 0.352 |
| Absent | 20 (48.8) | 15 (38.5) | 35 (43.8) | |
| **Past history** | | | | |
| Present | 13 (31.7) | 17 (43.6) | 30 (37.5) | 0.273 |
| Absent | 28 (68.3) | 22 (56.4) | 50 (62.5) | |
| **Family history** | | | | |

| | | | | |
|---|---|---|---|---|
| Present<br>Absent | 12 (29.3)<br>29 (70.7) | 14 (35.9)<br>25 (64.1) | 26 (32.5)<br>54 (67.5) | 0.527 |

(* Significant at p<0.05)

***Table 2*** depicts safety profile of patients in both intravenous and intramuscular ketamine groups. Overall and individually in both the groups, anxiety (42.5%) was the most common side effect followed by derealisation /depersonalisation (39%), tachycardia (36.5%), emotional abreaction (34.1%), blurring of vision (29.2%), raised blood pressure (24.4%), nausea and vomiting (24.4%) and sedation and drowsiness (22%) in intravenous group. Other less common side effects in IV group were heaviness of head (19.5%), dizziness (17.1%), and lightness of body (17.1%). Switching to mania was seen in 1 subject in the IV group.

In intramuscular group, common side effects were blurring of vision and sedation/drowsiness (30.8%), heaviness of head (28.2%), tachycardia (23.1%), emotional abreaction and raised blood pressure (20.5%). Other side effects noted were dizziness (17.9%), nausea/vomiting (15.4%), lightness of body (12.8%) and derealisation /depersonalisation (7.7%).

In derealisation /depersonalisation, the difference was statistically significant between both the groups. The difference was statistically insignificant in all other side effects. All side effects were transient and lasted less than 24 hours.

**Table 2: Safety profile of patients in both intravenous and intramuscular ketamine groups**

| | Mode 0f Injection | | | |
|---|---|---|---|---|
| **Side Effects** | **Intravenous N (%)** | **Intramuscular N (%)** | **Total N (%)** | **p-Value** |
| **Nausea/ Vomiting** | 10 (24.4) | 6 (15.4) | 16 (20.0) | 0.314 |
| **Sedation/ Drowsiness** | 9 (22.0) | 12 (30.8) | 21 (26.3) | 0.370 |
| **Dizziness** | 7 (17.1) | 7 (17.9) | 14 (17.5) | 0.918 |
| **Heaviness of Head** | 8 (19.5) | 11 (28.2) | 19 (23.8) | 0.361 |
| **Lightness of body** | 7 (17.1) | 5 (12.8) | 12 (15.0) | 0.594 |
| **Emotional Abreaction** | 14 (34.1) | 8 (20.5) | 22 (27.5) | 0.172 |
| **Derealisation/ Depersonalisation** | 16 (39.0) | 3 (7.7) | 19 (23.8) | 0.001* |
| **Blurring of vision** | 12 (29.2) | 12 (30.8) | 24 (30.0) | 0.883 |
| **Anxiety** | 19 (46.3) | 15 (38.4) | 34 (42.5) | 0.476 |
| **Raised blood pressure** | 10 (24.4) | 8 (20.5) | 18 (22.5) | 0.678 |
| **Tachycardia** | 15 (36.5) | 9 (23.1) | 24 (30.0) | 0.187 |
| **Elevated mood** | 1 (2.4) | 0 (0) | 1 (1.25) | - |

(* Significant at p<0.05)

## Discussion

The efficacy of ketamine in the rapid reduction of depressive and suicidal symptoms has been observed over the past few years around the globe. Exploration of it's safety in Indian sub-continent can aid in using ketamine for depression in near future. Multiple studies have studied the safety of ketamine in depression

and suicidality but there are nearly no studies comparing the safety of intramuscular and intravenous ketamine in MDD highlighting the need for this study.

Total 80 patients were studied, 41 in IV group and 39 in IM group. In our study, side effects noted after giving ketamine included nausea and vomiting, sedation and drowsiness, dizziness, heaviness of head, lightness of body, emotional abreaction, derealisation and depersonalisation, blurred vision, anxiety, tachycardia, raised blood pressure, and elevated mood. All side effects were transient and improved on its own within 24 hours. None of the participants withdrew because of the adverse effects of ketamine.

Overall, most common among all side effects was anxiety (42.5%) followed by blurring of vision (30.0%) and tachycardia (30.0%), emotional abreaction (27.5%), sedation/drowsiness (26.3%), derealisation/depersonalisation (23.8%), heaviness of head (23.8%), raised blood pressure (22.5%), nausea/vomiting (20%), dizziness (17.5%), lightness of body (15%) and elevated mood (1.25%).

In both groups, most common side effect was anxiety. In Intravenous group, other common side effects were derealisation/depersonalisation (39%), tachycardia (36.5%) and emotional abreaction (34.1%) while in Intramuscular group, other most common side effects were sedation/drowsiness (30.8%), blurring of vision (30.8%) and heaviness of head (28.2%). The difference was statistically insignificant in all side effects except in derealisation/depersonalisation where it was significant (0.001) between the two groups.

A study done by Ibrahim L et al., 2012 on ketamine vs riluzole as an add on to improve depressive symptoms found that perceptual disturbances, confusion, elevations in blood pressure and pulse, drowsiness and dizziness occurred during ketamine infusion, but resolved within 80 min and no clinically meaningful changes in respiratory rate, arterial oxygen saturation, or ECG occurred over the course of the study.

A study done by Brooke Short in 2018 was the first systematic review of the safety of ketamine in the treatment of depression after single and repeated doses. According to a review, anxiety was the most frequent acute psychiatric side-effect, followed by agitation or irritability, delusions or strange thoughts, euphoria, panic, or elevation of mood, and apathy. Studies that used intravenous delivery generally reported higher psychotomimetic or dissociative adverse effects than those that used other delivery methods (eg, oral, subcutaneous, intramuscular). This is in line with the findings of our study.

Our findings are also in accordance with the study done by Chilukuri H et al., 2014 who also noted that adverse effects in both IV and IM group were of mild nature and transient lasting less than an hour with sedation/drowsiness being the most common adverse effect followed by dizziness and emotional abreaction.

## Conclusion

Ketamine has emerged as a promising agent to alleviate depression and suicidality. While conventional antidepressants are slow to act, ketamine has a fast action in depression and in terminating suicidality. Though the safety of IV route has been studied a lot, we still have less research on the safety of IM route. Ketamine when given at a dose of 0.5 mg/kg infusion/ injection caused mild and transient side effects in both the groups. Since our study revealed that the intramuscular route had a good safety profile, it can be employed as a convenient and efficient substitute for intravenous infusion. Further research is needed to study the safety of other modes of ketamine.

## Limitations

Subjects being observed for only 24 hours, ketamine's safety profile could not be assessed for a longer

duration.
The study was done in only one hospital of Northern India reducing it's generalisablity.
Sample size was not calculated, rather a rough estimate was taken.
Ketamine has a high abuse liability, which can lead to misuse and addiction

**Financial support and sponsorship**
Nil.

**Conflicts of interest**
There are no conflicts of interest.

**References**

1. Bachmann S. (2018). Epidemiology of Suicide and the Psychiatric Perspective. International journal of environmental research and public health, 15(7), 1425.
2. Chilukuri, H., Reddy, N. P., Pathapati, R. M., Manu, A. N., Jollu, S., & Shaik, A. B. (2014). Acute antidepressant effects of intramuscular versus intravenous ketamine. Indian journal of psychological medicine, 36(1), 71–76.
3. Curran, H. V., & Morgan, C. (2000). Cognitive, dissociative and psychotogenic effects of ketamine in recreational users on the night of drug use and 3 days later. Addiction (Abingdon, England), 95(4), 575–590.
4. Fava, M., Freeman, M. P., Flynn, M., Judge, H., Hoeppner, B. B., Cusin, C., Ionescu, D. F., Mathew, S. J., Chang, L. C., Iosifescu, D. V., Murrough, J., Debattista, C., Schatzberg, A. F., Trivedi, M. H., Jha, M. K., Sanacora, G., Wilkinson, S. T., & Papakostas, G. I. (2020). Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). Molecular psychiatry, 25(7), 1592–1603.
5. Gotlib, I., Hammen, C. (2002). Handbook of Depression.NewYork: Guildford Press; 2002.
6. Ibrahim, L., Diazgranados, N., Franco-Chaves, J., Brutsche, N., Henter, I. D., Kronstein, P., Moaddel, R., Wainer, I., Luckenbaugh, D. A., Manji, H. K., & Zarate, C. A., Jr (2012). Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole: results from a 4- week, double-blind, placebo-controlled study. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology, 37(6), 1526–1533.
7. Krishnan, V., & Nestler, E. J. (2008). The molecular neurobiology of depression. Nature, 455(7215), 894–902.
8. Rajkumar, R., Fam, J., Yeo, E. Y., & Dawe, G. S. (2015). Ketamine and suicidal ideation in depression: Jumping the gun?. Pharmacological research, 99, 23– 35.
9. Short, B., Fong, J., Galvez, V., Shelker, W., & Loo, C. K. (2018). Side-effects associated with ketamine use in depression: a systematic review. The lancet. Psychiatry, 5(1), 65–7
10. Tweed, W. A., Minuck, M., & Mymin, D. (1972). Circulatory responses to ketamine anesthesia. Anesthesiology, 37(6), 613–619.