The efficacy of intravenous ketamine infusion therapy in depression: A follow up study.

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Abstract

Background: Depression is a common mental illness with a complex etiology and is one of the leading causes of disability worldwide, affecting around 10-20% of the general population in their lifetime. Ketamine, a glutamate receptor–blocking drug approved by the U.S. Food and Drug Administration for anesthetic use, has become a target of research for its antidepressant effects, and possible anti-suicidal effects.

Aim: To study the effect of subanesthetic dose of ketamine on severity of Depression and Anxiety at 1 hour, 1 week and 1 month post administration.

Materials and Methods: A total of 17 patients with severe depression were admitted for the study. Assessments were made at baseline and injection was given at a subanesthetic dose of 0.5 mg/kg intravenous infusion after preparation. Assessments were repeated 1 h after the first dose and patients were followed up and assessments were made at 1 week and 1 month post infusion.

Results: There was a significant improvement in the severity of depression, anxiety, after 1 hour post infusion which was maintained till 1 week and 1 month post infusion. Significant reduction in suicidal thoughts was seen at 1 hour post infusion of the first dose and no emergence was seen at 1 week and 1 month follow up. There were transient adverse effects observed in some patients which subsided within 1 hour.

Conclusion: Ketamine had a rapid effect on alleviating the symptoms of depression and the effect was maintained till 1 month.

Keywords: Ketamine, Anxiety, Depression

Introduction:

Depression is a common mental illness with a complex etiology and is one of the leading causes of disability worldwide, affecting around 10-20% of the general population in their lifetime[1]. Even though SSRIs (Selective serotonin reuptake inhibitors) are the first line of treatment, clinical improvement during the first week of treatment with antidepressants is minimal, as conventional pharmacotherapy modulating monoamine system usually takes 4-12 weeks to see clinical improvement. The pathophysiology of depression relies mainly on monoamine deficiency, but recent studies are postulating the role of glutamate in depression, in particular, N-methyl-D aspartate (NMDA) receptors along with serotonin receptors which are postulated to be involved in depression[2]. Ketamine, a glutamate receptor–blocking drug approved by the U.S. Food and Drug Administration for anesthetic use, has become a target of research for its antidepressant effects, and possible anti-suicidal effects. According to the study done by Shiroma PR, et al, the assessments were performed at days 0, 1, 3, 5, 8, 10, and 12 to assess the safety and efficacy of ketamine. There was improvement in terms of severity of symptoms which was highest at 24 hours and was maintained till 72 hours[3]. According to the results from the systemic review and meta-analysis done by Marcantoni WS, et al, a single ketamine (0.5 mg/kg) infusion was effective in reducing depression scores in treatment resistant depression participants[4]. Research so far have suggested the short-term efficacy of intravenous ketamine infusion therapy and there are very limited follow up studies in India suggesting the long-term efficacy of the therapy. There are also very limited studies comparing the change in the dosage of Antidepressant medication before and

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after ketamine infusion therapy.

Aims and objectives:

- To study the efficacy of intravenous ketamine infusion therapy in study population at post infusion 1 hour.
- To study the efficacy of intravenous ketamine infusion therapy in study population during follow up at post infusion 1 week and 1 month

Material and Methods

Inclusion criteria: Those patients fulfilling the criteria of Moderate to Severe Depression with or without suicidal ideas or thoughts, patients who is a known case of Depressive Disorder and who is not responding/ partially responding to adequate trials of antidepressants/ augmentation/ who wants early remission of symptoms, patients aged >18 years and patients willing participate in study and gives informed consent were included in the study.

Exclusion criteria: Patients with any major comorbid psychiatric disorder, organic disorders, or substance use disorders, not willing to give informed consent, elderly patients with comorbid hypertension & impaired renal function test, patients with electrocardiogram abnormalities such as ST segment elevation, ST segment depression and T wave changes were excluded from the study.

Methodology:

This study conducted over a duration of 2 months. This was an Open label, non- randomized, prospective study. Ethical clearance was obtained before conducting the study from the Institutional Ethical Review Board (IERB). Consecutive patients attending Psychiatry out patient department and those in the inpatient wards of a tertiary care centre who met the inclusion criteria and did not get excluded were considered for the study. They were informed about the study aim and protocol, and once they voluntarily agreed to participate, informed written consent was taken in their own understandable language. A self-designed proforma was used to collect information regarding socio-demographic data, clinical data, diagnosis of depression was done as per International Classification of Diseases-11 (ICD-11). Baseline score of Hamilton Depression Rating Scale (HAM-D[5] and Hamilton Anxiety Rating Scale (HAM- A)[5] were assessed during the first visit. Once patient was given intravenous ketamine infusion therapy HAM-D and HAM-A scores were assessed at 1 hour, and subsequently were followed up and assessed at 1 week and 1 month post infusion. The procedure was done under Anaesthetist's observation. To prevent secretions, glycopyrrolate 0.4 - 1 mg intravenous was kept ready if needed and for the management of emergence reactions Injection Promethazine (Phenargan) 0.25 mg IV was kept ready. Other resuscitation measures including intubation were made readily available in the designated area.

Statistical analysis:

Data entry was done in Microsoft Excel 2010 and analysis was done using SPSS 16.0 version software. Data was depicted in the form of percentages and frequencies and was analysed using paired t-test and chi-square test.

Results:

A total of 17 patients were recruited in our study. 13 (76.5%) were male patients and 4(23.5%) were females.

Socio-demographic details:

In the study majority of the patients were from urban background (70.6%) with education up-to degree (47.1%). Most of the patients were students (58.8%) belonging to middle socioeconomic status (88.2%). All patients belonged to Hindu religion.

Mean age of the sample population was 28.12±10.4 years. Most of the patients were diagnosed with major depressive disorder with suicidal thoughts (70.6%) with mean duration of illness of 11.06±10.02 months. Most of the patients had no past or family history of psychiatric illness. Most of the patients were on antidepressants.

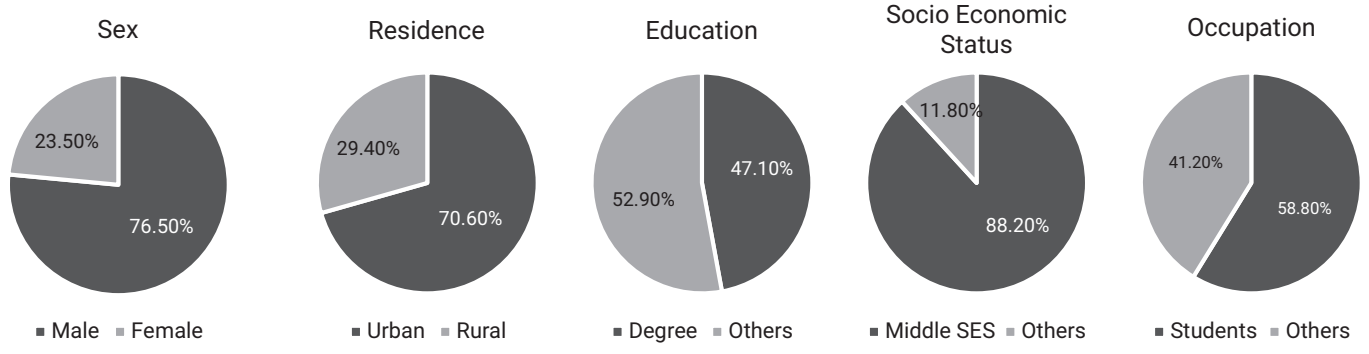

Figure 1: Socio-demographic details

Effect of intravenous Ketamine infusion therapy on Severity of Depression

The severity of depression reduced significantly at 1 hour post infusion. Similarly, there was a significant reduction in the severity of Depression at 1 week and 1 month post infusion (Table 1). The effect of the 1st Dose had significant effect on severity of depression immediately after 1 hour post infusion which was maintained at 1 week and 1 month.

Table 1: Hamilton Depression Rating Scale(HAM-D) scores following treatment of intravenous Ketamine infusion (n=17)

	Mean±SD	t	Df	Significance
Pair 1				
HAM-D scores baseline before the 1st infusion	25.59±7.8	3.38	16	**0.000***
HAM-D scores at 1-hour post infusion	14.82±9.4			
Pair 2				
HAM-D scores baseline before the 1st infusion	25.59±7.8	3.6	16	**0.000***
HAM-D scores at 1 week post 1st infusion	9.24±5.8			
Pair 3				
HAM-D scores baseline before the 1st infusion	25.6±7.8	11.9	16	**0.000***
HAM-D scores at 1 month post 1st infusion	5.35±2.2			

Effect of intravenous Ketamine infusion therapy on severity of Anxiety

There was significant reduction in the severity of Anxiety at 1 hour post infusion. Similarly, there was significant reduction in the severity of Anxiety at 1 week and 1 month post infusion(Table 2). The effect of the 1st Dose had significant effect on severity of Anxiety immediately after 1 hour post infusion which was maintained at 1 week and 1 month.

Table 2: Hamilton Anxiety Rating Scale(HAM-A) scores following treatment of intravenous Ketamine infusion (n=17)

	Mean±SD	t	Df	Significance
Pair 1				
HAM-A scores baseline before the 1st infusion	27.53±7.8	3.63	16	**0.000***
HAM-A scores at 1-hour post infusion	14.59±10			
Pair 2				
HAM-A scores baseline before the 1st infusion	27.53±7.8	3.62	16	**0.000***
HAM-A scores at 1 week post 1st infusion	7.9±6.0			
Pair 3				
HAM-A scores baseline before the 1st infusion	27.53±7.8	3.63	16	**0.000***
HAM-A scores at 1 month post 1st infusion	4.82±2.6			

Effect of intravenous Ketamine infusion therapy on Suicidal thoughts

Assessment of suicidal thoughts were done based on clinical interview and Hamilton depression rating scale. A total of 8 patients (47.1%) out of 17 had suicidal thoughts. 1 hour Post infusion of 1st session of intravenous Ketamine there was absence of suicidal thoughts with no emergence of suicidal thoughts at 1 week and 1 month follow up.

Table 3: Effect of intravenous Ketamine infusion on Suicidal thoughts

	Frequency	x^2	P- value
Pair 1			
Suicidal thoughts before the 1st infusion	8(47.1%)	**6.12**	**0.013**
Suicidal thoughts at 1-hour post infusion	0		
Pair 2			
Suicidal thoughts before the 1st infusion	8(47.1%)	**6.12**	**0.013**
Suicidal thoughts at 1 week post 1st infusion	0		
Pair 3			
Suicidal thoughts before the 1st infusion	8(47.1%)	**6.12**	**0.013**
Suicidal thoughts at 1 month post 1st infusion	0		

Discussion

In our study we administered intravenous ketamine 0.5mg/kg body weight in the form of infusion over 40 minutes and the assessment was done at 1 hour, 1 week and 1 month post infusion. There are several studies in which ketamine has been administered in the form of bolus[6]. These studies showed that there was significant clinical improvement in terms of severity of Depression and Anxiety in the standardized rating scales at 1 hour post administration and the effect continued till 2 weeks and later the same effect was maintained till 1 month.

Our study had similar results. There was significant improvement in terms of severity of Depression, Anxiety and Suicidal thoughts, 1 hour post infusion. There was rapid reduction in the severity of Depression, Anxiety as scaled by HAM-D and HAM-A respectively. These findings were similar to the study done by Zarate et al. on 19 patients of treatment resistant depression, which suggested the rapid antidepressant effect of IV Ketamine[7]. Although another RCT by Shiroma PR, done on patients with major depressive disorder, the severity of depression was assessed using MADRS (Montgomery and Asberg Depression Rating Scale), the peak antidepressant effect was seen at 24 hours.

In our study number of sessions of Ketamine infusion varied from patient to patient depending on the improvement in the patient's functioning. There are limited studies on repeated infusions. Our study also showed that the improvement in the symptom severity was also maintained over 1 week and 1 month.

There was significant reduction in the suicidal thoughts in 1 hour post infusion, and no emergence was seen at 1 week and 1 month follow up. Although a meta-analysis study including 15 independent trials showed the reduction in the suicidal thoughts after 4 hours post infusion which was maintained up-to 72 hours[8].

Conclusion

Patients with severe depression, with suicidal thoughts and comorbid anxiety, had significant improvement in terms of severity immediately 1 hour following administration of slow intravenous Ketamine and this effect is sustained over 1 week and there is an overall decrease in illness severity after 1 month with concomitant use of antidepressant drugs. Patients with severe depression, with suicidal thoughts and comorbid anxiety, had significant improvement in terms of severity immediately 1 hour following administration of slow intravenous Ketamine and this effect is sustained over 1 week and there is an overall decrease in illness severity after 1 month with concomitant use of antidepressant drugs.

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