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A study of role of ketamine in major depressive disorder: A prospective study

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Abstract
Background: Previous reports have shown that about one-third of major depressive disorder (MDD) patients failed to respond to existing antidepressants therapy. Those who respond take months to attain a significant effect. Ketamine is receiving attention for the treatment of depression. Patients using ketamine get relief from depression within 24 hours of use. Ketamine infusion therapy can be an effective treatment of depression symptoms under the medical supervision.
Aims and Objective: To study the role of ketamine in MDD.
Materials and Methods: This is five weeks observational study on 20 patients of MDD. On day one, first all of study patients received a 40-min IV dose of ketamine (0.5 mg/kg) under supervision of doctor, with continuous monitoring of vital-signs. Based on response from previous next doses were administered till the patients shows positive signs of the treatment.
Results:
Ketamine caused minimal positive psychotic symptoms; six patients out of 20 have shown significant but temporary dissociative symptoms. Mild side effects were recorded during and after each ketamine infusion. Out of 20 subjects 18 have met the response after the first and the 6th IV of ketamine. MADRS scores after the 7th infusion was 85% (±12%). After ketamine infusion 18 of 20 patients relapsed on average of 20 days after the sixth infusion between 7 to 50 days. Post ketamine treatment two patients remained without antidepressant with minimal symptoms of depression for more than 4 months.
Conclusion: Finding of this suggest the feasibility with positive outcomes of ketamine for the treatment of MDD.

Keywords: depression, MADRS scores, drug infusion ketamine

Introduction
Major depressive disorder (MDD) is the leading cause of disability affecting 350 million people worldwide. MDD is associated with severe consequences on the quality of life of the person [1].
Current treatment which targets the monoamine system has shown to provide relief from depressive symptoms only in half of the patients receiving it [2]. Moreover, the percentage is even low among the patients who have already failed to show improvement after two or three antidepressant treatments with sufficient dose and duration of treatments [3].
For many years ketamine is being used for the induction and maintenance of anesthesia because of its well established role to provide analgesia. Ketamine act as a non-competitive antagonist of N-methyl-D-aspartate type glutamate receptor. It also shows its effect on the dopamine and μ-opioid receptors [4].
Previous authors have showed rapid and robust antidepressant effects of single sub-anesthetic (0.5 mg/kg) intravenous (IV) dose of ketamine in symptomatic patients with MDD [5, 6]. The reported mechanism of action for exerting antidepressant effects is may be due to activating synaptic plasticity by increasing brain-derived neurotrophic factor (BDNF) translation and secretion, as well as via glycogen synthasekinase-3 (GSK-3) inhibition [7]. In present study we tried to evaluate the effectiveness of ketamine Major depressive disorder (MDD) because Indian data is lacking.

Material and Method
Twenty patients with chronic or recurrent MDD were Interviewed based on Structured Clinical Interview questioner. For this patients who had insufficient therapeutic response to more than two antidepressant drugs were selected. Patients who had score of ≥30 Inventory for Depressive Symptoms (IDS-C30) score at time of screening and after 24 hours before the first infusion of ketamine were included.
Patients who had lifetime history of psychotic symptoms, having substance use disorder for more than three months and had current active suicidal ideation were excluded from the present study. Patients having abnormal electrocardiogram, hyperthyroidism or hypothyroidism and pregnant women were also excluded from the present study. We also restricted psychotherapy and other non-pharmacological antidepressant treatments in these patients. A written informed consent and Institutional Ethics Committee approval was also obtained before starting the study.
Safety and tolerability of the drug was measured using four-item positive symptom subscale which consist of suspiciousness, hallucinations, unusual thought content, and conceptual disorganization of the Brief Psychiatric Rating Scale (BPRS). Clinician- Administered Dissociative States Scale (CADSS) and the Systematic Assessment for Treatment Emergent Effects Self- Report Inventory (SAFTEE-SI) were also recorded. Efficacy was measured using Montgomery-Åsberg Depression Rating Scale (MADRS). Any improper medical condition was assessed using interval assessment for Axis I disorders, administration of the IDS-C30, a physical examination and laboratory tests.
All the administration was performed within 2 weeks of time on day 1, 3, 5, 8, 10 and 12. IDS-C30 was administered again

before 24 hours of the first infusion to record the sufficient severity of depressive symptoms. Nasal cannula was used to provide oxygen. Pulse oximetry, respiratory rate, heart rate, blood pressure and heart rate every 10 for 90 mins before the infusion of ketamine were also recorded.

All the data analysis was performed using IBM SPSS ver. 20 software. Quantitative data was expressed as mean whereas categorical data is expressed as percentage. Student t test was performed to check the level of significance. P value of <0.05 is considered as significance.

Results

All 20 subjects received the first IV ketamine infusion on day first and 18 subjects met the response criteria at within 24 hours. These 18 subjects were eligible for subsequent infusions. One patient missed the fourth infusion.

During the first 40 min of infusion, BPRS+ scores were increased from 4.2 ± 0.1 at the time of infusion to a mean peak of 5.3±2.2 (p=0.1) which returned to the baseline score after 2 hour. No patient reported any distressing psychotic symptoms. The CADSS scores increased from 1.2 ±2.15 at time of infusion to 14.9 ± 23.1 after the 40min (p = 0.29).

During all six infusions all 20 subject had minimum BPRS+ and low CADSS scores (<=3) after 4 hours of infusion. There were no significant changes in these parameters within 40 min of the infusion.

At the time of first infusion 4 subjects had short-term hypertensive episodes and also developed the transient tachycardia and these symptoms resolved after 5 min of the infusion. These patients experienced these hypertensive episodes during subsequent infusions.

Out of 19 subjects who received repeated infusions, sixteen were relapsed within an estimated mean 30 ± 12 days after the first infusion and 18±12 days after the sixth infusion. Hence these 16 subjects remained well for almost 3 weeks after the treatment.

After the treatment, two patients relapsed after one week, six after 2 weeks, and four patients relapsed after 3 weeks, whereas two patients remained depression-free for more than four weeks, two patients for seven weeks and two patient remained depression-free for more than 3 months after the ketamine infusion. At the end of the study mean MADRS was 29.7±6.4 for sixteen patients.

Discussion

Preliminary data collected a part of this study shows that repeated-dose of IV ketamine shows positive results patients with MDD. Criteria for feasibility of the treatment are safety, tolerability, and duration of symptom relief during the course of treatment. As part of this study six ketamine IV were administered thrice-weekly for 40 min at a .5 mg/kg doses were well tolerated by all 20 subjects.

Other studies on repeated-dose IV ketamine in other populations also found the treatment to be safe. In a study by Lahti AC, *et al.* on patients with schizophrenia tolerated up to four infusions (0.1–0.5 mg/kg) administered over 2 weeks [8].

In another study by Goldberg ME, *et al.* on a group of patients with refractory pain receiving 10 4-hour infusions (10–20 mg/hour), treatment-related side effects were minimal with only approximately 10% of patients experiencing restlessness, headaches, or significant tachycardia [9].

In study by Mills IH, *et al.* on 15 patients with treatment-resistant eating disorders who received on average four 10-hour infusions (20 mg/hour), side effects reported by some (headaches, nausea, sedation, and revival of distant memories) were no longer apparent or unpleasant after the first or second infusion [10].

Tsai GE *et al.* [11] has raised concern regarding the long-term cognitive impairment caused by repeated ketamine administration, but in our study none of the subjects has reported any cognitive deficits more than what was recorded before infusion. For satisfactorily assessment of ketamine's effect on cognitive function, future studies should administer neuro-psychological tests pre-ketamine, immediately after infusion, post-ketamine, when ketamine responders are depression- free and again when there are relapse.

For this study the selected subjects had exposure to ketamine before the study and there for more study and research are needed on ketamine-naïve patients to further support the findings of the current study.

Conclusion

Current study show that the repeated IV of ketamine has shown promising results in the patients with MDD and it could be the next wonder drug for the treatment MDD.

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