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Ketamine Infusion in Treatment Resistant Depression: A Case Report and Brief Review of The Literature

Gökben Hızlı Sayar[1], Eylem Özten[1], Haluk A. Savaş[2]

ÖZET:

Tedaviye dirençli depresyonda ketamin infüzyonu: Bir vaka sunumu ve literatürün kısa gözden geçirilmesi

Glutamat N-metil-D-aspartat reseptör antagonisti olan ketamin antidepresan etkinlik gösterebilmektedir. Tedaviye dirençli depresyon olgularında yürütülmüş olan araştırmalarda ketamin infüzyonu hızlı başlangıçlı ve birkaç gün süren bir antidepresan etkinlik göstermiştir. Bu olgu sunumunda intravenöz ketamin uygulaması sonrası tek uçlu depresif dönemde belirtilerde ve intihar düşüncesinde hızlı yatışma izlenmiştir. Mevcut antidepresanların etki başlangıcı için uzun süre gerektirmesi nedeniyle akut ve şiddetli intihar düşüncesinin klinik tedavisinde yakın izlem veya hastaneye yatırma dışında çok az seçenek vardır. Ketaminin hızlı etkinliği intihar riski yüksek hastaların ele alınmasında bir avantaj sağlayabilir. Ketaminin optimal doz ve uygulama yollarının belirlenmesi için çalışmalar gerekli olmakla birlikte, NMDA üzerine etkili ajanlar dirençli depresyon tedavisi ve intihar riskinin azaltılması için bir seçenek olarak daha fazla araştırmayı hak etmektedir.

Anahtar sözcükler: depresyon, ketamin, intihar, tedaviye direnç

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ABSTRACT:

Ketamine infusion in treatment resistant depression: a case report and brief review of the literature

The glutamate N-methyl-D-aspartate (NMDA) receptor antagonist ketamine may exhibit antidepressant effect. Previous studies of treatment-resistant depression reveal that ketamine infusions may result in a rapid antidepressant response with improvement usually sustained for several days. This case suggests that intravenous administration of ketamine may be effective for immediate relief from symptoms in unipolar depression and may also relieve suicidal ideation. Due to the prolonged period between the initiation of treatment and the onset of action of currently available antidepressants, only a few things can be done for the management of acute and severe suicidal ideation other than close monitoring or hospitalization. Rapid effect of ketamine may be an advantage in the management of suicide risk. Although additional research is needed to ascertain optimal dosing schedules and route of administration of ketamine, NMDA agents warrant further investigation as a treatment option in treatment-resistant depression and as an agent intended to reduce suicides.

Key words: depression, ketamine, suicide, treatment resistance

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[1]Üsküdar University, Neuropsychiatry Istanbul Hospital, Istanbul-Turkey
[2]Gaziantep University, Faculty of Medicine, Department of Psychiatry, Gaziantep-Turkey

Yazışma Adresi / Address reprint requests to:
Gökben Hızlı Sayar,
Üsküdar University, Neuropsychiatry Istanbul Hospital, Istanbul-Turkey

Elektronik posta adresi / E-mail address:
gokben.hizlisayar@uskudar.edu.tr

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INTRODUCTION

An abundant number of patients diagnosed with major depressive disorder exhibit poor or no response to conventional antidepressants and they are identified to have treatment-resistant depression (1). The rapid onset of antidepressant effect generated by subanesthetic intravenous ketamine provides a hope. Ketamine has been used clinically as a dissociative anesthetic for more than three decades and is considered as a noncompetitive glutamate N-methyl-D-aspartic acid (NMDA) receptor antagonist (2). Recent observations in clinical settings imply that at subanesthetic doses, ketamine produces therapeutic effects in depressed patients (3). The antidepressant effects were characterized by a rapid onset of action (4), lasted for a time, and observed after a single dose, and was effective in treatment-resistant patients (5).

Here, we report a case with treatment-resistant

depression on which intravenous ketamine infusions led to treatment response and a beneficial effect on suicidal ideation.

CASE

The subject is a 48-year-old male teacher with the diagnosis of major depressive episode and had proven to be treatment-resistant despite use of at least five different antidepressants. He did not respond to augmentations either with lithium or thyroid hormone that were given in adequate doses for a relevant duration. He had his first depressive episode when he was in his mid-twenties, and the current episode was his sixth episode, which has lasted for ten months. He did not report any psychiatric or general medical comorbidity. He never had symptoms of mania or psychotic features. He denied use of any illegal substance or alcohol. He had two prior suicide attempts three and five years ago with overdosing of psychiatric medications. Besides anhedonia, depressed mood, psychomotor retardation, energy loss, and insomnia, he had plans for another suicide attempt. Electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) had also been performed on the current episode without any response. He also had six sessions of cognitive behavioral therapy but did not want to continue due to his belief that those treatments would not work on him. Due to inadequate symptom control with pharmacotherapy, the patient has been informed about the off-label therapeutic use and possible side effects of ketamine infusion, and then he gave written informed consent.

ECG, EEG, cranial imaging, chest X-ray, and blood analysis were performed. All have revealed normal results. The patient was administered the 17-item version of the Hamilton rating scale for depression (HAMD-17) at baseline and 120 minutes after each ketamine infusion. He was on the same treatment regimen of mirtazapine 45 mg/day, escitalopram 30 mg/day and olanzapine 10 mg/day for the last six weeks. He was kept on the same pharmacotherapy regimen throughout the ketamine infusions.

Ketamine infusions were administered in the presence of a psychiatrist and an anesthesiologist. Intravenous infusion of ketamine hydrochloride was given in an inpatient clinical setting as 0.5 mg/kg over 40 min. The patient went through a series of 5 infusions, once every two days. The patient well tolerated the treatment, and somnolence was the only adverse effect reported by the patient. He did indicate a decrease in his depressive symptoms after the first infusion. He scored 22 points on HAMD-17 at baseline and 11, 9, 7, 7 and 9 on the post-infusion ratings after 1st, 2nd, 3rd, 4th and 5th sessions, respectively. Two and three weeks after the end of the sessions, on his follow-up, his scores on HAMD-17 were 9 and 11, respectively. HAMD-17 total and HAMD-17 suicidality item scores at baseline, after 1st-5th infusions and 2-3 weeks after the end of sessions are given in Figure 1.

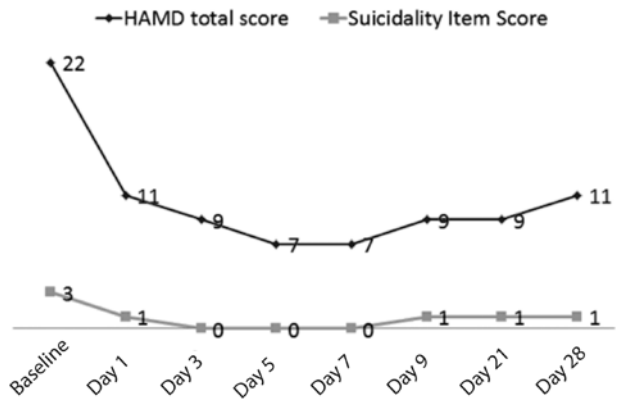

Figure 1: HAMD-17 total and suicidality item scores at baseline, after 1st-5th infusions and 2-3 weeks after the end of sessions

DISCUSSION

Researches in recent years have demonstrated that the excitatory glutamatergic / NMDA receptor signaling may play an important role in the pathophysiology of major depressive disorder. Recently ketamine has presented a novel target for the treatment of depression that is different from the contemporary antidepressants acting on monoamine oxidase system. There is also evidence for the efficacy of agents that directly target glutamatergic system such as lamotrigine in bipolar depression (6) and riluzole in major depression (7).

Ketamine targets glutamate, and it acts as an NMDA antagonist with slow open-channel blocking/unblocking kinetics. Ketamine exhibits antidepressant properties in different models of depression. These effects are mediated by activation of different pathways that results in neurogenesis and synaptic consolidation. In several studies, response rates regarding the antidepressant effect of ketamine over 3-72 hours have shown significant variations (14-70%) (8). Ketamine was first reported to have therapeutic effects on patients with depression in a placebo-controlled

double-blind trial in 2000. Seven subjects with major depression involved intravenous treatment with ketamine hydrochloride (0.5 mg/kg) or saline solution. Subjects evidenced significant improvement in depressive symptoms within 72 hours after ketamine but not placebo infusion (9). Murrough et al. evaluated the rapid antidepressant efficacy of ketamine in a large group of patients with treatment-resistant depression. In this randomized controlled trial, a single infusion of ketamine was compared with an active placebo, midazolam. The ketamine group had higher improvement in the depression rating scores than the midazolam group 24 hours after treatment (10).

Researchers also investigated the antidepressant efficacy of ketamine in bipolar depression. Ionescu et al. recently reported that anxious and non-anxious patients with bipolar depression had significant antidepressant responses to ketamine (11).

In a recent meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine for treatment of depressive episodes, data were integrated from eight randomized controlled trials applying an intravenous infusion or intranasal ketamine. In that study, ketamine was related with higher rates of both clinical response and remission relative to saline or midazolam at 24 h, 3 days and 7 days. The meta-analyses reported greater efficacy in unipolar depression compared to bipolar depression. They did not report any persistent psychosis or affective switches (8).

In this particular case we observed that repeated-dose ketamine has caused a significant reduction in depressive symptoms and the improvement in depressive symptoms remained even three weeks after the last (fifth) injection of it. Although several studies showed that ketamine promotes a rapid antidepressant effect, it is important to perceive that after a single dose, effect gradually fades in 3-7 days (12). Further investigation showed that the time until relapse is varying between 6 days to greater than 3 months. Some investigators have suggested repeated-dose ketamine as a potential antidepressant continuation strategy for patients who show initial response to ketamine infusion (13).

Caric et al. demonstrated that the rapid improvement with ketamine followed by medication alone could not maintain an adequate remission but sustained remission was achieved after ketamine infusion with a combination of maintenance ECT along with medications (14). Ketamine has been used as an anesthetic agent in ECT. One case study reported dramatic mood improvements after the use of ketamine anesthesia in ECT, suggesting synergistic antidepressant effects (15). Similarly, Sultan et al. demonstrated the novel use of pretreatment of ketamine as an augmentation strategy with ECT for treatment-resistant depression in an individual with severe depressive and catatonic symptoms (16). In another case series, ten depressive patients treated with ECT received anesthesia with either etomidate or ketamine. The subjects anesthetized with ketamine had significantly less impairment of short-term memory function than did patients who received ECT with etomidate anesthesia. That result implied that the impact of ECT on memory may be negotiated by glutamate at NMDA receptors and suggest that NMDA antagonists may grant protection from memory dysfunction during ECT (17).

Ketamine's rapid onset of the improvement of depressive symptoms suggests NMDA receptor modulation as a novel mechanism for rapid improvement in severe and chronic forms of depression. Although rapid effect is important especially in cases with suicide risk similar to the one presented here, ketamine lacks the maintenance and sustained effects of conventional antidepressants. This temporal pattern may be due to the use of ketamine in subanesthetic doses and as single or in a minor number of administrations. The serum half-life of ketamine was about 11 min (18). This indicates that effects are at time periods when the blood levels have long dropped below any active threshold. Mechanisms of action thus may be investigated either in secondary or compensatory processes, which do not necessitate the presence of active drug levels (19). The rapidity of ketamine action implies that major symptoms of depression can be without abundant structural plasticity or circuit rewiring. The effect is estimated to be by molecular cascades that promote synaptic plasticity and dendritic spine maturation in critical brain regions (20).

There is currently open-label evidence to imply benefit of oral ketamine (21) and sublingual administration (22); however, efficacy data is lacking. Oral ketamine, however, has limited bioavailability, and therefore other routes of administration are being studied, involving intramuscular and intranasal routes (23).

In most trials ketamine is administered intravenously (i.v) at the dose of 0.5 mg/kg along 40 minutes, vital signs and side effects being continuously monitored (10,24,25). Some authors suggest that repeated administrations, better than a single one, may be needed to obtain stable remission (26,27).

In trials wherein protocols with multiple administrations are adopted, ketamine is usually administered at 0.5 mg kg every other day until a maximum of 6 infusions along two weeks of treatment (28).

The majority of studies reported no serious adverse events. One study reported cardiovascular side-effects in 2 of 47 patients who received ketamine (refractory hypertension in one case, hypotension and bradycardia in the other) (10). In the meta-analysis of McGirr et al., drop-out rates were used as a proxy for tolerability. 13.3% of the ketamine receiving patients dropped out compared to 7.4% of patients who were on control interventions (8). A recent study demonstrated both neurocognitive effects of ketamine and particular associations between baseline neurocognition and antidepressant outcomes following ketamine. Ketamine was found to be with selective impairments in memory recall, and the adverse cognitive effects immediately after ketamine predicted lower response rate at 24 hours. Lower levels of baseline neurocognitive performance in treatment-resistant depression were found to be related with an increased antidepressant response rate to ketamine (29). It may be that a randomized controlled design employing psychoactive placebo is needed to elucidate the specificity of ketamine's antidepressant effect and neurocognitive adverse effects.

Although this case outlines that ketamine may be used in clinical practice to reduce rapidly the suicidal ideation of patients with major depressive disorder. On the other hand, clinicians may be concerned about the medical safety of administering ketamine infusion. However, in 833 infusions, a subanesthetic dose of ketamine was administered to healthy volunteers, some of whom were taking concomitant psychotropic medications, caused no serious adverse events (30). Nevertheless, oxygen saturation, EKG, blood pressure, and pulse should be monitored.

The presented case had an increased suicidality. When available biological treatments are insufficient, the clinicians need new treatment strategies to prevent suicide. Patients with suicidal ideation have traditionally been excluded from studies of biological treatments for ethical grounds, which decrease the chance of developing new treatments. Ketamine may be protective against suicidal ideation and suicide attempts due to its fast-acting property. There is a significant body of evidence for its rapid effect on mood in patients with suicidal ideation. Conventional antidepressants caused suicidal tendencies to remit as the overall syndrome remits. Due to the prolonged period between the initiation of treatment and the onset of action of currently available antidepressants, there is little that can be done for management of acute and severe suicidal ideation aside from close monitoring or hospitalization (31). Ketamine may have an advantage in the acute management of suicide risk. The presented case was treatment-resistant and did not benefit either from ECT or rTMS. In this case, ketamine showed a rapid onset of antidepressant effect. It is noteworthy that the major limitation of ketamine infusion is the short act of the antidepressant effect. Repeated doses of ketamine could be effective in improving depressive symptoms in depressed patients.

CONCLUSION

This case suggests that intravenous administration of ketamine may be efficacious for the rapid relief of symptoms in unipolar depression and may also decrease suicidal ideation. Although additional research is required to determine optimal dosing schedules, administration routes and the potential efficacy of glutamatergic agents, NMDA agents warrant further investigation as part of strategies dedicated to diminish suicide deaths.

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