

Modified IV Ketamine Infusion Protocol for Treatment-Resistant Depression and Suicidal Ideation - A Case Report

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Abstract

The evidence supporting the use of ketamine for treating depression has grown rapidly in recent years. However, infusion protocols used in clinical practice have not yet been optimized. This manuscript describes the clinical course of a patient with treatment-resistant depression and suicidal ideation, who was treated using a modified ketamine infusion protocol at the Florida Spine Institute (Clearwater, FL, USA). The severity of this patient's depression was evaluated using the Hamilton Depression Scale at each visit throughout the treatment period. Throughout the initial five-day infusion protocol her depressive symptoms were resolved (89% decrease from baseline). This treatment response was sustained over the course of 5 months with periodic booster ketamine infusions. Given this clinical observation, systematic controlled trials may be warranted using this modified infusion protocol for depression.

Keywords: Antidepressants; Esketamine; Ketamine hydrochloride; Ketamine infusion protocol; Suicidality; Treatment resistant depression

Abbreviations: Treatment Resistant Depression (TRD), Intravenous (IV), United States Food and Drug Administration (FDA), Hamilton Depression Scale (HAM-D), Montgomery-Åsberg Depression Rating Scale (MADRS)

Introduction

Depression is a debilitating disease currently affecting up to 6.7% of adults in the US [1]. The current therapies can take weeks to months to take effect creating a significant lag time in treatment. Although the currently available antidepressants provide a measurable degree of therapy, approximately 50% of individuals diagnosed with Major Depressive Disorder (MDD) do not respond adequately to first-line treatment [2]. At this point there is no clear consensus on the standards and range of treatments required before declaring Treatment-Resistant Depression (TRD), therefore its prevalence has not been adequately characterized [3]. However, it has been found that patients with depression that do not respond to two or more different antidepressants at adequate dosage and duration have a significantly lower likelihood of responding to other first-line antidepressants [3].

Ketamine is a noncompetitive, N-methyl-D-aspartate (NMDA) and glutamate receptor antagonist drug that is United States Food & Drug Administration (FDA)-approved for anesthetic use. More recently, an intranasal spray containing the *s*-enantiomer of ketamine, esketamine, was approved for the treatment of MDD. Although this new intranasal formulation has been approved by the FDA, it is not yet commercially available. However, there is a multitude of clinical evidence that intravenous ketamine is an option for rapid relief of depressive symptoms and, as such, IV ketamine is currently being used off-label in patients with TRD by many clinicians worldwide.

The mechanism of action is currently not yet fully understood. However, recent research has shown that there is a possible connection in reductions of neurogenesis and synaptic plasticity (dynamic capability of synapses to form and retract processes) that play a key role in the pathophysiology of MDD. In addition, the NMDA receptors

at excitatory synapses are also subject to trafficking and significantly decrease in synaptic density during long term depression [4]. Ketamine blocks NMDA receptors (NMDARs) and subsequently suppresses tonic glutamate input to GABAergic interneurons, resulting in disinhibition of glutamate signaling. This disinhibition facilitates the decrease in GABAergic inhibitory feedback of the pyramidal neurons in layer V of the PFC, a region widely implicated in the development of psychiatric disorders [5]. Another study confirmed this post-mortem after finding reductions in BDNF and TrkB expression in the hippocampus and PFC of MDD patients and depressed suicides [6].

Recent studies have shown ketamine infusions to have antidepressant effects often achieving superior antidepressant outcomes with repeated infusions however showing different trajectories of response and remission as seen in a study done in 2013 [7]. However, an optimal long-term dosing regimen to sustain the antidepressant effects of ketamine has not yet been determined [2]. There have been various studies using different ketamine protocols that reported clinical outcomes with varying degrees of success. For example, an extensive clinical trial involving 67 patients at two sites with documented TRD established the most definitive antidepressant efficacy of ketamine in comparison with midazolam used as an active placebo control condition [8]. The response rates to ketamine vs midazolam were 64% and 28%, respectively, with ketamine significantly reducing scores in the Montgomery-Åsberg Depression Rating Scale (MADRS) by 7.95 points (score ranges from 0-54). Ketamine-treated patients continued to exhibit improved scores over the 7-day period post-infusion compared to midazolam. However, the reduction in the depressive scores diminished after day 7. While this result was impressive, it's possible that the magnitude and duration of antidepressant effects of ketamine could be improved by optimizing the treatment protocol.

The case report described in this manuscript, utilized a modified ketamine infusion protocol that produced a sustained response over a 6-month period.

Case Report

A 56 year-old female patient presented to the Florida Spine Institute (Clearwater, FL, US) with a referral from a rehabilitation facility after attempted suicide due to treatment-resistant depression with suicidal ideation. She also had a history of bipolar depression, Posttraumatic Stress Disorder (PTSD), and anxiety. The patient previously tried and failed to achieve an adequate clinical response with bupropion, sertraline, and citalopram. The patient was offered the option of intravenous ketamine infusions with the understanding that this constituted an off-label use of the drug. The patient consented to IV ketamine infusions after a full description of the procedure. A signed consent form was obtained from the patient.

The patient was started on the ketamine infusion protocol set forth by FSI. On day 1, the patient was infused for approximately two hours with 1mg/Kg/Hr of ketamine in a 100-ml bag of saline. The ketamine dosage was kept the same throughout the five initial consecutive days of treatment. The patient then returned to the clinic for a two-day booster infusion approximately three weeks later and then again five weeks later. After those two boosters the patient returned again approximately 3 months later for another two-day booster. At each visit to the clinic, depression was assessed using the Hamilton Depression Scale (HAM-D) [9]. She did not demonstrate any treatment-related complications.

The overall clinical course of the patient in this study can be seen in Table 1 and plotted in Figure 1. Throughout the 5-month treatment period, her depression remained in remission (Hamilton Depression Scale <7). The patient's baseline HAM-D score was 36. Following the initial five consecutive infusions, her depression score fell to 4 (an 89% reduction). This response was maintained when the patient returned to the clinic for a booster infusion three weeks later (HAM-D = 3). The patient was scheduled for a follow up booster infusion approximately five weeks later. When she returned for the second 2-day booster infusion her HAM-D was 6, supporting that she was still in remission from TRD. Her final booster infusion session was pushed out to 3 months later. When she returned to the clinic for her final 2-day booster infusion session, her depression remained in remission (HAM-D =5). On the day of her final booster infusion, her HAM-D was 6. At this time, the clinical judgment was made to stop ketamine infusions since the patient had a complete response to the treatment. The patient was advised to continue to see her primary care provider and psychiatrist and that she could return to the Florida Spine Institute for evaluation should her depressive symptoms return.

Table 1:

Day of Treatment	HAM-D Score
0	36
1	37
2	7
3	7
4	4
26	3
31	0
66	6
67	3
153	5
154	6

Discussion and Conclusion

Intravenous ketamine is now considered by many to be one of the most important breakthroughs in mental health in recent years. This is evidenced by numerous case reports and placebo-controlled clinical trials that have shown improvement in patients with TRD and other psychiatric and neuropathic pain disorders. However, there is little consistency with regard to treatment protocols for any indication. The most commonly studied dosage for TRD is 0.5 mg/kg, infused over 40 minutes but there is little evidence showing that this optimal [10]. Other investigators have reported using lower doses but administered continuously for long periods of time with great outcomes [11]. Correll et al. reported two cases of low-dose ketamine infusions in patients with depression. One patient started therapy at 0.15 mg/kg/hr and titrated up to 0.27 mg/kg/hr. This dosage was maintained for 5 days. Over this period, the patient's HAM-D score improved from 36 to 11 (69% reduction), which is an impressive outcome but fell short of meeting typical criteria for remission (HAM-D < 7). Also, this type of inpatient continuous infusion protocol is far from ideal for the patient or health care provider since the infusion is maintained for 5 days. Comparatively, the case report presented here used a higher dose (1 mg/kg/hr) but infused for only 2 hours/day for 5 consecutive days resulting in a lower overall dose administered. Another noteworthy advantage of this approach is that the patient is allowed to return home between infusion sessions and, most importantly, our clinical outcomes were similar but superior (89 vs 69% decrease).

A recent double-blind, placebo-controlled trial of intravenous ketamine in patients with TRD attempted to find an optimal dose [12]. This was a well-designed study that randomized 99 subjects into 4 ketamine dose groups: 0.1, 0.2, 0.5, and 1.0 mg/kg. The investigators used a single 40-minute infusion for each dose group and used an active control (midazolam). Study assessments were performed on days 0, 1, 3 (endpoint), 5, 6, 14, and 30. Overall, the results for ketamine were clearly differentiated from the midazolam comparator when comparing HAM-D scores. Interestingly, when they compared HAM-D results for the 4 ketamine dose groups, only the top two doses 0.5 and 1.0 mg/kg separated from the comparator control group. These results suggest that doses lower than 0.5 mg/kg are unlikely to be effective when administered a single time.

Another recent double-blind, placebo-controlled trial of intravenous ketamine in patients with TRD looked at twice or thrice-weekly infusions at 0.5 mg/kg for 40 minutes/day [8]. The Montgomery-Åsberg Depression Rating Scale (MADRS) score was used to monitor levels of depression. In this study, outcomes between the two regimens were similar but the twice-weekly resulted in a numerically better outcome (64% vs 60% reduction in MADRS).

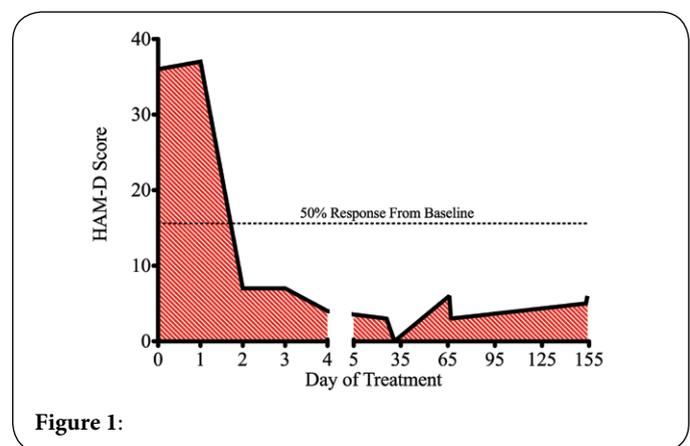


Figure 1:

There remains a need for optimizing intravenous ketamine protocols for the treatment of depression. In clinical practice, there is unlikely to be a single regimen that is optimal for all patients. Ultimately, dose-titration is likely to be required for most patients and repeated infusions will be required, at least for the titration phase. While the case report described here represents the clinical course of only a single patient, the results are relatively common for the Florida Spine Institute clinicians utilizing this protocol. Importantly, 2-day booster infusions have proven important to maintain the antidepressant response in many patients that ultimately relapse. This was illustrated in this case report, where booster infusions kept the patient in remission (HAM-D < 7) for the entire 5-month period of observation following the initial 5-day infusion series. Additional properly powered and placebo-controlled studies may be warranted using this repeat-infusion ketamine protocol for TRD.

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