Depression Severity with Ketamine Treatment in Clinical Procedures

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Abstract: Ketamine has developed as a rapid-acting antidepressant in treatment-resistant depression increasingly used in non-research, clinical settings. Few studies, have scrutinized neurocognitive activities of repeated racemic ketamine infusion treatments in patients with treatment-resistant depression. In an effort to identify potential effects after serial infusions, we conducted a retrospective chart review to identify statistically significant changes in cognition in patient undergoing serial intravenous infusions; concomitantly, we examined baseline cognition as potential predictor of anti-depressant potential. Twenty-two patients with treatment-resistant depression were examined after they finished the induction phase of 8–10 repeated intravenous ketamine infusions and completed the assessments of their depressive symptoms (measured by the 16-item Quick Inventory of Depressive Symptomatology-Self Report Scale: QIDS-SR16) and cognitive function (measured by the Montreal Cognitive Assessment: MoCA) before the first and the last ketamine treatments. Repeated ketamine infusions administered through an escalating dose protocol with 8–10 infusion sessions produced a 47.2% reduction response in depression. Ketamine was approved under a risk evaluation and mitigation strategy (REMS) that requires administration under medical supervision. Both ketamine and ketamine are currently viable treatment options for TRD that offer the possibility of rapid symptom improvement. The manuscript also reviews ketamine's use in other psychiatric diagnoses—including suicidality, obsessive–compulsive disorder, post-traumatic stress disorder, substance abuse, and social anxiety disorder—and its potential adverse effects. Despite limited data, side effects for antidepressant-dose ketamine—including dissociative symptoms, hypertension, and confusion/ agitation—appear to be tolerable and limited to around the time of treatment. Relatively little is known about ketamine's longer-term effects, including increased risks of abuse and/or dependence. Attempts to prolong ketamine's effects with combined therapy or a repeat-dose strategy are also reviewed, as are current guidelines for its clinical use. In addition to presenting a novel and valuable treatment option, studying ketamine also has the potential to transform our understanding of the mechanisms underlying mood disorders and the development of novel therapeutics.

Key Words: —*Ketamine, Depression, Risk evaluation, Therapeutics.*

I. INTRODUCTION

Ketamine, an N-methyl-D-aspartate receptor antagonist, was demonstrated to have a rapid antidepressant action in a randomized double-blind trial for the first time in 2000 [1]. Since then, emerging studies have indicated rapid and robust antidepressant effects of ketamine in adults with TRD [2]. A single subanesthetic (0.5 mg/kg) dose infusion of intravenous (IV) ketamine has rapid-acting and robust antidepressant effects in at least 50% of patients, however, the effects dissipate by day 10 to day 14 [3].

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Patients not responsive to a single infusion of ketamine may improve with subsequent infusions, and improvement following a single infusion can be sustained by subsequent infusions [4]. As a sample, in one uncontrolled, open-label study [5], fourteen patients with TRD received IV 0.5 mg/kg-0.75 mg/kg ketamine at a frequency of two per week for entire six infusions. In a completer analysis, the response rate was only 7% after the first three infusions but 42% after all six infusions. The remission rate was 17% after six infusions. The findings of this study suggest that patients may require multiple ketamine sessions to respond. Cognition plays a key role in recovery and functional outcomes in MDD [6]. Given known harmful effects of ketamine in cognition when used in cohorts struggling with ketamine use disorders, there has remained concern that serial administration of low dose ketamine could have the potential to negatively affect cognition. Human results of acute ketamine use on memory are mixed [7]. Results of studies on chronic ketamine use have suggested that individuals who had abused it for a long period of time could be more prone to experiencing serious

neurocognitive impairment [8]. Furthermore, a single infusion of ketamine (0.4 or 0.8 mg/kg) induced dose-dependently impaired episodic and working memory and slowed semantic processing, recognition memory, and procedural learning, and infusion of analgesic doses (8–20 mg/h) in healthy volunteers was shown to produce significant deficits in cognition [9]. On the other hand, Ning's group noted no deterioration in cognitive function from six ketamine infusions at 0.5 mg/kg over 12 days [10]. Instead, a single infusion of 0.5 mg/kg in TRD patients was seen to be slightly beneficial in attention and response control [11]. As concerns regarding ketamine and cognition have evolved, concomitant curiosity regarding the predictive value of baseline neurocognitive function has emerged [12]. Murrough et al. [13] have suggested individuals with TRD performing with lower neurocognitive function at baseline were more likely to obtain a positive antidepressant response from a single ketamine infusion. On the other hand, a study conducted by Bönke's group indicated no significant correlation between baseline cognitive performance and a change in symptom severity, nor a correlation between a change in cognitive performance and antidepressant responses from six series ketamine infusion treatments [14]. In 2018, we began to treat patients with TRD by ketamine infusion in the clinical Ketamine Service at McLean Hospital. Over the years, we have refined a serial infusion ketamine protocol based on the evolving literature and our clinical experience. The protocol includes an induction phase and either a booster or maintenance phase. The induction phase consists of 8–10 treatments on a twice-weekly schedule with the IV ketamine dose initiated at 0.5 mg/kg over 40 min; thereafter, titration to response was permitted in a conservative fashion at the discretion of the ketamine team with the maximum dose up to 1.0 mg/kg [15]. In this real-world context, the investigation below seeks to report the neurocognitive effects of repeated ketamine infusions in patients with TRD who have finished the induction phase through a retrospective chart review and examine whether there is an association between cognition at baseline and antidepressant effects induced by repeated ketamine infusion [16].

II. METHODS

DSM-5 Diagnostic Criteria were used to define patient with MDD. Ketamine treatment was offered to patients with severe and refractory MDD with at least two or more failures of anti-depressant treatment at adequate dosing, while patients with a history of psychosis, current substance use disorder, or uncontrolled medical illness, were not eligible for ketamine treatment. After psychiatric consultation and medical assessment, patients who were appropriate for ketamine treatment reviewed and signed a consent for ketamine treatment that emphasized that ketamine was not approved by the U.S. FDA for any psychiatric indication, and was provided off-label for depression, in addition to potential risks and benefits. At each visit, patients were evaluated and monitored by a staff psychiatrist, a nurse, and an anesthesiologist as needed. Depression symptom severity was evaluated with the 16-item Quick Inventory of Depressive Symptomatology-Self Report scale (QIDS-SR16) that is scored on a scale of 0 to 27, with 0 representing a complete absence of depressive symptoms and 27 representing the most severe symptoms [17]. The QIDS-SR16 was administered before the first treatment and every subsequent visit and data were entered into Research Electronic Data Capture (REDCap) system. Cognition was evaluated with the Montreal Cognitive Assessment (MoCA) [18]. The 30 item MoCA, a brief cognitive screening tool for cognitive impairment, is recognized as a sensitive measure of cognitive function that can capture declines in cognition over repeated administrations. The MoCA is scaled from 1 to 30, with higher MoCA scores indicating better cognitive function; a MoCA score < 26 indicates impaired cognitive function [19]. The MoCA includes six cognitive domains, including visuospatial abilities; language; combined attention, concentration, and working memory; executive function; short-term memory recall; and orientation to time and place, although subsequent consensus has emerged that the total score is most meaningful. To avoid learning effects, clinicians only administered MoCA test twice during the whole ketamine induction phase treatment: the first one was before the first ketamine treatment as a baseline and the second one was at the last treatment of induction phase which two tests usually were administrated 4–5 weeks apart. In addition, two different versions of MoCA tests were randomly utilized among three different versions (version 7.1, 7.2, 7.3) to further prohibit better performance due to learned effects. Studies had shown all three MoCA versions are largely equivalent and the test–retest reliabilities show that this score is suitable to monitor cognitive change over time [20]. MoCA scores were entered into REDcap system. Eligible participants for ketamine infusions received an acute induction course consisting of 8–10 infusions twice weekly over 4–5 weeks. Most participants received the first dose of 0.5 mg/kg of ketamine with possible dose escalation up to 1.0 mg/kg contingent on patient tolerability to the index dose and patient's response. In terms of dosing strategy, there is

currently no established consistent and optimal dose of intravenous ketamine for TRD [21]. Nevertheless, small, randomized trials that compared different doses of ketamine suggest that generally, the preferred dose may be 0.5 mg/kg of body weight [22]. However, dose adjustments may be appropriate for specific patients [23]. A dose of up to 1 mg/kg may be suitable for patients not responsive to 0.5 mg/kg [15]. In terms of frequency, in most randomized trials, the drug was given only one time and the benefit appeared to diminish over the following week. We have been using a twice-weekly schedule, consistent with the finding from a study that indicated infused ketamine twice-weekly or thrice-weekly for up to six weeks led to an improvement of depression with the two dosing frequencies comparable [24]. All infusions were administered over a period of 40–45 min, and participants were monitored at the clinic for up to two hours following treatment. During the treatments, other pharmacological and psychotherapeutic treatments were continued as part of the usual regimen. In the procedure, patients who experienced transient dissociative symptoms or anxiety during the infusions could receive either intravenous infusion or 1 mg of oral lorazepam to improve the tolerability of the infusion. Patients who experienced nausea could receive intravenous or oral ondansetron. Blood pressure, heart rates, oxygen saturation, and respiration rates were monitored at regular intervals (5 min, then 10 min, then each 15 min) during the infusion and for 30 min afterward, with contingency planning for additional monitoring as clinically appropriate. Patients with a clinically significant increase in blood pressure could receive intravenous or oral labetalol. Criteria for discharge readiness included a return to baseline mental status, absence of gait disturbance and nausea, and normal blood pressure.

III. RESULTS

Among those patients, twenty-two patients completed their depressive symptoms measured by QIDS-SR16 and neurocognitive function measured by MoCA before the first and last treatment. All patients received the first dose of ketamine IV infusion at 0.5 mg/kg with possible dose escalation up to 1.0 mg/kg contingent on patient tolerability to the index dose and patient's response. The average dose of ketamine at the last treatment for those twenty-two patients was 0.67 mg/kg with standard error at 0.03. Before the ketamine treatment, the average QIDS-SR16 was 16.77 which indicated severe depression. After repeated ketamine IV infusions, the average QIDS-SR16 was 8.86 which indicated mild depression. There was a significant reduction (47.17%) of QIDS-SR16 measured at the last treatment compared to the baseline QIDS-SR16 (two-tailed paired t-test $P < 0.001$). Among those 22 patients, QIDS-SR16 scores from six patients were in the range of 1–5 which indicated no depression.

3.1 Evidence for single infusion intravenous ketamine

the first double-blind, placebo-controlled human study of ketamine for the treatment of MDD, seven patients received a single intravenous (IV) infusion of ketamine (0.5 mg/kg). Compared to saline infusion, ketamine significantly improved depressive symptoms within 72 h [22]. A subsequent, adequately powered, randomized, double-blind, placebo-controlled trial of single-dose IV ketamine infusion (0.5 mg/kg) in 18 individuals with TRD found that, within two hours of infusion, ketamine significantly improved depressive symptoms compared to placebo saline infusion. Patients had undergone a psychotropic medication taper and a two-week drug-free period, and depressive symptoms were assessed using the 21-item Hamilton Depression Rating Scale (HAM-D). Later studies of single-infusion ketamine supported these findings. For instance, a meta-analysis of nine randomized, placebo-controlled studies found that ketamine had antidepressant effects that began approximately 40 min post-infusion, peaked approximately 24 h later, and lost superiority to placebo after 10–12 days [24]. Other meta-analyses have corroborated these findings [25–28]. In this proof-of-concept, randomized, double-blind, active placebo-controlled, crossover study, 17 adolescents aged 13–17 received either a single-dose IV ketamine infusion (0.5 mg/kg) or midazolam (an active placebo control; 0.045 mg/ kg), two weeks apart. Compared to active placebo, ketamine was associated with a significantly greater reduction in depressive symptoms as measured by the Montgomery-Asberg Depression Rating Scale (MADRS). Participants experienced and tolerated transient, dissociative symptoms with ketamine. Further studies are needed to assess ketamine's ability to treat depressive symptoms in this vulnerable population. Finally, it should be noted that the bulk of this evidence has been collected from studies examining single, subanaesthetic-dose IV ketamine administration in TRD. While other routes of ketamine administration have been explored for the treatment of MDD—including oral, rectal, intramuscular, subcutaneous, and epidural—limited data exist for these alternate routes of administration, and further study is needed to support their efficacy.

3.2 Evidence for intranasal ketamine

In 2019, the FDA approved intranasal ketamine, the S-

enantiomer of ketamine, in conjunction with oral antidepressant for the treatment of TRD in adults. In 2020, it was FDA-approved to treat adults with MDD and acute suicidal ideation or behaviour. Due to concerns of possible adverse effects and potential abuse, ketamine was approved through a Risk Evaluation and Mitigation Strategy (REMS). Under this agreement, intranasal ketamine can be dispensed and administered only in a REMS-certified healthcare setting under medical supervision, and patients must be monitored for at least two hours following ketamine administration. The antidepressant efficacy of ketamine was demonstrated in two studies, both of which used a placebo solution that contained a bittering agent (denatonium benzoate) to simulate the taste of ketamine solution and maintain the blinding. In the first, randomized, placebo-controlled, double-blind study (TRANSFORM-1), 346 participants with TRD were recruited to assess the efficacy of twice-weekly intranasal ketamine (either 56 or 84 mg) plus a newly-initiated oral antidepressant [29].

IV. Discussion

we examined the effects of repeated escalating doses of ketamine intravenous treatment on the cognitive function. To the best of our knowledge, this is one of few studies that have investigated the effects of repeated escalating doses of ketamine intravenous treatment on the cognitive function of patients with TRD and compared the relationship of baseline cognitive function with antidepressant response in the clinical practice setting. The fear of cognitive impairment can be a major barrier to repeated ketamine treatment in clinical practice. Studies have indicated that a cumulative dose of ketamine leads to neurocognitive impairments, decreased hippocampal function, and BDNF, suggesting potential dose-, frequency- and duration-dependent effects on cognition with ketamine. Higher doses, higher frequencies, or longer durations of ketamine may cause more serious neurocognitive problems. In our clinical practice, we have demonstrated that repeated ketamine intravenous treatment at escalating dose protocol with 8–10 infusion sessions did not impair cognitive performance. There was no significant change in MoCA scores between post-infusions and baseline. Compared to previous studies, which have indicated that a single ketamine infusion at 0.5 mg/kg improved specific cognition as measured by the go/no-go task and six ketamine infusions at 0.5 mg/kg improved verbal learning and speed of processing, we did not find that repeated ketamine treatment improved cognitive function as measured by MoCA. Possible explanations for this discrepancy could be due to a different dosing schedule and different cognitive tests. In our clinical procedure, the starting dose was 0.5 mg/kg of ketamine, with a possible dose escalation of up to 1.0 mg/kg contingent on patient tolerability to the index dose and patient's response. In addition, we administered the MoCA test post 8–12 sessions, instead of a single session [27] or six sessions [26]. Finally, the MoCA test could be different compared to other cognitive tests in terms of its sensitivity.

V. Conclusion

Repeated ketamine intravenous treatment at escalating dose protocol with 8–10 infusion sessions did not impair cognitive performance. There was a moderate association between baseline cognition and antidepressant response from repeated intravenous ketamine treatments. A higher baseline MoCA score may predict a better antidepressant outcome. A growing body of scientific research supports the rapid antidepressant and anti-suicidal effects of ketamine in treating TRD and bipolar depression. In particular, clinical use of ketamine is rapidly expanding, despite the lack of sufficient data and few standardized guidelines to direct its use, particularly for maintenance treatment and for other formulations such as sublingual, oral, [11] and intramuscular. Larger studies of repeat-dose administration and long-term treatment data are both needed to inform evidence-based practice guidelines. Further evidence is needed to better understand ketamine's safety profile over longer periods of time, and its use should continue to be reserved for patients who have failed to respond to multiple existing treatment options [21]. Despite these challenges, studying the mechanistic processes and biomarkers that underlie ketamine's unique properties has fundamentally changed our understanding of the pathophysiology of mood disorders [22]. Efforts to elucidate ketamine's mechanism of action have focused attention on several areas, including: glutamatergic receptors (e.g., AMPA, mGluR); mediation via opioidergic mechanisms; the interplay between the glutamatergic and GABA-ergic systems; and downstream effects on signal transduction cascades such as mTOR, cellular proliferation, and neuroplasticity cascades.

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