Clinical Response of Ketamine Infusions in Adolescents with Treatment-Resistant Depression

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INTRODUCTION

Major Depressive Disorder (MDD) frequently emerges, and is substantially un-recognized, throughout adolescence [3]. This transition from childhood to adulthood is a period of emotional instability, which leaves many susceptible to depression or other mental illnesses [2]. Depression is related to a range of negative emotional behaviors, from lingering sadness to serious suicidal inclinations. Recent studies have shown that 10-20% of youth will experience a major depressive episode by the end of adolescence [4]. Only two-thirds of depressed patients respond to standard anti-depressant medications. The limited effectiveness of current treatment methods is contributing to greater morbidity and public health costs [1]. In order to reduce this (and considering the high prevalence and severe consequences), there is an immediate need for advanced neurobiological treatments.

Ketamine has recently been studied for its anti-depressant effects in adults with treatment-resistant depression (TRD). Recent data suggests that multiple infusions may have more sustained effects. The common anesthetic drug is associated with the N-methyl-D-aspartate glutamate receptor as an antagonist and is causing rapid anti-depressant effects even in those who failed to respond to previous treatments [1]. After administration of six intravenous ketamine infusions, adults with TRD have shown an overall response rate of 70.8%, and the duration of effects has lasted an average of 18 days [1]. The effects of ketamine has sparked ample interest among researchers, however, there are no reports on the effects of ketamine in adolescent TRD.

OBJECTIVES

- Examine efficacy and durability of anti-depressant effects in an adolescent TRD sample
- Identify what specific symptoms of depression contributed most to the improvement
- Establish the superior dosing regimen for maximization of effects
- Compare overall response rates and duration of anti-depressant effects in adolescents to adults

METHODS

Participants underwent six open-label intravenous ketamine (0.5 mg/kg) infusions over a two-week period. Initially, the dose was based on ideal weight. After the first five subjects, the dose was then based on actual weight. The primary response measure was the Children's Depression Scale-Revised (CDRS-R). Response was defined as ≥ 50% decrease in CDRS-R scores from baseline to one day after the last infusion, as seen in the equation below.

$$\frac{\textit{(Baseline CDRS – Exit CDRS)}}{\textit{(Baseline CDRS – 17)}}$$

The Montgomery-Asberg Depression Rating Scale (MADRS) was used to track depression severity throughout the study by measuring specific symptoms, as scored by the scale below [5]. MADRS scores were assessed at baseline, pre- and post- infusion, one day post-treatment, and at follow-ups.

0-6 → normal/symptoms absent
7-19 → mild depression
20-34 → moderate depression
34+ → severe depression

Initially, participants were followed for six weeks post-treatment only if they met response criteria. After the first five subjects, all participants were monitored.

RESULTS

Change in Children's Depression Rating Scale-Revised (CDRS-R) Scores from Baseline to Exit for Total (N=10) Participants

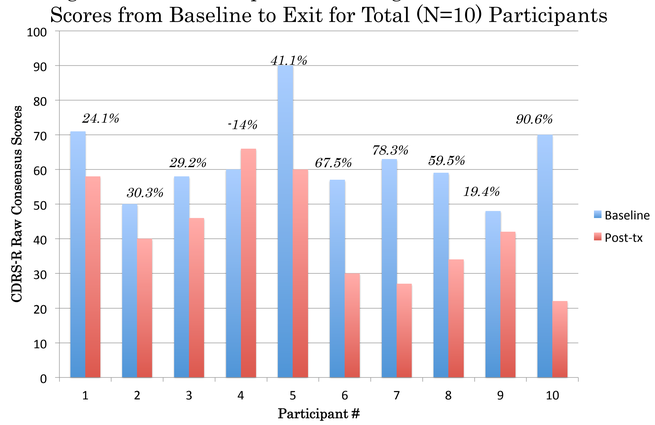

Figure 1. Change in Children's Depression Rating Scale-Revised (CDRS-R) scores from baseline to exit for all participants. These scores were used in the CDRS-R equation to determine participants as a responder or non-responder. Those who met response criteria with ≥ 50% change in scores were participants 6, 7, 8, and 10. This creates an overall response rate of 40%.

Average Improvement of Specific Symptoms of Depression in Responders According to the Montgomery-Asberg Depression Rating Scale (MADRS)

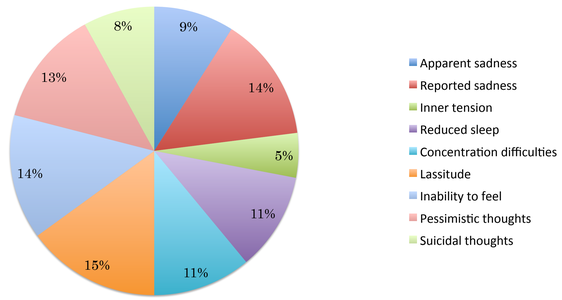

Figure 3. Improvement of depression severity in responders by specific symptoms of the Montgomery-Asberg Depression Rating Scale (MADRS). Those who met response criteria by the CDRS-R were examined for specific improvement in treatment-resistant depression. The figure depicts large improvement in lassitude, reported sadness, inability to feel, and pessimistic thoughts from baseline to exit.

Responders vs. Non-responders Montgomery-Asberg Depression Rating Scale (MADRS) Average Scores Throughout Study

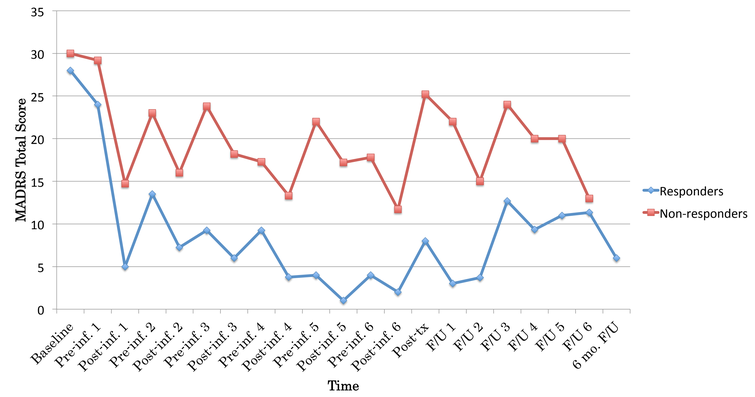

Figure 2. Change in Montgomery-Asberg Depression Rating Scale (MADRS) scores for responders and non-responders throughout study. The figure depicts changes in depression severity from the ketamine infusions and follow-up phase. The time-point of response appears to be immediate. The first five participants were not monitored after the infusions, as they were non-responders, until the protocol was changed to follow-up with all participants. The follow-up phase for non-responders on the figure is represented by the one non-responder after the protocol change (participant 9). The follow-up phase for responders is represented by three participants who have completed the follow-ups to date, as well as one participant who completed the 6 month follow-up.

CONCLUSION

To date, ten participants have completed the infusions. Of these, four participants have met criteria for response. All of the responders were in the second set of patients, for whom the dose was based on actual rather than ideal body weight. The overall response rate in adolescents (40%) is significantly lower than in adults (70.8%) [1]. Although the time-point of response is similar in both adolescents and adults, the duration of anti-depressant effects in adolescents (>42 days) is significantly different than in adults (~18 days) [1]. The average improvement seen in adolescent responders is 74%, with the strongest improvement in lassitude, reported sadness, inability to feel, and pessimistic thoughts. While most of the non-responders also showed a dramatic decrease in symptoms after the first infusion as measured by the MADRS, the symptoms continued to reappear by the following infusion. Non-responders showed slight improvement overall with an average of 22% reduction in CDRS-R scores. Currently, the results show that the use of ketamine in adolescents with treatment-resistant depression has not yielded a response rate as high as adults, but the adolescents who do benefit from ketamine tend to experience more sustained anti-depressant effects. This could be due to the versatility of the growing adolescent brain allowing the ketamine to work more efficiently. The preliminary results also suggest that actual-weight dosing, versus ideal-weight dosing, may be the superior ketamine regimen for adolescents with severe depression. The anti-depressant effects of ketamine could provide a massive leap forward in public health and the struggle to find advanced neurobiological treatments, however, more studies are required.

REFERENCES

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[5] Test: Montgomery-Asberg Depression Rating Scale (MADRS) in BioPsychoSocial Assessment Tools for the Elderly - Assessment Summary Sheet. The University of Western Ontario, London, Ontario, Canada, http://instruct.uwo.ca/kinesiology/9641/Assessments/Psychological/MADRS.html