Neurocognitive Effects of Intravenous Ketamine Treatment in Treatment Resistant Depression

Courtney E. Seri1, Sagar V. Parikh1, Eric Achtyes2, Dan Maixner2, Karina Drake1, Brendon Watson1, Vijay Tarnai1, Daniela Lopez1, LeAnn Smart1, Erica Vest-Wilcox1, Ivana Senic1, the Bio-K Study Team1,2, John Graden1

Affiliation: 1University of Michigan Department of Psychiatry and Depression Center, 2Pine Rest Christian Mental Health Services, Grand Rapids, USA

BACKGROUND

• Ketamine is an NMDA receptor antagonist associated with learning and memory
• Limited pre-clinical evidence suggests neurotoxicity
• There is disagreement over how ketamine treatment for treatment resistant depression (TRD) impacts cognitive function1,2,3
• We conducted a clinical trial to examine biomarkers of remission to ketamine for resistant unipolar or bipolar depression
• We administered 3 acute intravenous ketamine infusions at a sub-anesthetic dose of 0.5 mg/kg over 11 days

AIMS

• Investigate possible effects of intravenous ketamine on cognition using the Repeatable Battery for the Assessment of Neuropsychological Status Update® (RBANS-Update) pre- and post-infusions
• Determine if there are any deleterious effects of intravenous ketamine on cognition
• The RBANS-Update is a brief, individually administered battery to measure cognitive decline or improvement

METHODS

• At baseline and 24 hours after the last infusion, the RBANS-Update was administered
• RBANS-Update is a validated and reliable cognitive battery of 12 subtests focused on 5 indexes of cognition: immediate memory, visuospatial/constructional, language, attention, and delayed memory
• Subtest raw scores are converted to standardized index scores by same-age peer groups
• The RBANS-Update was administered by trained raters for standardization
• Regular checks were made to insure inter-rater reliability

RESULTS

• We report 27 subjects that completed the acute phase of infusions and RBANS-Update at the University of Michigan and satellite Michigan State University – Pine Rest sites
• Preliminary analysis shows, regardless of clinical outcome, there was a significant improvement in all five cognitive indexes and by percentile rank (see Table below)
• Overall (total scaled score), there was significant improvement from percentile rank by age group at baseline (M=49.67, SD=27.19) to 24 hours post infusion 3 (M=72.14, SD=30.48) conditions; t(26)=-4.898, p = .000

RBANS Means and Standard Deviations by Index (N = 27)

<table>
<thead>
<tr>
<th>Index</th>
<th>Baseline M (SD)</th>
<th>Post M (SD)</th>
<th>Baseline M (SD)</th>
<th>Post M (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Memory</td>
<td>99.96 (16.10)</td>
<td>120.62 (17.99)</td>
<td>90.64 (31.58)</td>
<td>80.65 (23.68)</td>
</tr>
<tr>
<td>Visuospatial/Constructional</td>
<td>96.79 (16.50)</td>
<td>103.69 (17.84)</td>
<td>43.37 (33.22)</td>
<td>58.62 (34.22)</td>
</tr>
<tr>
<td>Language</td>
<td>96.04 (9.25)</td>
<td>101.35 (12.14)</td>
<td>40.11 (21.93)</td>
<td>53.39 (25.96)</td>
</tr>
<tr>
<td>Attention</td>
<td>101.82 (18.49)</td>
<td>107.65 (16.02)</td>
<td>53.20 (33.41)</td>
<td>64.39 (29.85)</td>
</tr>
<tr>
<td>Delayed Memory</td>
<td>98.21 (14.38)</td>
<td>109.00 (15.38)</td>
<td>49.67 (24.61)</td>
<td>70.25 (26.68)</td>
</tr>
<tr>
<td>Total Scaled Score</td>
<td>98.07 (14.72)</td>
<td>113.25 (26.68)</td>
<td>49.79 (27.19)</td>
<td>72.14 (30.48)</td>
</tr>
</tbody>
</table>

DISCUSSION

• These preliminary data provide evidence of cognitive improvement, not decline, following administration of 3 IV ketamine infusions for depression
• Cognitive improvement may be mediated by improvement in depression, however, even individuals not achieving remission demonstrated cognitive improvement
• Because there was no difference between participants that experienced remission and did not experience remission at baseline, baseline differences between groups cannot account for the overall improvement

CONCLUSIONS

• These data are clinically reassuring that low doses of ketamine do not cause neuro-cognitive deficits
• Preliminary results may provide a glimpse into how ketamine effects neurocognitive functioning
• Future analysis on the mediators of cognitive improvement in this group will be explored, (e.g. demographics, multiple mental health diagnoses, and comorbidities)
• We also plan to explore how depression improvement mediates improved cognition as well as how cognitive performance may be linked to suicidal ideation

What about remitters?

• An ANOVA compared the effect of remission on percentile rank
• Remission was defined as a score of ≤ 9 on the Montgomery–Åsberg Depression Rating Scale MADRS
• There was no significant difference in remitter group at baseline testing on percentile rank; F(1, 25) = .228, p = .638

REFERENCES