The Use of Ketamine to Treat Suicidal Ideation

Angelia C. Smith

Pacific University
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Abstract

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The Use of Ketamine to Treat Suicidal Ideation

Angelia Smith

A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, 2017

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography
[Redacted for privacy]
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Acknowledgements

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List of Abbreviations
US United States
CDC Center for Disease Control
SI Suicidal Ideation
MDD Major Depressive Disorder
DSM-V The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
RCT Randomized Controlled Trial
MADRS-SI Montgomery-Asberg Depression Rating Scale
C-SSRS Columbia Suicide Severity Scale
BSI Beck Scale for Suicidal Ideation
QIDS-SR Quick Inventory of Depressive Symptomatology-Self Report
CAST Concise Associated Symptoms Tracking
BPRS Brief Psychiatric Rating Scale
CADSS Clinician-Administered Dissociative States Scale
PRISE Patient Rated Inventory of Side Effects
HDRS Hamilton Depression Rating Scale
IAT Implicit Association Test
SSRI Selective Serotonin Reuptake Inhibitors
The Use of Ketamine to Treat Suicidal Ideation

BACKGROUND

In the United States (US) suicide is considered to be one of the leading causes of death. Statistics from the Center for Disease Control (CDC) show that there were 41,149 suicides in 2013 ranking it as the tenth leading cause of death.\(^1\) The rate of suicide has increased 24\% within the last 15 years making it a serious public health concern.\(^2\) The rates in minorities such as American Indians, Alaska Natives, Pacific Islanders and those reporting multiple ethnic backgrounds are even higher than the average.\(^3\) The CDC has also reported that nearly 494,000 of those in the US receive emergency medical care for self-inflicted injuries, resulting in a 10.4 billion cost.\(^1\)

To reduce the rate of suicide it has been suggested by the CDC to use a 4-step approach.\(^4\) The 4 steps include defining the problem, identifying the factors contributing to suicide, implementing prevention strategies and ensuring widespread adoption. Defining the problem will require exhaustive collection of past and present data regarding completed suicides, suicide attempts and suicidal ideation (SI). Data showing who is at higher risk will help target preventative efforts.

Next, identifying risk factors and prevention factors will play an integral role as to why suicide has become such a large public health concern. Already established risk factors include a history of mental illness, substance abuse, previous suicide attempts, family history of suicide attempts, physical illness, feelings of being alone and being male (although females are reported to have more frequent suicidal ideation). Research\(^5\) on the psychological autopsy studies of suicide suggest that the most effective suicide prevention strategies should focus on the treatment of mental disorders specifically. This
is primarily suggested because mental disorders such as major depressive disorder (MDD) had the strongest associations with suicide when compared to a variety of other factors.

Decreasing risk factors of suicide, education of the warning signs of suicide and the promotion of patient protective factors may act as prevention strategies. Currently, suicide prevention focuses on the treatment of MDD which the DSM-V classifies as a depressive disorder. Depressive disorders vary but are all characterized by feelings of sadness, emptiness, irritability and a decreased capacity to function.

In 2012, a review of research concluded that the glutamate N-methyl-D-aspartate (NMDA) receptor antagonist ketamine has been shown to significantly decrease depressive symptoms in adults with MDD. The ongoing research on ketamine’s effect on depression has led specifically to the study of ketamine and its effect on suicidal ideation (SI). Preliminary research published in February 2015 has shown that ketamine effectively reduces SI. The purpose of this systematic review is to expand on the current understanding of ketamine as a way to treat SI. If this additional research supports previous findings, this review may help ensure widespread adoption of this technique to decrease suicide risk.

METHODS

A comprehensive search of literature was performed using MEDLINE-Ovid, Google Scholar and Web of Science. The searched keywords included “suicide” and “ketamine”. The abstracts from articles published between 2015 to present were evaluated for inclusion. Studies were required to focus on the effects of ketamine on suicidal ideation. Additional inclusion criteria required articles to be published in the
English language and for the studies to be conducted on human subjects. Articles that met the inclusion criteria were evaluated using the GRADE method. This method assesses the design, limitations, inconsistency, indirectness, imprecision and publication bias of each study.

**RESULTS**

A total of 88 articles were reviewed for relevancy. Following the examination of the article’s titles and abstracts, two studies met the eligibility criteria for this review. The first study was a randomized controlled trial (RCT) examining the use of ketamine to reduce SI in adults with mood and anxiety spectrum disorders. The second study was an open-label secondary analysis focusing on the use of ketamine to reduce SI in adults with MDD. See Table 1.

**Murrough et al**

This randomized controlled trial sought to evaluate the effects of ketamine on clinically significant SI. Patients were recruited through both an inpatient psychiatric service and an academic outpatient psychiatric clinic. Men and women between the ages of 18 and 80 years old were admitted to the study upon obtaining a Montgomery-Asberg Depression Rating Scale (MADRS-SI) of ≥4. A Columbia Suicide Severity Scale (C-SSRS) score of ≥4 lead to the exclusion of outpatients. This was due to the correlation of this score with a high intent to commit suicide. Co-morbidities were screened by using the MINI interview. Patients were excluded for having a lifetime history of primary psychotic disorders, recent substance abuse, history of ketamine abuse, unstable medical illness or current psychotic or manic symptoms.
Twenty-four patients were randomized into a ketamine group or midazolam group. Before the initiation of treatment, each participant underwent baseline screening to assess SI severity. After screening they received either 0.5mg/kg of racemic ketamine hydrochloride or 0.045mg/kg of midazolam using a double-blind technique. Each participant was evaluated at 24, 48, 72 hours and finally at 7 days after receiving treatment.\textsuperscript{10}

The primary outcome of SI was measured with the 21-item self-report Beck Scale for Suicidal Ideation (BSI) with scores ranging from 0-42. Suicidality was also measured using the MADRS-SI with scores ranging from 0-6. A MADRS-SI score of 4 indicated moderate SI without a specific plan of harm and a score of 6 indicated active intention of committing suicide. Additional secondary outcomes included depression severity evaluated with MADRS and the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR). Symptoms of SI were measured using the Concise Associated Symptoms Tracking (CAST) scale. Tools such as the Brief Psychiatric Rating Scale (BPRS), The Clinician-Administered Dissociative States Scale (CADSS) and the Patient Rated Inventory of Side Effects (PRISE) were utilized to monitor patient safety and tolerability of treatment.\textsuperscript{10}

At the 24, 72-hour and 7-day evaluations the BSI score differences between the ketamine and midazolam groups were not clinically significant. At the 48-hour evaluation, however, a significant difference between the 2 groups emerged (8.8±8.3 ketamine and 15.3 ±10.9 midazolam) suggesting a greater decline in SI for the ketamine group. When evaluating MADRS-SI scores it was shown that those receiving ketamine had a significantly lower rating 24 hours post-treatment when compared to the
midazolam group (1.8±1.9 ketamine and 3.3±1.6 midazolam). General depression levels did not vary significantly. Additional secondary outcomes can be seen in Table 2.

Undesired side effects of treatment emerged throughout the study. Some of the participants receiving ketamine reported transient dissociation, headaches, dizziness, anxiety, poor concentration, poor coordination and restlessness. Those receiving midazolam reported headache, dizziness, nausea/vomiting, diarrhea and anxiety. Both treatment groups had reports of acute psychotomimetic effects or mood elevation. Limitations noted in this study included a relatively small sample size.

Ionescu et al

This secondary analysis of an open-label study sought to evaluate the ability of ketamine to reduce thoughts of suicide in patients with treatment-resistant depression and current SI. Patients between the ages of 18-65 were recruited and screened at Massachusetts General Hospital. Inclusion criteria included meeting the DSM-IV criteria for MDD, plus scoring a ≥20 on the Hamilton Depression Rating Scale (HDRS). Treatment-resistant depression was defined as ≥3 failed treatment attempts of the current depressive episode. The study’s participants were all prescribed antidepressant medications for ≥4 weeks prior to the administration of ketamine. Participants were withdrawn from the study in the event of requiring antidepressant dose changes. The CADSS was utilized in baseline testing, 60 minutes and 120 minutes post-infusion to evaluate for adverse side effects. Outcomes throughout the life of the study were measured using the HDRS and C-SSRS scales. In addition to explicit outcome, implicit measures of SI were measured using the death/suicide Implicit Association Test (IAT) which measures response times of automatic mental association about specific topics.
Fourteen patients were enrolled into the study, 12 of which received all 6 infusions of ketamine. Loss of participants was attributed to intolerable side effects and scheduling difficulties. Before the initiation of treatment, each participant underwent 3 cycles of pretreatment screening to ensure they met the inclusion criteria and to evaluate the baseline data. After screening they received 2 ketamine infusions per week for a total of 3 weeks. The first 3 infusions were 0.5mg/kg, followed by 0.75mg/kg for the last 3 infusions. Participants were routinely evaluated before, during and after the treatment. Post-treatment evaluations occurred every 2 weeks for 3 months.\textsuperscript{11}

Acute treatment phase results showed that explicit SI measured by C-SSRS ideation scores decreased significantly. These scores decreased by an average of -0.27 per patient after each infusion. To isolate reduction of SI, the HDRS core depression items were controlled for yielding a coefficient of -0.12 implying that -0.12 of the -0.27 decrease was a reduction in SI specifically. The change in dosage showed no significant effects. In addition to the C-SSRS ideation scores, the C-SSRS intensity scores were shown to decrease as well; however, these scores were not significant when compared individually. C-SSRS intensity scores were not influenced significantly by dose. Acute treatment phase results also showed that there was a significant reduction in implicit SI. The change in IAT scores yielded a coefficient of +0.05, suggesting that patients responded faster to words associated with death/suicide. The IAT scores were no longer significant after controlling for HDRS core depression items.\textsuperscript{11}

There were 11 patients who completed the follow-up phase. Seven of these patients achieved remission (HDRS <7) after the acute treatment phase and 2 of these patients continued this remission through the end of the follow-up phase. This suggests
that reduction in SI is maintainable for some. Limitations of this study included a relatively small sample size, lack of a blind experimental design and the absence of a control group.\textsuperscript{11}

**DISCUSSION**

Since its development in 1962 as an anesthetic, ketamine has been established as having a variety of clinical uses. In addition to its anesthetic use, ketamine is now considered to be a pain-manager, anti-inflammatory and anti-depressant when administered in sub-anesthetic dosages.\textsuperscript{12} Between 2009-2012, data has shown that the prevalence of depression in Americans $\geq$ 12 years of age is 7.6%.\textsuperscript{13} Since patient well-being encompasses mental as well as physical health, one could see how the utilization of ketamine as an anti-depressant and agent to reduce SI is significant in improving general health outcomes.

In the two reviewed studies,\textsuperscript{10,11} a decrease in SI was significant following the infusion of ketamine. In the RCT\textsuperscript{10} it was shown that a single dose of IV ketamine was superior to a single dose of midazolam. A significant reduction in SI was apparent 48-hours post-infusion, but this significance vanished in the longer term samples. Until this point, prior research\textsuperscript{8} has mainly focused on ketamine’s ability to reduce SI in those with depressive disorders such as MDD. However, the participants of this study had differing co-occurring mood and anxiety spectrum disorders which supports the finding that ketamine is useful in treating SI in a larger demographic. It was suggested by the authors of the RCT study\textsuperscript{10} that more research is needed to further separate the isolated effects of ketamine on SI independent of co-occurring disorders.
In the secondary analysis\textsuperscript{11} of an open-label study it was shown that repeated IV infusions of ketamine rapidly reduced suicidal ideation and intensity. This reduction in SI occurred 4 hours post-infusion. There was, however, a lack of significance of isolated intensity reduction of SI when depression core items were controlled for. In contrast to the RCT study\textsuperscript{10} it was found in the secondary analysis\textsuperscript{11} that ketamine has the ability to provide long-term remission of SI. While discussing the increase in death/suicide IAT scores regarding implicit SI, the authors of this study suggested that the resulting scores were difficult to interpret. This was attributed to the small sample size and the participant’s dislike of participating in the implicit measures of SI versus the explicit ones. The authors then suggested that a larger more controlled study is needed to study ketamine’s anti-suicidal effects.

The quality assessment of the two reviewed studies\textsuperscript{10,11} can be seen in Table 1. An important limitation of these studies was the relatively small sample size. Having a small sample size can lead to the skewing of results which in turn can lead to inaccurate data. Due to this, the RCT\textsuperscript{10} was downgraded to a “moderate” quality. To increase study precision and overall quality of future studies a larger sample size should be considered. Other importation limitations of secondary analysis\textsuperscript{11} was the lack of collector and participant blinding. This shortcoming in conjunction with the small sample size leads this study to be considered “very low” quality. However, research on this topic is in the beginning stages, thus explaining the lower quality of these studies. Through study refinement the limitations should diminish, leading to more accurate and reliable results.
CONCLUSION

Current standard of care is to treat depression and SI with anti-depressants such as selective serotonin reuptake inhibitors (SSRIs) which are notorious for taking weeks before symptom resolution is established. In comparison, this systematic review provides evidence that ketamine more rapidly treats both depression and SI which may lead to improved patient outcomes. The results of this systematic review in conjunction with the prior systematic review are suggestive that the new and possibly more efficient treatment of SI with ketamine could become standard practice. Further research is needed to explore the potential of ketamine to rapidly and efficiently reduce SI both short and long-term. Within this, the long-term side effects and isolated effects of ketamine on SI should be further evaluated. Although IV ketamine was utilized in both of the reviewed studies it may be beneficial to study less invasive routes of administration such as intranasal. The intranasal administration of ketamine could be easily utilized in an outpatient setting while still allowing for rapid administration, thus reducing the cost of administration. This in itself could be integral in ensuring widespread prevention of suicide by the use of ketamine.
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\(^a\) Small sample size
\(^b\) Lack of blinding of data collectors and participants in the Ionescu et al study\(^11\)
\(^c\) No control group in the Ionescu et al study\(^11\)
Table 2: Effects of ketamine compared to midazolam on secondary outcomes in participants with clinically significant suicidal ideation

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<td>72 h</td>
<td>20.9 ± 14.5</td>
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