

## Low-Dose Ketamine for Depression and Suicide Ideation in the Emergency Department: An Open-Label Feasibility Study

Gregory Luke Larkin<sup>1\*</sup> and Radu Radulescu<sup>2</sup>

<sup>1</sup>Northeast Ohio Medical University, Rootstown, OHIO, USA

<sup>2</sup>Yale University, New Haven, CT, USA

\*Corresponding Author: Gregory L Larkin, Northeast Ohio Medical University, Rootstown, OHIO, USA.

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### Abstract

**Background:** Given the high and rising frequency of Emergency Department (ED) visits for severe depression and suicide ideation (SI), rapid-onset antidepressants could represent a novel treatment for the acute-care population at risk for self-harm. This study explores the feasibility, tolerability and preliminary efficacy of a single intravenous (IV) bolus of ketamine in depressed, suicidal ED patients.

**Methods:** In a large (80K visit/year) ED, fourteen patients with depression and SI received a single IV bolus of low-dose racemic ketamine (0.20 - 0.30 mg/kg) over 1 - 2 minutes. After treatment, patients were closely monitored over the next 4 hours and closely followed-up over the following 10 days. Primary outcomes were ED length of stay (LOS) and clinical safety evaluated using the Young Mania Rating Scale (YMRS) and the Brief Psychiatric Rating Scale (BPRS+). Preliminary efficacy was assessed using the Montgomery-Asberg Depression Rating Scale (MADRS).

**Results:** Depressed, ketamine-treated patients with SI were in the ED for a median time of 7.1 hours, compared to 7.47 hours for age- matched ED patients with identical SI symptoms ( $p = NS$ ). Consistent with its cognitive and behavioral effects in other ED populations, ketamine transiently increased mean scores on the YMRS (SEM) to 0.3 (0.2), 0.1 (0.5), and 0.1 (0.1) at 40, 80, and 240 minutes, respectively. Mean BPRS+ scores remained 0 (SEM:0) at each time point. Mean baseline MADRS scores fell from 40.4 to 11.5 at 240 minutes ( $p < 0.0001$ ), with reductions sustained at 10 days (9.8). Baseline SI scores (MADRS item 10) fell significantly from 3.9 (SEM:0.4) to 0.6 (SEM:0.2) at 40 minutes post-administration; these reductions were sustained for 10 days.

**Conclusions:** Low-dose racemic ketamine given as a single IV bolus from 0.2- 0.3 mg/kg is well-tolerated in select, severely depressed ED patients and it is feasible to test as a rapid-acting, SI-lytic medication in the Emergency Department (ED).

**Keywords:** Emergency Department (ED); Suicide Ideation (SI); Single Intravenous (IV); Brief Psychiatric Rating Scale (BPRS+); Montgomery-Asberg Depression Rating Scale (MADRS)

### Introduction

Suicidal behavior is a pervasive and pressing public health problem, which translates to more than 500,000 visits to US Emergency Departments (EDs) each year [1,2]. ED visits for mood disorders in general, and for both major depression (MDD) and SI, in particular, have increased significantly over the last 20 years [3]. Most suicidal ED patients are seen only in general EDs and are discharged home without admission. While they are routinely referred to outpatient mental health services, these SI patients are notoriously poor at engaging with outpatient mental health services following ED discharge [4]. Intervening early with efficacious ED-based treatments when patients are still accessible could achieve a more rapid, effective, and safe disposition, especially when high quality psychiatric services are not readily available.

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Unlike the ED use of neuroleptics and anxiolytics for acute psychoses and panic attacks, respectively, there are no validated “SI-lytic” agents for severe depression or suicidality in the ED setting. Commonly used antidepressant drugs have slow onset of action, and inherent short-term liabilities [5]. Hence, many suicidal patients are admitted to the hospital for safety reasons alone, despite the disruptive and costly nature of this step [6]. Recent studies, however, suggest that ketamine, an N-methyl-D-aspartic acid (NMDA) receptor antagonist, may exert a rapid antidepressant effect in research subjects with treatment-resistant depression (TRD) and suicide ideation [7-12]: In these trials, a slow sub-anesthetic hour-long infusion of IV ketamine (0.5 mg/kg) rapidly reduced depressive symptoms within several hours of drug administration; this response was maintained in some patients for up to 7 days. Recent studies also suggest that a single low dose of IV ketamine may exert what we call an “SI-lytic” or anti-suicidal effect [10]. Thus, there is a possibility that one day, rapidly acting antidepressant medications might play a role in alleviating distress, reducing SI, and mitigating hospitalization in select ED patients. As a first step toward exploring this hypothesis, this study evaluated the feasibility and preliminary efficacy of a low-dose IV ketamine bolus on depression and suicide ideation in ED patients.

## Methods

The study was designed as a small, feasibility, pilot study and it was approved by the Human Investigations Committee (HIC/IRB) of Yale University/Yale New Haven Hospital (Protocol No. 0909005766). Voluntary, signed informed consent was obtained from all ED patients prior to their participation, according to the principals for protection of human subjects and as outlined in the Declaration of Helsinki.

## Patients

Patients were recruited from a large 80,000-visit, adult, urban, academic, Level I Trauma center. For inclusion in the study, ED patient participants met the following criteria: 1) A primary presenting complaint of depression with suicide ideation; 2) met DSM-IV criteria for major depressive disorder as assessed by the Mini-International Neuropsychiatric Interview (M.I.N.I.) [13]; 3) Scored  $\geq 24$  on the Montgomery-Asberg Depression Rating Scale (MADRS) [14]; and 4) Scored  $\geq 2$  on the Beck Scale for Suicide Ideation (SSI) [15].

Patients were excluded from consideration for the study if: 1) they were pregnant or breast-feeding or had acute medical problems or screening medical laboratory abnormalities that required clinical intervention; 2) met DSM-IV criteria for diagnosis of alcohol dependence or substance dependence other than nicotine; 3) had lifetime diagnoses of psychosis, mania or hypomania; 4) were currently receiving routine antipsychotic or NMDA-antagonist medications (e.g. amantadine, rimantadine, lamotrigine, memantine, dextromethorphan); 5) any lifetime use of ketamine or phencyclidine (PCP).

## Design

The study was designed as a single-arm, open-label, ED feasibility pilot study. Subjects were ED patients and remained in the ED for screening, consent, and treatment. Treatment consisted of a single sub-anesthetic IV bolus of racemic ketamine (0.20 - 0.30 mg/kg) given over 1-2 minutes in the Emergency Department, with continuous monitoring of vital signs, adverse events and psychotomimetic side-effects for 4 hours post-administration. Ratings included the 10-item MADRS and the 21-item SSI to assess both depression and Suicide Ideation (SI). The tolerability and safety of the treatment was assessed using the 11-item Young Mania Rating Scale (YMRS) [16], (to assess mania) and the 4-item Brief Psychiatric Rating Scale (BPRS+) to assess the psychotomimetic effects of low-dose ketamine. The BPRS+ domains include the following: Suspiciousness; Unusual thought content; Hallucinations; and Conceptual disorganization [17].

MADRS ratings were obtained real time, in person, in the ED at baseline, and at 40, 80, 120 and 240 minutes. Subsequent MADRS ratings were obtained daily for 10 days post-administration. Daily follow-up interviews were conducted in person for those patients who were hospitalized, and by telephone for patients who had been discharged. All subjects continued to receive standard and routine treatments (treatment-as-usual) including psychosocial and psychopharmacological treatments in both the inpatient and outpatient settings.

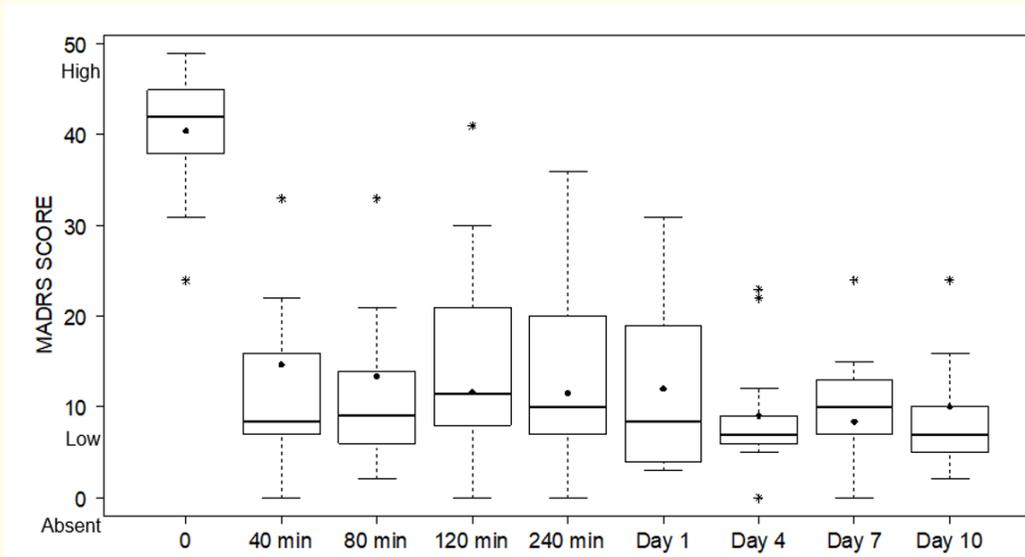
**Statistical analysis**

Primary outcome measures included the MADRS for depression, and Item 10 of the MADRS (MADRS-SI) for suicide ideation. Secondary measures included the YMRS and BPRS+. Changes from baseline in the MADRS, YMRS and BPRS+, were assessed using repeated measures ANOVA and box-plot analyses. Any violations of sphericity were corrected by adjusting the degrees of freedom in the ANOVA using the Greenhouse-Geisser correction. Missing data, when present, were handled by carrying forward the subjects highest (more symptomatic) scores. Time data were transformed using  $\log_{10}$ . Kaplan-Meier survival analysis was used to analyze the time to remission (defined as a MADRS score  $\leq 10$ ).

**Results**

Fourteen ED patients (7 males) aged 18 - 53 years [mean (SEM) 31.1 (3.4) years] participated in the open-label ketamine treatment pilot. The subjects' mean weight (SEM) was 82.9 (5.7) kg (range 60 - 123 kg). The racemic ketamine doses given ranged from 0.2 mg/kg in 9 subjects to 0.3 mg/kg in the 5 remaining subjects. Median ED length of stay (LOS) for ketamine-treated patients was 7.1 hours; this compares favorably to a median LOS of 7.47 hours for 30 age and symptom-matched SI patient controls collected from the same ED during the same time period (median test P = NS). The average length of stay for severely depressed and suicidal ED patients at the time of this study was 9.97 hours ranging from 2.42 to 22.33 hours.

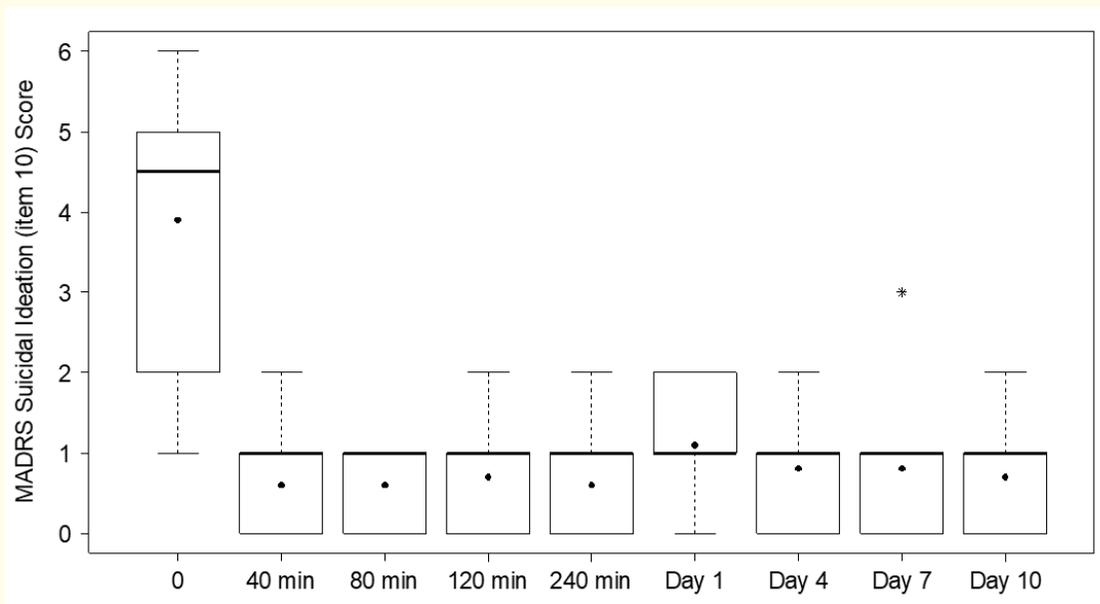
Median (Interquartile Range, IQR) baseline scores of these 14 patients on the MADRS and the SSI were 42 (IQR 38-47) and 19 (IQR 12 - 28), respectively. Mean MADRS scores at baseline, 40, 80, 120 and 240 minutes post-administration were 40.4, 14.7, 13.4, 11.6, and 11.5 respectively (repeated measures ANOVA: F = 23.7, df = 95, P < 0.001); these reductions were sustained at 7 days [mean MADRS (SEM): 8.4 (1.6)] for all patients, and for all 13 patients followed to 10 days [mean MADRS: 9.2 (1.7)] (Figure 1). One subject was lost to follow-up at Day 8 and considered a non-responder. Of the 13 subjects followed for 10 days, 12 maintained response criterion (> 50% reduction in MADRS scores compared to baseline).



**Figure 1:** Course of mood, measured by MADRS\*, over 10 days in 14 patients who received ketamine.  
 \*MADRS: Montgomery-Asberg Depression Rating Scale.

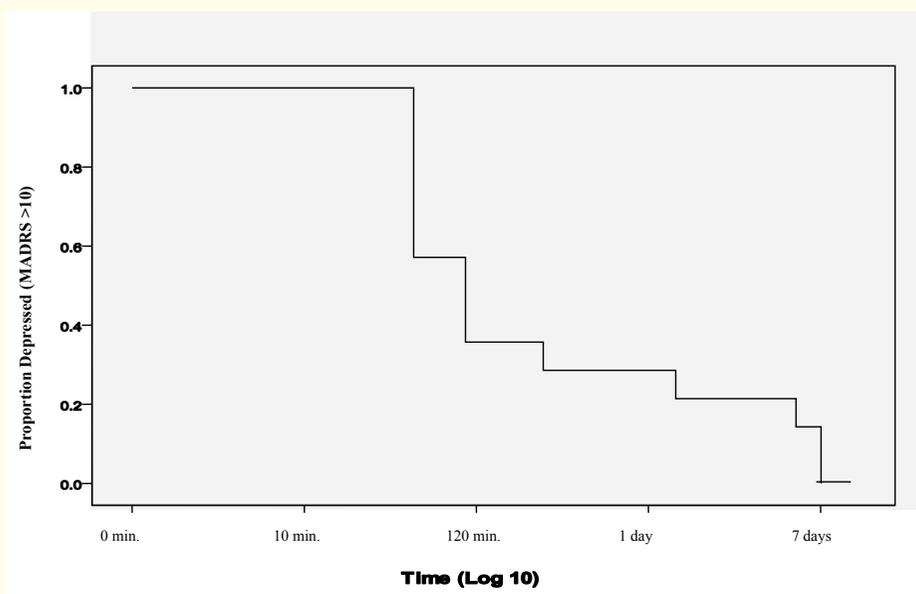
The mean (SEM) baseline MADRS-SI score was 3.9 (0.4); this SI score decreased significantly in all patients post-administration, as represented by mean MADRS-SI scores of 0.6 (0.2), 0.6 (0.2), 0.7 (0.2) and 0.6 (0.1) at 40, 80, 120, and 240 minutes, respectively (Figure

2). Suicide ideation completely resolved in all patients by 40 minutes, with this reduction being sustained at 7 days in all patients, and in all 13 patients followed to Day 10 [MADRS-SI scores were 0.8 (0.1) and 0.7 (0.2) at days 7 and 10, respectively]. Repeated-measures ANOVA shows the 10-day SI reductions to be significant ( $F = 29.7$   $df = 97$ ,  $P < 0.001$ ). For both the total MADRS score and the MADRS-SI, all post-treatment scores were significantly lower than baseline scores, and the scores at all time points beyond 40 minutes following ketamine administration were not significantly different from each other.



**Figure 2:** Course of suicide ideation, measured by MADRS\* item 10, over 10 days in 14 patients who received ketamine.  
 \*MADRS: Montgomery-Asberg Depression Rating Scale.

Figure 3 reveals the cumulative proportion of subjects achieving remission of depressive symptoms during the 10-day study using Kaplan-Meier survival analysis. (Remission was defined as a MADRS score  $\leq 10$ ). The mean time to remission was 240 minutes (95% Confidence Interval (CI) 70 - 720). The median time to remission was 80 minutes (95% CI: 38 - 190). Of the 13 subjects followed for 10 days, 12 maintained the response criterion (defined as a  $> 50\%$  reduction in MADRS scores compared to baseline) at 10 days post-treatment.



**Figure 3:** Kaplan-Meier Survival plot of time to remission of depression after ED bolus ketamine.

As assessed by BPRS+, ketamine elicited no more than mild positive psychotic-like symptoms, all of which resolved within 40 minutes. Hence, mean BPRS+ scores (SEM) were 0 (0) at 40 minutes and they remained 0 (SEM:0) at each time point thereafter. Consistent with its cognitive and behavioral effects in other ED populations, ketamine transiently increased mean scores on the YMRS (SEM) to 0.3 (0.2), 0.1 (0.5) and 0.1 (0.1) at 40, 80 and 240 minutes, respectively. Two patients experienced unpleasant dissociative symptoms, as assessed by the YMRS, but these resolved within 30 minutes of the ketamine bolus. At the end of the study, all subjects affirmatively endorsed the statement: "The benefits of receiving this medication outweigh any inconvenience, discomfort, or side-effects".

## Discussion

Ketamine is classified as a dissociative anesthetic and is chemically defined as (racemic) 2-*o*-chlorophenyl-2-methylamino-cyclohexanone hydrochloride and has been in clinical use for over half a century. Racemic ketamine is an inexpensive and safe agent used routinely in the Emergency Department (ED) setting at IV doses of 1 - 2 mg/kg for conscious sedation in both adults and children.

This pilot study suggests that administering low-dose ketamine to severely depressed patients in a busy ED setting is feasible, safe and potentially effective in inducing a rapid remission of depression and suicide ideation, as assessed by total MADRS, and MADRS-SI scores. In this open-label trial, symptoms diminished rapidly and significantly within 40 minutes, with these reductions sustained for 10 days in all 13 patients followed to 10 days, without rebound.

Our findings are consistent with and extend prior research reporting ketamine's rapid response in unipolar, bipolar, and treatment-resistant depression [8,12,18], and in suicide ideation [9]. In several small studies slow infusions (over 40 minutes) of ketamine have been shown to rapidly reduce depressive symptoms in patients with refractory depression [7-12] and bipolar disorder [18]. While one study has shown a reduction in suicide ideation 24 hours after a slow infusion of ketamine in TRD patients [10], our study is the first to show this effect can be achieved with a rapid bolus, a more feasible mode of delivery for a busy ED setting. There is no scientific rationale for slow infusions, but the psychiatrists conducting prior studies were prudent, exercising caution, given their relative inexperience in administering ketamine to patients. Trained emergency physicians (EPs) have longstanding experience administering ketamine to a wide variety of patients and are well familiar with managing ketamine-induced adverse effects as they routinely administer much higher doses than those used herein.

Ketamine is the first ED medication to produce a rapid reduction in suicide ideation without a short-term risk of SI rebound. Analogous to the rapid ED anxiolysis achieved in panic patients with parenteral benzodiazepines, we have coined the term "SI-lysis" to describe the rapid antidepressant phenomenon observed with low-dose ED ketamine. Anti-depressant and anti-suicidal effects emerge during lithium [19], and clozapine [20], treatment, but only during long-term therapy. Apart from ECT, which can rapidly reduce suicide ideation [21], there are few options currently available for ED patients in acute crisis.

Given that the sustained antidepressant effects of ketamine far outlast its 2 - 3 hour half-life, this study adds evidence to the hypothesis that ketamine's antidepressant-type effects are due to achieving a threshold concentration, referred to as C<sub>max</sub>, versus the cumulative total dose given, (area under the curve, AUC). The mechanism of ketamine's rapid antidepressant and anti-suicidal actions are unclear but appear to be related to increased glutamate neurotransmission [8,12] and a ketamine-induced signaling cascade involving AMPA, brain-derived neurotrophic factor (BDNF), mammalian target of rapamycin (m-TOR) and ultimately, an increase in synaptic connectivity [22].

The ideal "SI-lytic" dose of ED ketamine is still unknown. While most of the treatment-resistant depression literature to date has focused on slow infusions of 0.5 mg/kg of ketamine given over 40 - 60 minutes, our pilot showed promising results with half that dose given as a bolus over 1 - 2 minutes. It was serendipitous that small errors in dose/weight estimation lead 5 subjects to get doses of 0.3 mg/kg; the remaining 9 subjects received the intended bolus doses of 0.2 mg/kg. Both the 0.2 mg/kg and 0.3 mg/kg doses are well below the standard range of doses of ketamine used in the ED (1.0 - 2.0 mg/kg). This nontrivial dose variation is still within the bounds of very low-dose ketamine. In addition, this variance did not materially impact the observed side effects or antidepressant effects in this cohort. Both

dosing groups had BPRS+ scores of 0 at each time point. Both groups had dramatic and sustained decreases in SI scores at 40 minutes and beyond. Properly designed dose-finding studies should be conducted henceforth to further delineate the optimal starting dose of ED ketamine for SI-lysis.

Beyond the variance in dosing, this study had other important limitations including the small number of patients, the open-label design, the lack of placebo or active comparators, short duration of follow-up, and the use of a single item to assess suicide ideation. The small number of patients, for example, might obscure the likelihood of observing adverse events that occur rarely. Despite small numbers, our study is the first to show the feasibility and potential utility of ketamine as a rapidly acting antidepressant in a busy ED setting.

Another perceived limitation is that ketamine, while safe, engenders concern around its reputation as a potential drug of abuse. However, given that low-dose (0.2 - 0.3 mg/kg) racemic ketamine administered as a slow IV bolus does not generally produce either euphoria or psychotomimetic effects, it is unlikely to have high abuse potential. Our results herein further suggest that neither euphoria nor disassociation are required to mitigate SI or depression symptoms in the short term.

“SI-lysis” achieved by low-dose ED ketamine may provide a future therapeutic bridge that allows for more rapid and safe disposition of mental health patients in crisis. Subjects in this trial were admitted to the psychiatry service for safety and received other conventional treatments after leaving the ED.

### Conclusion

Low-dose bolus ketamine for depressed and suicidal ED patients is feasible, safe, and potentially efficacious. This study is the first to suggest that “SI-lysis” can be reliably achieved within 40 minutes of IV bolus ketamine doses in the range of 0.2-0.3 mg/kg. Low-dose ketamine may provide a future therapeutic bridge that allows for more rapid and safe disposition of SI patients in crisis. In the future, ketamine-bridging therapy combined with tailored therapy (e.g. Cognitive Behavioural Therapy (CBT) and SSRIs) may provide a needed safety net when inpatient resources are unavailable. To ensure safety, tailored ED treatment would still need to include access to robust psychosocial and mental health resources. Despite EPs’ longstanding familiarity with ketamine, we urge caution in its use until further randomized evidence shows the optimal way to integrate this strategy into clinical practice with this highly vulnerable population.

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