Early Response to Ketamine for Suicidal Crisis Reduces Suicidal Events at 3 Months

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Abstract

Background: Intravenous (IV) ketamine has demonstrated rapid reduction of suicidal ideation (SI), but its impact on suicidal attempts remains unclear. This study investigates the effect of IV ketamine on SI at 7 days and suicidal events (suicide attempt or hospitalizations for SI) at 3 months in a real-world clinical setting.

Methods: We conducted an observational retrospective study including 100 adult French patients who received 1 or 2 IV ketamine infusions (0.5 mg/kg) within 1 week for a suicidal crisis between June 2022 and June 2024. Depressive symptoms (Montgomery-Asberg Depression Rating Scale) and SI severity (Columbia-Suicide Severity Rating Scale [C-SSRS]) were assessed at baseline and 7 days postinfusion. Suicidal events were collected from clinical records at 3 months.

Results: Ketamine significantly reduced depressive symptoms ($\beta = -11$; $P < .001$) and SI severity ($\beta = -2.0$; $P < .001$) at 7 days after controlling for age, sex, and number of infusions. A direct ($\beta = -0.78$; $P < .001$) and indirect effect ($\beta = -0.29$; $P = .007$) on SI through depression reduction was observed. Sixty-one percent of patients were SI responders (≥50% reduction in C-SSRS severity). SI responders at 7 days had 75% lower odds of experiencing suicidal events at 3 months (OR = 0.25; $P = .009$).

Conclusion: This is the first study demonstrating that early SI response to IV ketamine is associated with a reduced risk of suicidal events at 3 months. These findings support ketamine's unique antisuicidal properties beyond its antidepressant effects, highlighting its potential role in suicide prevention.

Trial Registration: ClinicalTrials.gov identifier: NCT06806475

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Suicide remains a major public health concern and is one of the leading causes of mortality worldwide. In 2019, suicide accounted for approximately 700,000 deaths, making it the fourth leading cause of death among individuals aged 15–29 years.[1] Suicide attempts and suicidal ideation (SI) are strong predictors of future suicide risk,[2] yet current therapeutic options remain insufficient, with standard treatments often requiring weeks to take effect. Given the urgent need for rapid-acting interventions,[3] ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, has emerged as a promising treatment for acute suicidal crisis. Indeed, randomized controlled trials have shown that a single dose of intravenous (IV) racemic ketamine can rapidly decrease depressive symptomatology and SI[4,5] with effects appearing within hours postadministration.[6,7] According to meta-analyses, the efficacy on SI may last a few days,[7–12] in some cases extending up to 1 month.[13–15] While repeated dosing strategies have been explored, their effectiveness remains inconsistent, with some studies suggesting cumulative benefits,[11,12,16] while others find no difference between single versus multiple doses.[13,17]

Notably, ketamine's impact on SI extends beyond its antidepressant effects.[18] A meta-analysis found that 10% to 46% of ketamine's effect on SI reduction is explained by improvements in depressive symptoms, suggesting a distinct antisuicidal mechanism.[6] While mood improvement contributes to SI reduction, additional mechanisms have been proposed such as reduction of psychological pain,[19] alleviation of anhedonia,[12] and modulation of sleep architecture.[20] Neuroimaging studies have demonstrated widespread changes in functional brain connectivity after ketamine administration, particularly in regions involved in emotion regulation, cognitive control, and reward processing.[21] Interestingly, all of these dimensions are all related to both SI and suicidal attempts.

Despite the growing evidence for ketamine's impact on SI, data on its ability to prevent actual suicidal attempt remain scarce. Most clinical trials have focused on SI reduction as a primary outcome, treating suicidal attempt or suicide death as treatment-emergent adverse events rather

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Clinical Points

- One or two intravenous ketamine infusions significantly reduce suicidal ideation within 1 week.
- Reduction of suicidal ideation severity >50% within the week following ketamine infusion was associated with reduced suicidal events (hospitalization for suicidal ideation or suicide attempt) at 3 months.
- Ketamine offers a critical window for intervention, allowing time to initiate longer-term treatments in acute suicidal crises.

than key end points.[22] In this context, we aimed to assess whether the significant reduction of SI at 7 days following an IV ketamine administration for suicidal crisis did decrease the occurrence of subsequent suicidal events (hospitalization for SI or suicide attempt) at 3 months. We hypothesized that IV ketamine would significantly reduce SI and depressive symptoms in the week following ketamine administration and that reduction by 50% of SI severity (SI response) at 7 days would be protective against suicidal events at 3 months. The risk of suicide is highest within 3 months of discharge from psychiatric facilities, supporting this as a critical evaluation period.[23]

METHODS

Study Design and Population

We conducted an observational retrospective study involving 100 adult French outpatients who received at least 1 ketamine infusion for a suicidal crisis. Patients were consecutively recruited between June 2022 and June 2024 in the Emergency Psychiatry and Acute Care Unit at the University Hospital of Montpellier. Ketamine administration was based on clinical judgment. Patients were excluded if they had an unstable cardiovascular condition, untreated or unstable hypertension, current psychotic symptoms, or a lifetime history of schizophrenia or schizoaffective disorder.

Intervention

Participants received 1 or 2 ketamine infusions diluted in saline solution over 1 week based on the clinical judgment of the emergency room psychiatrist. The number of infusions was determined by the clinician. The patient was placed in a dedicated room in the presence of the nurse during 40 minutes. Each infusion was administered in a dedicated room, with the patient continuously monitored by a nurse during the procedure. Racemic ketamine was delivered intravenously at a dose of 0.5 mg/kg over 40 minutes using an electric syringe pump. Vital signs (blood pressure, heart rate, and respiratory rate) were monitored for 2 hours—every 10 minutes during the infusion and every 20 minutes during the subsequent hour. Prior to infusion, subjects had to be fasting, have a blood pressure <140/90 mm Hg, and avoid benzodiazepine use in the 6 hours before infusion.

Assessment

Data on sociodemographic characteristics (age, sex, socioprofessional status) and psychotropic treatment were collected. Before the infusion, a trained clinician assessed general psychopathology (except personality disorders) according to *DSM-5* criteria,[24] depressive symptomatology using Montgomery-Asberg Depression Rating Scale (MADRS),[25] and severity of SI within last week and lifetime history of suicidal attempt using Columbia-Suicide Severity Rating Scale (C-SSRS).[26] Patients also self-rated depressive symptomatology using Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR)[27] and anxious symptomatology using Generalized Anxiety Disorder-7 (GAD-7).[28] Immediately after the infusion, patients rated the subjective efficacy of ketamine based on a 5-point Likert scale.

At 7 days postinfusion, depression levels (MADRS and QIDS-SR) and SI severity (C-SSRS) were reassessed. At 3 months, we collected the occurrence of suicidal event (suicide attempt or hospitalization for SI) from the clinical records of psychiatric emergency of University Hospital of Montpellier, the only one in the city. For patients receiving a second infusion within the week, we considered baseline assessment before the first infusion and follow-up assessment (7 days and 3 months) after the second infusion.

SI response was defined as a reduction of at least 50% in the C-SSRS severity subscore or a decrease in subscore from 5 (ie, active SI with specific plan and intent) at baseline to 3 (ie, active SI with any methods without intent to act) at 7 days.

The local Ethics Committee of Nimes Academic Hospital approved the study protocol (registration number 23.11.07). The study was registered in ClinicalTrials.gov (identifier: NCT06806475). All participants received and provided an informed consent form for both clinical treatment and participation to research.

Data Analyses

Descriptive statistics were used to summarize the population, reporting median values and corresponding percentages. Mixed models were employed to evaluate the following outcomes: reduction of depressive symptoms and SI severity at 7 days postinfusion. With an $\alpha = .05$ and 90% power, a sample size of 100 patients enables us to detect a moderate-sized mean reduction in SI ($dz = 0.3$), corresponding to a decrease of around 0.5 to 1 point on the C-SSRS. Beta estimates and 95% confidence intervals (CIs) were reported. Additionally, a mediation model was implemented to explore the potential mediating role of depressive symptom reduction in the effect of ketamine on SI. To assess the robustness of our findings, we applied

Table 1.

Description of the Sample

	Median [min–max]/N (%)
Sociodemographic characteristics	
Age (years)	28 [18–86]
Female	77 (77%)
Single	66 (66%)
Professionally active	35 (35%)
Current psychopathology	
Major depressive episode	100 (100%)
Unipolar disorder	84 (84%)
Bipolar disorder	16 (16%)
Alcohol/substance use disorder	12 (12%)
Anxiety disorder	33 (33%)
Eating disorder	16 (16%)
C-SSRS	
Severity of suicidal ideation	4.00 [1.00–5.00]
History of suicide attempt	72 (72%)
Number of suicide attempt	1.0 [0.0–23.0]
Anxiodepressive symptomatology	
MADRS score	34 [12–53]
QIDS score (missing data = 17%)	22 [4–39]
GAD-7 (missing data = 18%)	16.0 [1.0–21.0]
Psychotropic treatment (missing data = 4%)	
Anxiolytic/hypnotic	71 (74%)
Antidepressant	73 (76%)
Antiepileptic	0 (0%)
Antipsychotic	72 (75%)
Lithium salts	8 (8.3%)

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale, GAD-7 = Generalized Anxiety Disorder-7, MADRS = Montgomery-Asberg Depression Rating Scale, QIDS = Quick Inventory of Depressive Symptomatology.

bootstrapping (5,000 samples) to estimate confidence intervals for the indirect effects. Differences between ketamine SI responders and nonresponders were examined using comparative tests. Lastly, a logistic regression model was used to assess the occurrence of suicidal events at the 3-month follow-up. To account for multiple comparisons, a false discovery rate (FDR) correction was applied. All analyses were performed using R software, with a significance level set at $P < .05$.

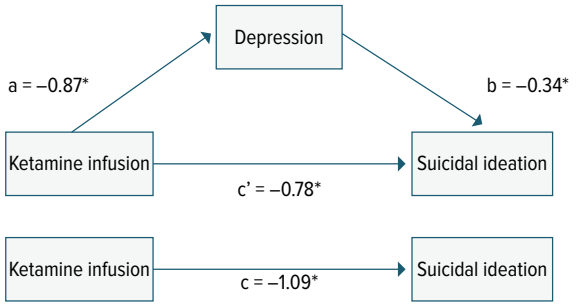
RESULTS

Description of Sample

The sample consisted of 100 patients, predominantly females (N=77, 77%), with a median age of 28 years (min–max: 18–86) and a moderate to severe major depressive episode (median MADRS score = 34 [min–max: 12–53]; QIDS score = 22 [min–max: 4–39]). According to C-SSRS, 90 (90%) patients had active SI in the past week (C-SSRS severity >1), and 72 (72%) had a past history of suicide attempt. Twenty-four patients received 2 ketamine infusions within 1 week based on clinical judgment. The characteristics of the sample are described in Table 1.

Figure 1.

Standardized Regression Coefficients for the Relationship Between Ketamine Infusion and Effect on Suicidal Ideation as Mediated by Depression Change (*$P < .05$).



Efficacy of Ketamine at 7 Days

At 7 days postinfusion, we observed a significant reduction in depressive symptoms and SI intensity as measured by MADRS score (β = −11; 95% CI, −13 to −8.2; $P < .001$) and C-SSRS severity subscore (β = −2.0; 95% CI, −2.4 to −1.6; $P < .001$) after controlling for age, sex, and number of infusions.

We found no significant association between the number of ketamine infusions and SI response.

Using a mediation model, we showed a direct effect of ketamine infusion on SI (β: −0.78; CI, −1.07 to −0.48), as well as an indirect effect via depressive symptoms reduction (β: −0.29; CI, −0.55 to −0.07), while adjusting for age and sex (Figure 1). The amount of 27.5% of the total effect of ketamine on SI was attributable to depressive symptoms reduction.

At 7 days postinfusion, 61% of patients were responders (C-SSRS severity subscore reduction ≥50% or a decrease in subscore from 5 at baseline to 3). Relative to nonresponders, responders were older (34 vs 24 years, FDR P value = .008) and rated a higher subjective efficacy of ketamine on SI (3.5 vs 3, FDR P value = .037) (Table 2). The type of mood disorder (bipolar vs unipolar) did not influence SI response.

Association Between SI Response at 7 days and Suicidal Events at 3 Months

At 3 months, we recorded 32 suicidal events (23 hospitalizations for SI and 9 suicide attempts) for 31 patients. During this period, 22 patients received additional ketamine infusions beyond the initial 1 or 2 administered at baseline. Among these 22 patients, 14 did not experience any suicidal events. To avoid potential bias related to the protective effects of these additional infusions, we excluded these 14 patients from the subsequent analyses. After excluding these

Table 2.
Characteristics of Responders vs Nonresponders

Characteristic	Nonresponders N = 39	Responders N = 61	*P* value	*P* value FDR
Sociodemographic				
Age (years)	24 (18–53)	34 (18–86)	**<.001**	**.008**
Females	34 (87%)	43 (70%)	.053	.3
Single	29 (74%)	37 (61%)	.2	.4
Professionally active	14 (36%)	21 (34%)	.9	.9
Current psychopathology				
Unipolar disorder	35 (90%)	49 (80%)	.2	.4
Bipolar disorder	4 (10%)	12 (20%)	.2	.4
Alcohol/substance use disorder	4 (10%)	8 (13%)	.8	.9
Anxiety disorder	16 (41%)	17 (28%)	.2	.4
Eating disorder	9 (23%)	7 (11%)	.12	.4
C-SSRS				
Severity of suicidal ideation	4.00 (1.00–5.00)	5.00 (1.00–5.00)	.10	.4
History of suicide attempt	26 (67%)	46 (75%)	.3	.5
Number of suicide attempt	1.0 (0.0–23.0)	1.0 (0.0–10.0)	.8	.9
Anxiodepressive symptomatology				
MADRS score	34 (19–53)	34 (12–52)	.8	.9
QIDS (missing data = 17%)	23 (13–36)	21 (4–39)	.3	.4
GAD-7 (missing data = 18%)	16 (3–21)	16 (1–21)	.4	.5
Subjective efficacy on SI (missing data = 7%)	3.0 (0.0–4.0)	3.5 (2.00–4.0)	**.005**	**.037**

Bold value stands for statistical significance ($P < .05$).
Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale, FDR = false discovery rate, GAD-7 = Generalized Anxiety Disorder-7, MADRS = Montgomery-Asberg Depression Rating Scale, QIDS = Quick Inventory of Depressive Symptomatology.

patients, the final analysis included 86 patients. In this subset, we found that SI response at 7 days was associated with a lower risk of suicidal event at 3 months (OR = 0.25, 95% CI, 0.09 to 0.69, $P = .009$).

DISCUSSION

This study is the first to demonstrate an association between IV ketamine administration and a reduction in suicidal events over a 3-month period. We found that a ≥50% reduction in SI at 1 week postinfusion was significantly associated with a lower incidence of suicidal events at 3 months. While numerous studies have demonstrated the short-term anti-SI effects of ketamine, its potential for preventing actual suicidal attempt or death had not been investigated until now. Current clinical trials evaluating ketamine for SI have primarily considered suicide attempts and hospitalizations as adverse events rather than treatment outcomes. In a systematic review by Siegel et al[22], which included studies investigating both intranasal esketamine and IV ketamine in patients with current SI, the proportion of patients experiencing suicide attempts—recorded as treatment-emergent adverse events—during the follow-up phase was 3% in treatment groups and 1.4% in control groups.

Our findings support the notion that IV ketamine could be integrated into the clinical management of acute suicidal crises, not only as a short-term intervention but also as a strategy to reduce the risk of SI but also suicidal attempt in the medium term. Importantly, the patients included in our study were at high risk for suicide, as evidenced by the severity of their SI assessed using the C-SSRS and the fact that that nearly three-quarters had a history of suicide attempts. Despite this elevated risk, the majority of patients responded to ketamine by day 7, showing a significant reduction in SI, which was associated with a decreased likelihood of suicidal events during the 3-month follow-up period. This is particularly clinically relevant, as it provides a critical window during which patients can engage in long-term therapeutic interventions, such as psychotherapy or structured psychiatric care.

We also confirmed that IV ketamine exerts both direct and indirect effects on SI reduction. The indirect effect occurs via the reduction of depressive symptoms, as reported in previous studies. A meta-analysis by Wilkinson et al[6] estimated that 10% to 46% of the variance in SI reduction could be explained by improvements in depressive symptoms, a finding replicated in later individual studies.[16,29,30] However, our results, along with previous findings, suggest that ketamine has a specific antisuicidal mechanism that extends beyond its antidepressant effects. Ketamine reduces psychological pain, which is strongly linked to SI and suicide attempts.[9–11] Ketamine also alleviates anhedonia, a key transdiagnostic symptom across psychiatric disorders, which may contribute to its rapid impact on SI.[12] Ketamine-induced dissociative and perceptual effects may play a role in disrupting maladaptive cognitive patterns associated with SI, though this mechanism remains under investigation.[31]

We observed that patients who responded to ketamine at 1 week (SI reduction ≥50% according to C-SSRS) were significantly older. However, baseline SI severity was not associated with SI response, in contrast to Ballard et al,[30] who found that nonresponders had more severe baseline SI. We found no significant association between bipolar disorder and SI response, which contradicts a recent large RCT showing that IV ketamine was particularly effective in this subgroup.[19] However, the number of bipolar patients in our sample was limited, preventing firm conclusions. Similarly, anxiety disorders were not associated with SI response in our study. Previous findings on this topic remain inconsistent, with some studies suggesting that anxious depression may predict better SI reduction to ketamine,[32] while others found no such association.[33] We observed no difference in past suicide attempts between responders and nonresponders. Literature on this topic is conflicting. Some studies suggest that past self-injury is negatively associated with ketamine response.[30] Others indicate that patients with previous suicide attempts may respond better to ketamine.[34] These discrepancies highlight the need for further research to identify clinical and biological predictors of SI reduction.

Interestingly, patients who perceived ketamine as effective immediately after infusion were more likely to be responders at 1 week. This raises important questions about the role of acute perceptual modifications, dissociation, and placebo effects in ketamine's antisuicidal action. Some hypothesize that dissociative experiences could contribute to its therapeutic effects, although the causal link remains unclear.[35] We found no significant association between the number of ketamine infusions and SI response. Previous studies have suggested that a cumulative anti-suicidal effect may emerge with repeated infusions. Phillips et al[11] found a progressive reduction in SI when patients received 3 infusions per week over 2 weeks, with effects maintained by weekly maintenance infusions. Accordingly, McIntyre et al[12] showed significant improvements in a protocol where patients received 4 infusions over 2 weeks. Zhan et al[16] reported that 50% of patients achieved remission after 1 infusion, increasing to 70% after 6 infusions, with patients exhibiting higher baseline SI requiring more infusions for remission. A 2024 network meta-analysis by Shen et al[17] supported the benefits of repeated infusions, yet a recent meta-analysis found no significant difference between single-dose and multidose strategies in both the acute phase and follow-up.[13]

The main strengths of our study are the record of suicidal event, the large sample size compared to many previous naturalistic studies, and the use of a comprehensive assessment of SI, as well as the naturalistic design, reflecting real-world clinical practice. Limitations include the retrospective nature of the study, limiting causal inferences, and the absence of control group, preventing direct comparison with alternative treatments. A limitation of our mediation analysis is the simultaneous measurement of depression and SI at T1, which limits the establishment of temporal precedence. Moreover, this design precludes control of other variables that might have differed between groups, such as other specific or nonspecific interventions in the context of suicidal crisis (hospitalizations, nature and frequency of psychiatric care over time, concurrent medication or psychotherapy treatments). These pitfalls warrant further investigation in controlled trial settings. Finally, suicidal events were assessed retrospectively from medical records, potentially leading to underreporting. Overall, our study provides novel evidence that ketamine has specific antisuicidal properties beyond its antidepressant effects. Moreover, early SI response to ketamine was associated with a reduced risk of suicidal events at 3 months, marking an important step forward in suicide prevention research. Future studies should aim to confirm these findings in controlled trials with long-term follow-up and to further investigate the biological and psychological mechanisms underlying ketamine's antisuicidal effects.

Given its rapid onset and potential medium-term protective effects, ketamine could represent a critical intervention in the management of acute suicidal crises, allowing clinicians to bridge the gap until longer-term treatments take effect.

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