Effects of Low-Dose Ketamine Infusion on the Positive and Negative Domains of Hopelessness and Suicidal Thoughts

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Abstract

Background: Low-dose ketamine infusion has been demonstrated to exert antisuicidal effects on patients with treatment-resistant depression (TRD) and strong suicidal ideation. Although evidence suggests an association between hopelessness and suicidality, very few studies have investigated the antihopelessness effects of ketamine.

Methods: This study included 84 patients with TRD and strong suicidal ideation. The diagnosis of depression was based on the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, diagnostic criteria for major depressive disorder. They were randomly assigned to receive a single infusion of either 0.5 mg/kg ketamine or 0.045 mg/kg midazolam. Hopelessness and suicidal symptoms were assessed at baseline, at 240 minutes postinfusion, and on Days 2, 3, 7, and 14 postinfusion. The assessments were performed using the self-report Beck Hopelessness Scale (BHS) and Positive and Negative Suicide Ideation Inventory (PANSI). The analysis focused on the positive and negative domains of the BHS and PANSI, respectively. The clinical trial was conducted between August 15, 2018, and November 30, 2021.

Results: Statistical analyses performed using a generalized linear model revealed that the ketamine group had significantly higher PANSI-positive ($P = .008$) and lower PANSI-negative ($P = .015$) suicidal ideation scores on Day 2 postinfusion than did the midazolam group. At 240 minutes postinfusion, the ketamine group had significantly lower BHS-negative domain scores than did the midazolam group ($P = .031$). Notably, the observed ketamine-induced reduction in hopelessness at 240 minutes postinfusion was associated with its antisuicidal effect on Day 2 postinfusion.

Discussion: A single infusion of low-dose ketamine resulted in a brief (~4 hours) yet significant reduction in hopelessness. Subjective antisuicidal effects of ketamine were noted on Day 2 postinfusion. Further studies are needed to elucidate the neuromechanisms underlying the antihopelessness and antisuicidal effects of ketamine.

Trial Registration: UMIN Clinical Trials Registry identifiers: UMIN000033916 and UMIN000033760

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Suicide is a major societal and public health concern, with considerable global implications.[1] The Global Burden of Disease study reported that the total years of life lost from suicide were as high as 30 million years in 2019.[1] The prevalence of suicide remains high in Taiwan, with approximately 16/100,000 suicides reported between 2012 and 2019.[2] Over this decade, the antidepressant and antisuicidal effects of low-dose ketamine have gained widespread recognition. Thus, in the current clinical psychiatric practice, ketamine is commonly prescribed to patients with treatment-resistant depression (TRD) and those with strong suicidal symptoms.[3–5]

In their 10-year follow-up study conducted among patients hospitalized for suicidal ideation, Beck et al[6] discovered that hopelessness, but not depressive mood, is a reliable predictor of subsequent suicidality, including suicidal thoughts and suicide. In a prospective study, 1,958 outpatients with various mental health problems (major affective disorders, 40%; anxiety disorders, 15%; both affective and anxiety disorders, 25%; and other psychiatric disorders [eg, substance use disorder], 20%) were monitored for an average period of 4 years; the study reported a significant association between hopelessness (measured using the Beck Hopelessness Scale [BHS]) and suicide.[7] A longitudinal network analysis involving 1,615 young individuals indicated that

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Clinical Points

- A low-dose ketamine infusion may exert a short-term (~4 hours) antihopelessness effect.
- The subjective antisuicidal effect of low-dose ketamine peaked on Day 2 postinfusion.
- A significant association was observed between ketamine's hope-inducing effect at 240 minutes postinfusion and its antisuicidal effect on Day 2 postinfusion.

hopelessness can predict and subjective happiness can protect against suicidal symptoms, including suicidal ideation and suicide attempts.[8] Ribeiro et al[9] reported that hopelessness significantly predicted various suicide outcomes during a 9-year follow-up period; the odds ratios for suicidal ideation, suicide attempt, and suicide were 2.19, 1.95, and 1.98, respectively. Qiu et al[10] followed 142 patients with depression over 10 years and demonstrated that hopelessness predicted suicide ideation but not attempts during the follow-up. Ropajl[11] suggested that hope protects against suicidal symptoms, including thoughts and actions.

In a study conducted by Grunebaum et al,[12] 230 minutes after low-dose ketamine infusion, substantial reductions were noted in individuals' scores on the "suicidal desire and ideation" subscale, but not the "planning" subscale, of the Scale for Suicidal Ideation. Surprisingly, patients with strong suicidal ideation exhibited a low response to ketamine infusion; the researchers attributed this result to hopelessness, a characteristic feature of suicidal states.[12] Furthermore, Witte et al[13] found a significant association between individuals' scores on the "suicidal desire and ideation" subscale and those on the BHS. DiazGranados et al[14] reported that individuals' scores on the hopelessness subscale of the Beck Depression Inventory significantly decreased 40, 80, 120, and 230 minutes after low-dose ketamine infusion. Domany et al[15] indicated that low-dose ketamine can alleviate hopelessness and the effects persist for up to 3 days. However, whether low-dose ketamine can enhance hopeful thoughts in patients with depression and suicidal ideation remains unknown.

As mentioned, low-dose ketamine has gained prominence for its rapid antisuicidal effects.[3–5] However, most studies have focused on negative aspects—suicidal symptoms, such as ideation of death and suicidal thoughts; few studies have explored positive ideation (PI) against suicide, such as considering life to be worth living and having confidence in the future.[16] Preclinical studies have revealed that ketamine can enhance resilience against stress and despair.[17,18] However, whether low-dose ketamine can induce a positive attitude toward life in patients with depression and suicidal ideation remains unknown.

In the present study, we reanalyzed data derived from our previous randomized, double-blind, midazolam-controlled trial involving low-dose ketamine infusion in patients with TRD and strong suicidal ideation.[5] Using the self-report Positive and Negative Suicide Ideation Inventory (PANSI) and BHS, we investigated the effects of low-dose ketamine infusion on the positive and negative domains of hopelessness and suicidal symptoms in these patients. We hypothesized that low-dose ketamine infusion would augment PI against suicide, induce hopeful thoughts, alleviate hopelessness, and reduce suicidal ideation.

METHODS

Participants and Study Procedure

The clinical trial was conducted between August 15, 2018, and November 30, 2021. Details of the study procedure have been reported in our previous paper.[5] Briefly speaking, 84 adult patients with TRD and strong suicidal thoughts were randomly assigned to 2 single infusion groups, namely, 0.5 mg/kg ketamine and 0.045 mg/kg midazolam. The diagnosis of depression was based on the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, diagnostic criteria for major depressive disorder. TRD was defined as major depressive disorder with at least 2 failures of antidepressant treatment with adequate doses and duration.[5] Strong suicidal thoughts were defined by scores of ≥4 at the Montgomery-Asberg Depression Rating Scale (MADRS) suicide item,[19] which complied with the definition of clinically significant suicidal ideation (MADRS suicide item score ≥4) in the study of Price et al.[20] This study accorded with the Declaration of Helsinki and was approved by the Institutional Review Boards of Taipei Veterans General Hospital and Cheng Hsin General Hospital. All participants gave their informed consent. Clinical trial registration information is as follows: UMIN Clinical Trials Registry (UMIN-CTR), registration numbers UMIN000033916 and UMIN000033760.

Assessment of Hopeless and Suicidal Thoughts

The self-reported suicidal and hopeless symptoms were examined at baseline, at 240 minutes postinfusion, and sequentially on Days 2, 3, 7, and 14 postinfusion using the self-reported PANSI and BHS.[16,21] The PANSI combines with risk (negative suicide ideation [NSI]; ie, felt lonely or sad that you wanted to kill yourself so that you could end your pain) and protective (PI; ie, felt excited because you were doing well at school or at work) factors to evaluate individual suicidal ideation.[16,22,23] The BHS is a 20 true-false-item self-report inventory to assess the positive (ie, hope and enthusiasm; future will be happier) and negative (ie, future vague and uncertain; no use in trying) domains

of hopelessness.[21,24] Both the 9-item positive-expectation subscale ($\alpha = .76$) and the 11-item negative-expectation subscale ($\alpha = .80$) had strong internal consistency.[24] The classic total score of the BHS was analyzed as a single score, with positive items inverted and added to the negative items to calculate the total score.[21]

Statistical Analysis

The study used 1-way analysis of variance and Fisher χ^2 tests for continuous and nominal variables, respectively, to evaluate the differences in demographic and clinical data between the 2 infusion groups (0.5 mg/kg ketamine or 0.045 mg/kg midazolam). In order to directly compare the differences in the positive and negative domains of the PANSI and BHS, the subtotal scores of the PANSI-PI and PANSI-NSI and the BHS-Positive Domain (BHS-P) and BHS-Negative Domain (BHS-N) were Z-transformed. In addition, the Δ was defined by the Z-transformed positive domain scores minus the Z-transformed negative domain scores. The generalized estimating equation (GEE) models with the autoregressive method and with the adjustment corresponding baseline scores were used to examine the changes in Z-transformed PANSI-PI, PANSI-NSI, BHS total, BHS-P, BHS-N, ΔPANSI, and ΔBHS scores over time during the study period. The infusion group (0.5 mg/kg ketamine vs 0.045 mg/kg midazolam) was used as a between-patient factor, and time (baseline, 240 minutes postinfusion, and follow-up) was used as a within-patient factor. Furthermore, generalized linear models (GLMs) with adjustment of baseline scores were used to assess the differences in Z-transformed PANSI-PI, PANSI-NSI, BHS total, BHS-P, BHS-N, ΔPANSI, and ΔBHS scores at each time point from 240 minutes to Day 14 postinfusion. Finally, we investigated the associations between hopelessness symptoms at baseline or at 240 minutes postinfusion and suicidal symptoms at Day 2 postinfusion using the GLMs with adjustment of baseline suicidal scores, which allowed us to elucidate which clinical factors may predict the most antisuicidal effect of a low-dose ketamine infusion. Two-tailed $P < .05$ was considered statistically significant. All data processing and statistical analyses were performed using SPSS, version 17 (SPSS Inc).

Data Availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to the ethical regulation in Taiwan.

RESULTS

Table 1 shows no differences in the age, sex, age at depression onset, and baseline self-reported PANSI and BHS scores between groups (all $P > .05$). The BHS-N scores were significantly lower ($P = .045$) at 240 minutes postinfusion in the ketamine group than in the midazolam group, while the PANSI-PI scores were significantly higher ($P = .028$) at Day 2 postinfusion in the ketamine group than in the midazolam group (Table 1).

The GEE model revealed that the ketamine group had a significantly higher ΔPANSI trajectory than the midazolam group (group effect: $P = .030$) (Figure 1). However, we found no between-group effect ($P = .258$) in the trajectory of ΔBHS (Figure 2). Furthermore, the GLMs showed that significantly higher PANSI-PI ($P = .008$) and lower PANSI-NSI ($P = .015$) scores were noted at Day 2 postinfusion in the ketamine group than in the midazolam group (Figure 1). The significantly greater ΔPANSI was particularly noted at Day 2 and Day 7 postinfusion between groups (Figure 1). Figure 2 shows significantly lower total BHS ($P = .040$) and BHS-N ($P = .031$) scores at 240 minutes postinfusion in the ketamine group than in the midazolam group using the GLM analysis. The greater ΔBHS was only noted at 240 minutes postinfusion between groups ($P = .043$).

Finally, using the GLM with an adjustment of the corresponding baseline PANSI scores, we found associations between BHS-P scores ($\beta = 0.432$, $P = .019$) and BHS-N scores ($\beta = -0.438$, $P = .006$) at 240 minutes postinfusion, but not at baseline, and PANSI-PI scores at Day 2 postinfusion. In addition, BHS-P scores ($\beta = -0.766$, $P = .029$) and BHS-N scores ($\beta = 0.898$, $P = .005$) at 240 minutes postinfusion were associated with PANSI-NSI scores at Day 2 postinfusion.

DISCUSSION

Our findings revealed a brief yet noteworthy reduction in hopelessness following a single infusion of low-dose ketamine. Its antisuicidal effects, characterized by an enhancement in PI and a reduction in suicidal ideation, were most pronounced on Day 2 postinfusion and persisted for up to 7 days. We observed that ketamine's hope-inducing effect manifests earlier but disappears sooner than its antisuicidal effect. Furthermore, a significant association was observed between ketamine's hope-inducing effect at 240 minutes postinfusion and its antisuicidal effect on Day 2 postinfusion.

We found that the observed rapid reduction in hopelessness following a single infusion of low-dose ketamine was associated with its hopelessness-reducing effect, rather than its hope-inducing effect. These findings align with those of DiazGranados et al and Domany et al[14,15] However, unlike the study of Domany et al,[15] where the hope-inducing effect of ketamine

Table 1.

Demographic Characteristics and Clinical Symptoms Between Groups

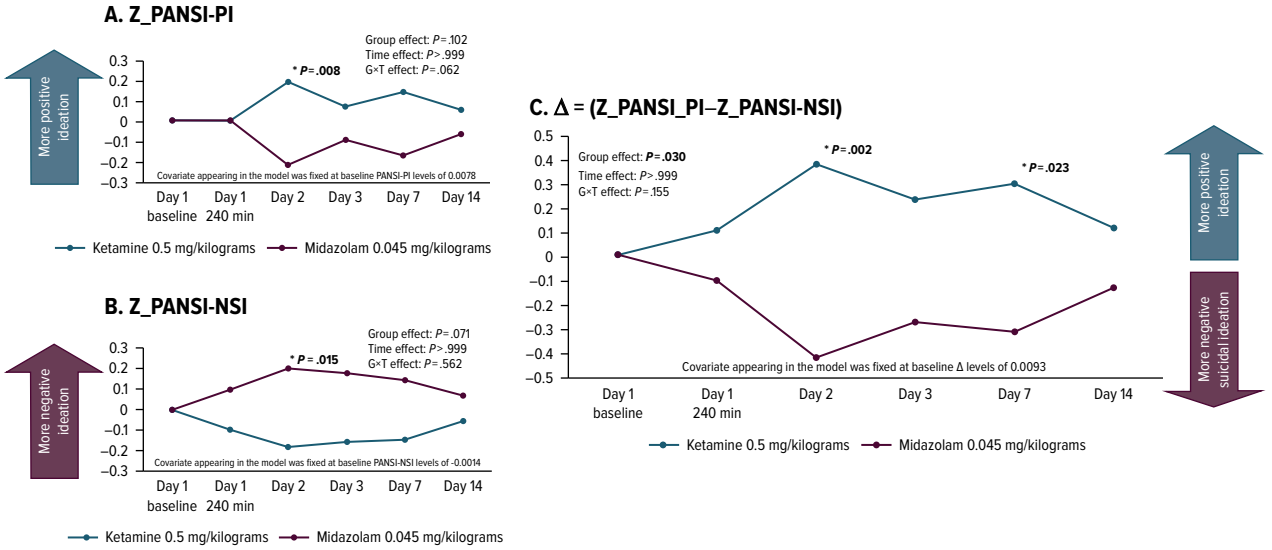
	Patients with TRD and strong SI		
	Ketamine group (n = 42)	Midazolam group (n = 42)	*P* value
Age, y (SD)	34.26 (13.34)	36.88 (12.21)	.351
Female, n (%)	28 (66.7)	31 (73.8)	.634
Age at illness onset, y (SD)	24.07 (9.71)	24.43 (9.31)	.864
History of attempted suicide, n (%)	36 (85.7)	38 (90.5)	.738
BHS-P, scores/Z-scores (SD)			
Baseline	2.62 (2.07)/−0.02 (0.91)	2.69 (2.50)/0.02 (1.09)	.887
Day 1 240 min	3.62 (2.48)/0.09 (0.96)	3.14 (2.69)/−0.09 (1.04)	.402
Day 2	3.58 (2.84)/0.05 (1.03)	3.29 (2.73)/−0.05 (0.98)	.625
Day 3	3.68 (2.93)/0.04 (1.00)	3.45 (2.96)/−0.04 (1.01)	.722
Day 7	3.64 (2.68)/0.04 (0.96)	3.43 (2.93)/−0.04 (1.05)	.726
Day 14	3.93 (2.97)/0.10 (1.04)	3.33 (2.71)/−0.11 (0.95)	.341
BHS-N, scores/Z-scores (SD)			
Baseline	8.57 (2.33)/−0.07 (0.98)	8.88 (2.43)/0.07 (1.03)	.553
Day 1 240 min	7.26 (3.02)/−0.22 (1.11)	8.52 (2.43)/0.22 (0.84)	.045
Day 2	7.76 (3.29)/−0.12 (1.08)	8.48 (2.79)/0.12 (0.91)	.284
Day 3	7.24 (3.18)/−0.11 (0.98)	7.98 (3.34)/0.11 (1.02)	.310
Day 7	7.21 (3.31)/−0.11 (1.01)	7.93 (3.78)/0.11 (1.00)	.332
Day 14	7.45 (3.09)/−0.07 (0.95)	7.90 (3.44)/0.07 (1.06)	.536
PANSI-PI, scores/Z-scores (SD)			
Baseline	12.21 (4.87)/0.07 (1.03)	11.88 (4.53)/−0.07 (0.98)	.746
Day 1 240 min	13.50 (4.15)/0.07 (0.87)	13.33 (4.83)/−0.07 (1.12)	.866
Day 2	14.59 (4.58)/0.18 (0.90)	12.29 (4.80)/−0.18 (1.07)	.028
Day 3	13.66 (4.83)/0.15 (0.91)	12.50 (5.23)/−0.15 (1.08)	.298
Day 7	13.45 (4.90)/0.15 (0.91)	11.75 (5.33)/−0.12 (1.08)	.136
Day 14	12.81 (4.63)/0.03 (0.91)	12.05 (5.58)/−0.03 (1.09)	.504
PANSI-NSI, scores/Z-scores (SD)			
Baseline	30.45 (7.06)/0.04 (1.04)	29.55 (6.71)/−0.04 (0.97)	.594
Day 1 240 min	25.02 (9.50)/−0.02 (1.08)	26.24 (7.35)/0.02 (0.93)	.514
Day 2	23.00 (9.78)/−0.24 (1.00)	26.21 (8.21)/0.24 (0.95)	.108
Day 3	22.56 (10.43)/−0.11 (1.04)	25.50 (8.78)/0.12 (0.96)	.168
Day 7	22.95 (10.04)/−0.17 (1.03)	25.23 (8.35)/0.16 (0.95)	.207
Day 14	23.50 (10.44)/−0.08 (1.09)	24.03 (8.65)/0.07 (0.91)	.805

Abbreviations: BHS-P = Beck Hopelessness Scale-Positive Domain, BHS-N = Beck Hopelessness Scale-Negative Domain, PANSI = Positive and Negative Suicide Ideation Inventory, PI = positive ideation, NSI = negative suicide ideation, SI = suicidal ideation, TRD = treatment-resistant depression.

persisted for 3 days, our study revealed that this effect lasted for approximately 4 hours. In a longitudinal qualitative study, patients in a ketamine clinical trial were interviewed about their experiences; some patients reported experiencing hopelessness after the gradual diminishment of ketamine's effects.[25] In addition, using a single item (discouraged about future) of hopelessness from the Beck Depression Inventory, Ballard et al[26] discovered no association between hopelessness and suicidal ideation in the postketamine follow-up. In a preclinical study involving the chronic mild stress model (mice) of depression, low-dose ketamine infusion normalized anticipatory reward deficits in the mice.[27] The rapidly manifesting and subsequently disappearing pattern of ketamine's hope-inducing effect is consistent with the findings of our previous positron emission tomography studies,[28,29] which revealed an increase in glucose metabolism in individuals' prefrontal cortex and an associated reduction in their depressive symptoms; however, these effects were observed only at 40 minutes postinfusion but not on Day 2 postinfusion. The rapid activation of the prefrontal cortex may serve as a catalyst for the antidepressant effects of ketamine.[28,29] A growing body of evidence supports the prefrontal cortex's crucial role in the neuromechanisms, which are involved in complex cognitive and motivational processes, of an optimistic brain.[30,31] Wu et al[30] highlighted the importance of the dorsolateral prefrontal cortex and dorsomedial prefrontal cortex in maintaining individuals' spontaneous, optimistic self-evaluative tendencies. In addition to the prefrontal cortex, the anterior cingulate cortex has been implicated in the optimistic processing of the brain.[32] In our positron emission tomography study, rapid and sustained activation of the anterior cingulate cortex was observed 40 minutes and 2 days, respectively, after low-dose

Figure 1.

GEE Models With Adjustment of Age, Sex, and Corresponding Baseline Scores for the Trajectory of (A) Z_PANSI-PI Scores, (B) Z_PANSI-NSI Scores, and (C) Δ (Z_PANSI-PI Scores – Z_PANSI-NSI Scores)



Abbreviations: GEE = generalized estimating equation, NSI = negative suicide ideation, PANSI = Positive and Negative Suicide Ideation Inventory, PI = positive ideation, Z = Z-transformed scores.

ketamine infusion.[28] Morris et al[32] suggested that ketamine normalizes the activity of the subgenual anterior cingulate cortex, thereby mitigating anticipatory reward deficits in patients with TRD

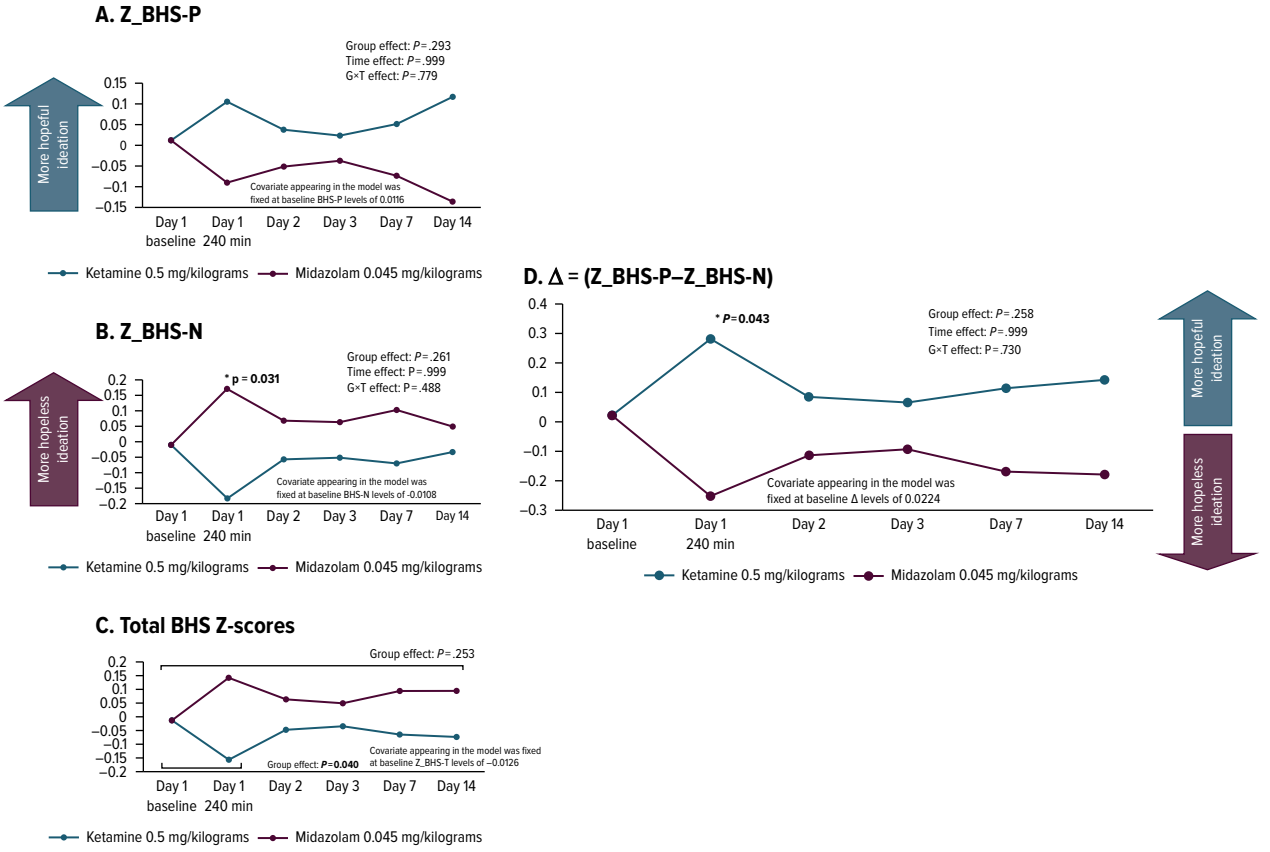
Animal studies have reported that ketamine may enhance resilience against stress and despair.[17,18] McGhee et al[33,34] revealed that perioperative ketamine, but not midazolam, reduced the incidence of posttraumatic stress disorder in Operation Iraqi Freedom/Operation Enduring Freedom soldiers who sustained burns. However, a recent meta-analysis involving 503 combatants failed to corroborate the findings of McGhee et al; the meta-analysis revealed no significant difference in the incidence of posttraumatic stress disorder between ketamine-treated troops and untreated troops.[35] In their clinical trial, Abbar et al[36] subjected patients with suicidal ideation to 40-minute intravenous infusion of ketamine (0.5 mg/kg) or placebo (saline) at 2 time points: baseline and 24 hours; on Day 3 postinfusion, the proportion of patients achieving complete remission was higher in the ketamine group than in the placebo group (63% and 31.6%, respectively; $P < .001$). The researchers indicated that the antisuicidal effects of ketamine can be explained by its analgesic effects on mental pain.[36] These findings are consistent with our findings revealing that low-dose ketamine reduced suicidal ideation and increased PI against suicide in the study cohort.

In this study, a sequential pattern was found after ketamine infusion: a reduction in hopelessness was associated with an increase in PI against suicide and a decrease in suicidal ideation. This finding suggests that ketamine-treated patients with TRD and strong suicidal ideation initially experience a reduction in hopelessness and then develop positive thoughts against suicide and have reduced suicidal thoughts. Hopelessness can predict suicidal ideation in youths with depression, independent of changes in depression severity; thus, hopelessness is a precursor of suicidality.[37] The concept of hopelessness and the emergence of suicidal thoughts may partially explain the aforementioned sequential pattern. However, further neuroimaging studies are required to elucidate the neuromechanisms underlying the hope-inducing and antisuicidal effects of low-dose ketamine infusion.

This study has some limitations. First, our patients did not discontinue their ongoing medications during the study period. The decision to adopt an add-on study design was driven by ethical considerations for patients with severe depression, with an aim to offer realistic insights. Second, hopelessness, PI against suicide, and suicidal ideation were assessed using self-report questionnaires, not clinician-rated scales such as Hope Index Scale.[38] Self-report questionnaires may provide subjective insights, enabling clinicians to understand the authentic feelings of their patients. Future clinical trials

Figure 2.

GEE Models With Adjustment of Age, Sex, and Corresponding Baseline Scores for the Trajectory of (A) Z_BHS-P Scores, (B) Z_BHS-N Scores, (C) Total BHS Z-Scores, and (D) Δ (Z_BHS-P Scores – Z_BHS-N Scores)



Abbreviations: BHS-N = Beck Hopelessness Scale-Negative Domain, BHS-P = Beck Hopelessness Scale-Positive Domain, GEE = generalized estimating equation, Z = Z-transformed scores.

should use objective hopelessness rating scales to validate our findings. Third, our study was a post hoc analysis of the data from our clinical trial targeting the antidepressant and antisuicidal effects of low-dose ketamine among patients with TRD and strong suicidal ideation.[5] The primary outcomes of our clinical trial were measured by clinician-rated depression and suicide scales, including MADRS and the Columbia-Suicide Severity Rating Scale, but not by the reported measures (BHS and PANSI) in the present study. It may limit us to identify clear group differences. Furthermore, the multiplication of group comparisons may increase the risk of false-positive findings.

In conclusion, low-dose ketamine infusion can rapidly alleviate hopelessness in patients with TRD and strong suicidal ideation. The sequential effects of ketamine treatment include the augmentation of PI against suicide and the reduction of suicidal ideation in these patients. Further studies are needed to elucidate the neuromechanisms underlying the antihopelessness and antisuicidal effects of ketamine.

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