

Original Research

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Efficacy of low-dose ketamine infusion in anxious vs nonanxious depression: revisiting the Adjunctive Ketamine Study of Taiwanese Patients with Treatment-Resistant Depression

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Abstract

Background. The antidepressant effect of low-dose ketamine infusion on Taiwanese patients with anxious vs nonanxious treatment-resistant depression (ANX-TRD vs NANX-TRD) has remained unknown.

Methods. In total, 71 patients with TRD were randomized to three groups. Each group had participants who received saline infusions mixed with 0 (a normal saline infusion), 0.2, and 0.5 mg/kg of ketamine. Participants were followed up for 2 weeks. Anxious depression was defined as major depressive disorder with a total score of 7 or more on the 17-item Hamilton Depression Rating Scale Anxiety-Somatization factor. Generalized estimating equation models were used to investigate the effects of treatment (ketamine vs placebo) and depression type (ANX-TRD vs NANX-TRD) in the reduction of depressive symptoms during the follow-up period.

Results. Patients with ANX-TRD were less likely to respond to a single low-dose ketamine infusion than those with NANX-TRD. Among patients with NANX-TRD, low-dose ketamine infusion was significantly superior to placebo for reducing depressive symptoms. However, among patients with ANX-TRD, ketamine was not superior to placebo; nonetheless, approximately 30% of the patients responded to ketamine infusion compared to 13% who responded to the placebo.

Conclusions. Low-dose ketamine infusion was effective for Taiwanese patients with NANX-TRD but not so effective for those with ANX-TRD. A higher level of anxiety severity accompanying depression was related to greater depression severity. This may confound and reduce the antidepressant effect of ketamine infusion.

Introduction

Patients with major depressive disorder commonly suffer from anxiety, nervousness, and various somatic symptoms, such as autonomic and gastrointestinal symptoms, related to these conditions.¹ The higher level of anxiety accompanying major depressive disorder has been associated with greater severity of depression, greater illness chronicity, poorer cognitive function, lower quality of life and well-being, and suicidality.^{1–3} The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial reported that patients with anxious depression were significantly more likely to be older, unemployed, less educated, more severely depressed, and have suicidal ideations.³

Increasing evidence has suggested the adverse effect of anxiety comorbidity and greater levels of anxiety in the treatment response to antidepressant medications.^{1,4–6} Fava et al¹ defined anxious depression as a score ≥ 7 on the anxiety/somatization factor of the 17-item Hamilton Depression Rating Scale (HAMD). They demonstrated that patients with anxious depression were less likely to respond to antidepressant drugs than those with nonanxious depression. The international study to predict optimized treatment in depression demonstrated that situational anxiety and somatic anxiety predicted poorer treatment outcomes from the administration of escitalopram, sertraline, or venlafaxine.^{4,5}

In this decade, low-dose ketamine infusion has been proved to exhibit a rapid antidepressant effect for treatment-resistant depression (TRD).^{7,8} However, only a few studies have assessed the potential effect of baseline anxiety and anxious depression in the treatment response to low-dose

ketamine infusion among patients with TRD.^{9–11} In a multisite, double-blind, placebo-controlled trial of 99 patients with TRD who were randomized to either a low-dose ketamine or midazolam placebo infusion, Salloum et al⁹ demonstrated that treatment response to ketamine infusion did not differ between patients with anxious and nonanxious TRD (ANX-TRD and NANX-TRD, respectively). In an open-label study of 26 patients with TRD receiving a single infusion of ketamine, Ionescu et al¹⁰ discovered that patients with ANX-TRD responded better to ketamine than those with NANX-TRD. However, small sample size, open-label study design, and enrollment of only Caucasian patients were major limitations of the aforementioned studies. The potential role of anxious depression in the treatment response to ketamine infusion has remained unknown for Asian patients with TRD.

In this study, we reanalyzed data from our adjunctive ketamine study on Taiwanese patients with TRD.⁸ We focused on the antidepressant effect of low-dose ketamine infusion for patients with ANX-TRD and NANX-TRD. Because anxiety has been demonstrated to be a significant predictor of poor treatment response in TRD when traditional antidepressants are used, we hypothesized that patients with ANX-TRD were less likely to respond to low-dose ketamine infusion than those with NANX-TRD.

Methods

Inclusion criteria and study procedure

The detailed study design, patient enrollment and clinical results of our study have been published.^{8,12} Seventy-one patients aged between 21 and 64 years with TRD were randomized to three groups. Each group respectively received a single 40-minute intravenous saline infusion mixed combined with either 0 (a normal saline infusion), 0.2, and or 0.5 mg/kg of ketamine. Patients with TRD who had major medical or neurological diseases or a history of alcohol or substance use disorders were excluded in current study. Patients were assessed using the HAMD prior to initiation of infusions and at 40, 80, 120, and 240 minutes postinfusion and sequentially on days 2, 3, 4, 5, 6, 7, and 14 after ketamine or placebo infusion.^{13,14} This study was performed in accordance with the Declaration of Helsinki and was approved by the Taipei Veterans General Hospital Institutional Review Board. Informed consent was provided by all the participants. Clinical trials registration: UMIN Clinical Trials Registry (UMIN-CTR): Registration number: UMIN000016985.

Anxious depression definition

Anxious TRD (ANX-TRD) was defined as major depressive disorder with a total score of 7 or more on the HAMD Anxiety-Somatization factor (HAMD-AS). Six items from the original 17-item HAMD makes up HAMD-AS: psychic anxiety, somatic anxiety, somatic symptoms-gastrointestinal, somatic symptoms-general, hypochondriasis, and insight.¹⁵ HAMD-AS subscale has been used in STAR*D and was proven reliable in assessing anxious depression.¹

Statistical analysis

Continuous and nominal variables were analyzed through one-way analysis of variance and Fisher's chi-square tests, respectively, to assess the differences in the demographic and clinical data between the two groups (ANX-TRD vs NANX-TRD). Three generalized estimating equation (GEE) models were performed to investigate the roles of treatment group and depression type in treatment

outcome. First, GEE model with the autoregressive method for correlations of repeated measures for the same individual over time was used to examine the effects of ketamine on reduction of depressive symptoms during the treatment period with the group (0.5 or 0.2 mg/kg ketamine or placebo) and depression type (ANX-TRD vs NANX-TRD) as a between-patient factor and time (baseline, 40 and 240 minutes, days 2-7, and day 14) as a within-patient factor as well as all possible interactions. Second, stratified by depression type, GEE models with the autoregressive method for correlations of repeated measures for the same individual over time was used to examine the effects of ketamine on depression symptoms during the treatment period with the group as a between-patient factor, time as a within-patient factor, and baseline depression score as a between-patient predictor as well as all possible interactions. Furthermore, stratified by treatment group, GEE models with the autoregressive method for correlations of repeated measures for the same individual over time was used to examine the effects of ketamine on depression symptoms during the treatment period with the depression type as a between-patient factor, time as a within-patient factor, and baseline depression score as a between-patient predictor as well as all possible interactions. Two-tailed $P < .05$ was considered statistically significant. All data processing and statistical analyses were performed using SPSS, version 17 (SPSS Inc.).

Results

In all, 42 patients with ANX-TRD and 29 with NANX-TRD were enrolled in our study and were randomized to three treatment groups (Table 1). Patients with ANX-TRD had the

Table 1. Demographic and Clinical Data Among Patients with TRD.

	ANX-TRD (n = 42)	NANX-TRD (n = 29)	P-value
Age (years, SD)	51.24 (8.37)	41.79 (11.11)	<.001
Sex (female, n, %)	32 (76.2)	21 (72.4)	.785
Education (years, SD)	11.48 (3.45)	13.48 (3.20)	.016
Duration of illness (years, SD)	12.37 (8.77)	9.66 (7.18)	.173
Number of previous antidepressant trials (n, %)			.561
2	13 (31.0)	11 (37.9)	
3–4	17 (40.5)	13 (44.8)	
5–6	10 (23.8)	5 (17.2)	
≥7	2 (4.8)	0 (0.0)	
Concomitant use of benzodiazepine (n, %)	37 (88.1)	26 (89.7)	>.999
Clinical severity at baseline (SD)			
HAMD	25.26 (3.87)	20.03 (3.58)	<.001
HAMD-AS	8.31 (1.35)	4.97 (0.94)	<.001
Treatment group (n, %)			.824
0.5 mg/kg ketamine	13 (31.0)	11 (37.9)	
0.2 mg/kg ketamine	14 (33.3)	9 (31.0)	
Placebo	15 (35.7)	9 (31.0)	

Abbreviations: ANX, anxious; HAMD, Hamilton Depression Scale; HAMD-AS, Hamilton Depression Rating Scale Anxiety-Somatization factor; NANX, nonanxious; SD, standard deviation; TRD, treatment-resistant depression.

older age ($P < .001$), lower education ($P = .016$), and higher baseline scores of HAMD ($P < .001$) and HAMD-AS ($P < .001$) compared with those with NANX-TRD (Table 1).

Table 2 showed that only treatment group ($P = .003$), but not depression type ($P = .393$), predicted the reduction of depression symptoms during the follow-up period (Table 2). Stratified by depression type, GEE model found that among patients with NANX-TRD, both 0.5 and 0.2 mg/kg ketamine infusion significantly reduced the depressive symptoms during the follow-up period compared with placebo infusion (group effect: $P < .001$) (Figure 1). But, the depression reduction did not differ between

three groups among patients with ANX-TRD (group effect: $P = .436$) (Figure 1). Furthermore, stratified by treatment group, patients with NANX-TRD were more likely to have the greater reduction in depressive symptoms after a single 0.5 mg/kg ketamine infusion than those with ANX-TRD (group effect: $P < .001$) (Figure 2). However, the depression reduction did not differ between patients with ANX-TRD and with NANX-TRD after 0.2 mg/kg ketamine (group effect: $P = .688$) or placebo (group effect: $P = .098$) infusion (Figure 2). Supplementary Information, Table S1 showed the role of depression type in the treatment response, which was defined by response ($\geq 50\%$ reduction of mood ratings) at any two daily HAMD measures during the period of 24 to 96 hours (days 2–5),⁸ to ketamine infusion (Table S1).

Table 2. Effect of Anxious Depression Status and Treatment Group on Trajectory of Depressive Symptoms.

	Depression (HAMD score) reduction	
	df	P-value
Group	2	.003
Depression type (ANX-TRD vs NANX-TRD)	1	.393
Time	8	<.001
Group × depression type	2	.096
Group × time	16	.032

Abbreviations: ANX, anxious; df, degree of freedom; HAMD, Hamilton Depression Scale; NANX: nonanxious; TRD, treatment-resistant depression.

Discussion

Our findings support the hypothesis that patients with ANX-TRD are less likely to respond to a single low-dose ketamine infusion than those with NANX-TRD. Among patients with NANX-TRD, low-dose ketamine infusion was significantly superior to placebo in the reduction of depressive symptoms. However, among patients with ANX-TRD, ketamine infusion was not superior to placebo; nonetheless, approximately 30% of patients still responded to ketamine infusion, a higher proportion than the 13% who responded to placebo. This finding is supported by a vast literature describing the difficulty of treating this population.

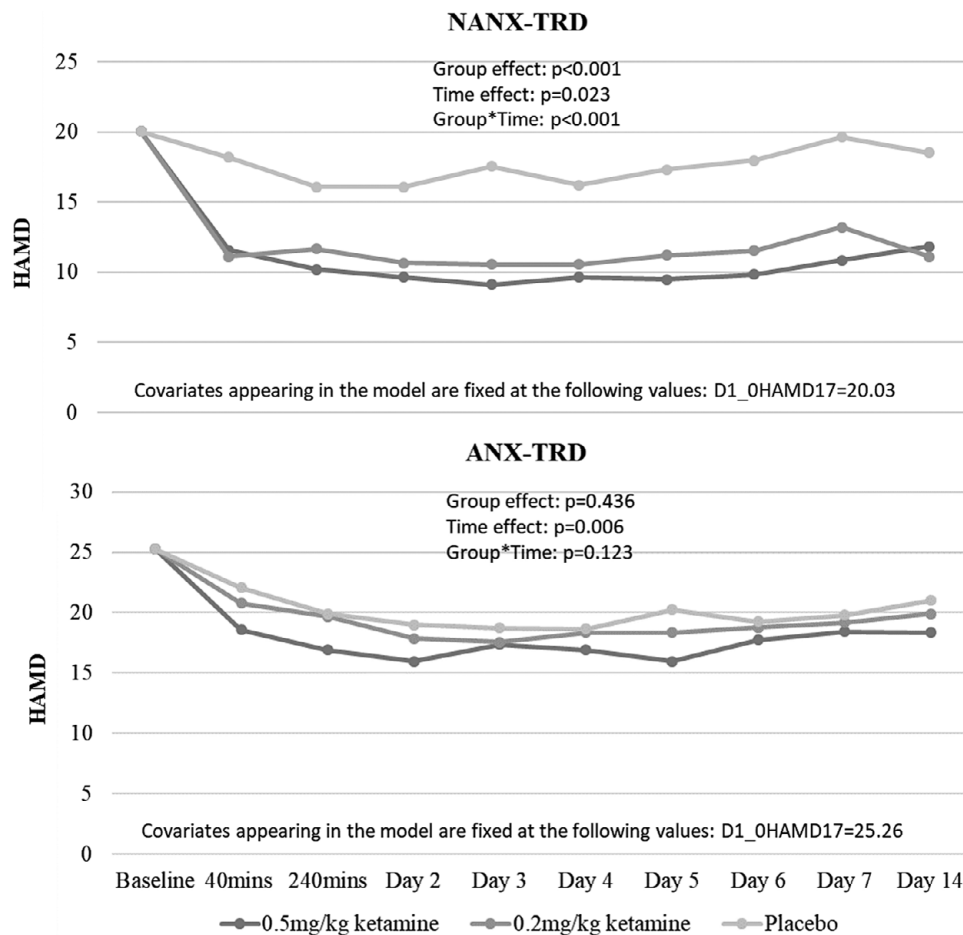


Figure 1. Clinical trajectory of patients with TRD after ketamine/placebo infusion, stratified by depression type. ANX, anxious; HAMD, Hamilton Depression Scale; NANX, nonanxious; TRD, treatment-resistant depression.

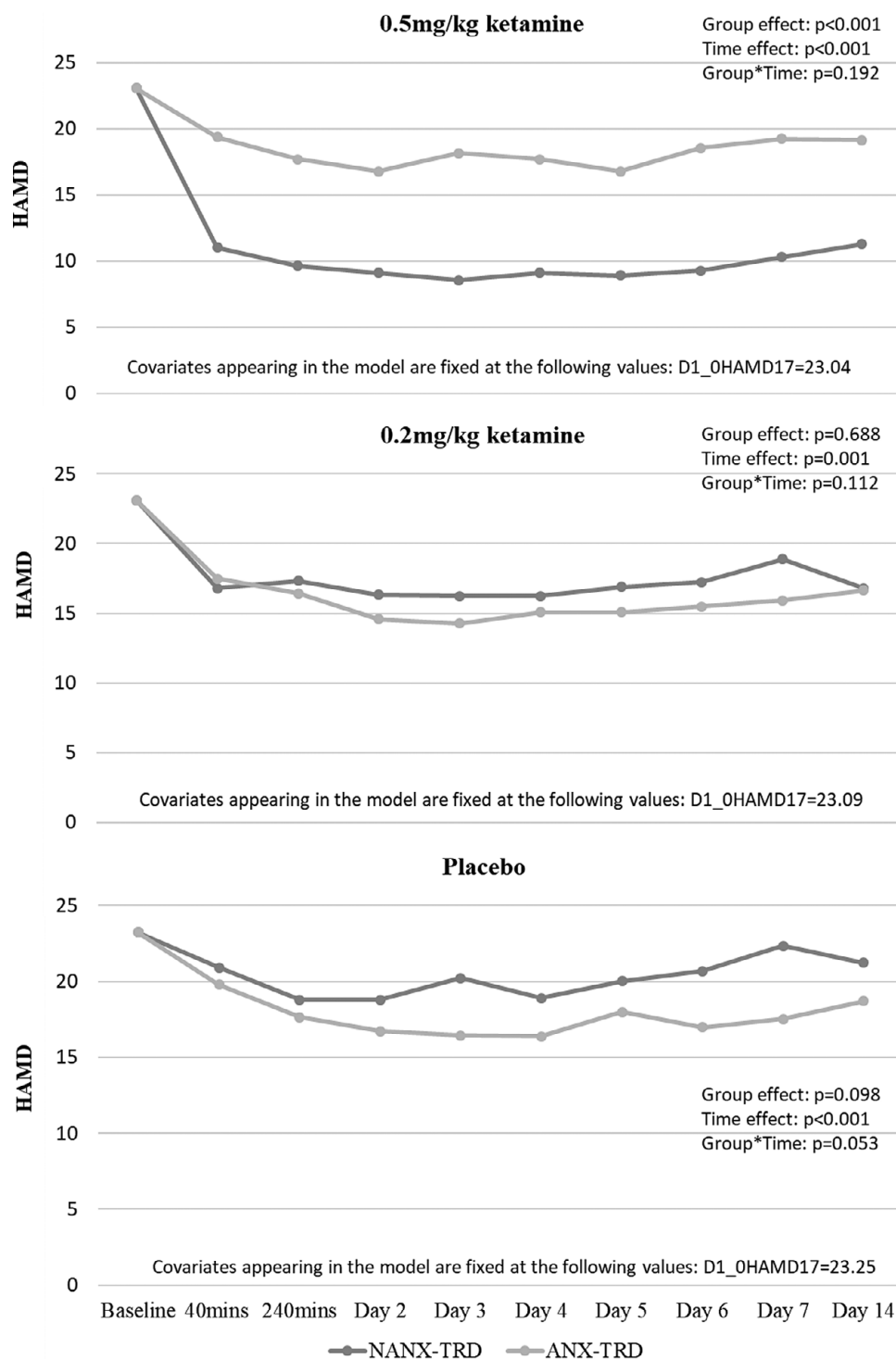


Figure 2. Clinical trajectory of patients with TRD (ANX vs NANX) after ketamine/placebo infusion, stratified by treatment group. ANX, anxious; HAMD, Hamilton Depression Scale; NANX, nonanxious; TRD, treatment-resistant depression.

As mentioned, anxious depression is related to a higher level of depression severity, longer duration of illness, greater functional impairment, and poorer response to antidepressant medications.¹⁻³ STAR*D demonstrated that baseline clinical characteristics can be used to identify subgroups that exhibit responses ranging from a low likelihood of response (18%) to citalopram (comorbid generalized anxiety disorder, <16 years of education) to a high likelihood (68%) of response (no comorbid posttraumatic stress disorder;

PTSD).¹⁶ Fava et al¹ discovered that patients with anxious depression fared significantly worse in both switching (to bupropion, sertraline, or venlafaxine) and augmentation (with bupropion or buspirone) options. In addition to pharmacological treatment, anxious depression may also be associated with a poorer response to repetitive transcranial magnetic stimulation (rTMS).¹⁷ Clarke et al reported that only approximately 40% of patients with ANX-TRD responded to rTMS, which was much lower than the average

response rate (up to 60%) of rTMS treatment.^{17,18} It is noteworthy that previous studies have demonstrated that low-dose ketamine may be equally effective for Caucasian patients with ANX-TRD and NANX-TRD. This result is discordant with our findings that Taiwanese patients with ANX-TRD are less likely to respond to ketamine infusion than those with NANX-TRD. Furthermore, the exact mechanism that causes the differential response to ketamine vs other conventional antidepressants in anxious depression has remained unclear.⁹

The therapeutic efficacy of low-dose ketamine infusion in anxiety disorders and anxious distress accompanying depression has remained unclear.^{19,20} Glue *et al*¹⁹ discovered preliminary positive results of ketamine infusion in refractory generalized anxiety disorder and/or social anxiety disorder with a dose–response pattern for anxiolytic effects. Feder *et al*²¹ reported that compared with midazolam, ketamine infusion—when assessed 24 hours after infusion—was associated with significant and rapid reduction in PTSD comorbid depressive symptoms. However, Taylor *et al*²⁰ compared the effects of ketamine and placebo infusions among patients with social anxiety disorder and found that self-reported anxiety on a visual analog scale did not differ between the ketamine and placebo groups. Whether anxiety distress and severe anxiety symptoms may reduce the antidepressant effect of ketamine warrants further investigation. In addition, our previous study observed lower serum levels of ketamine and norketamine among Taiwanese patients with TRD. This may compromise the antidepressant efficacy among patients having higher levels of depression severity (ie, ANX-TRD).⁸ Taking the findings from our and other previous studies together, we hypothesize that a higher dose, such as 1.0 mg/kg, of ketamine infusion may be necessary for Taiwanese patients with ANX-TRD, and the standard dose (0.5 mg/kg) or a lower dose (0.2 mg/kg) may be beneficial for those with NANX-TRD.

Our study has several limitations: first, it was an add-on ketamine study because the medications used by patients with TRD were not discontinued during ketamine treatment. Thus, the observed antidepressant effects of ketamine could have resulted from a combination of ketamine and a patient's simultaneously consumed medication. However, patient medications were not changed during the ketamine treatment. Therefore, our findings can be justifiably explained as stemming from the add-on effects of low-dose ketamine infusion; an add-on study design is ethically appropriate in patients with severe depression and may provide more naturalistic data. Second, the sample size was still small; however, our study is—as far as we know—the largest randomized, placebo-controlled trial to date insofar as it involved 42 patients with ANX-TRD and 29 with NANX-TRD. In addition, the identification of lower serum levels of ketamine and norketamine in Taiwanese patients with TRD is another important clinical issue. Further study with a larger sample size and a higher dose of ketamine (0.75 or 1.0 mg/kg) may be required to clarify the potential antidepressant effect of ketamine infusion in patients with ANX-TRD. Third, patients with ANX-TRD were much older than those with NANX-TRD. In the GEE model with adjustment of age, we found that age was not related to the trajectory change of depression symptoms ($P = .872$). However, further studies with the age-matched sample of ANX-TRD and NANX-TRD may be required to validate our findings. Fourth, previous studies suggested that concomitant benzodiazepine use may attenuate the antidepressant response of low-dose ketamine infusion.²² In our study, up to 80% of patients with TRD were concomitantly treated with benzodiazepines. But, the benzodiazepine use did not differ between patients with

ANX-TRD and those with NANX-TRD. Whether benzodiazepines may attenuate the antidepressant response of ketamine in Asian patients with TRD would need further investigation. Fifth, normal saline was used as the placebo in current study. Active placebo, such as midazolam, would be considered in the future research. Finally, we only assessed the role of ANX- vs NANX-TRD in a single infusion of low-dose ketamine. Further studies would be necessary to clarify the role of anxious depression in the multiple infusions of low-dose ketamine.

In conclusion, low-dose ketamine infusion was effective for Taiwanese patients with NANX-TRD but was not so effective for those with ANX-TRD. Higher level of anxiety severity accompanying depression was related to greater depression severity. This may confound and reduce the antidepressant effect of ketamine infusion. The exact mechanism behind the differential response to ketamine in ANX-TRD and NANX-TRD warrants further investigation.

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Supplementary Materials. To view supplementary material for this article, please visit <http://dx.doi.org/10.1017/S1092852920001194>.

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