



Plasma VEGF Concentrations and Ketamine's Effects on Suicidal Ideation in Depression With Suicidal Ideation

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Objectives: Accumulating evidence supports a role for vascular endothelial growth factor (VEGF) in the pathogenesis of depression, but its relationship with the antisuicidal effects of ketamine is not clear. Our objective was to determine whether there was an association between the plasma VEGF (pVEGF) concentrations and the antisuicidal response to serial ketamine infusions.

Methods: Six ketamine infusions (0.5 mg/kg) over a 12-day period were administered to sixty depressed individuals suffering from suicidal ideation. The Hamilton Depression Rating Scale (HAMD) suicide item, the Montgomery-Åsberg Depression Rating Scale (MADRS) suicide item, and the Beck Scale for Suicide Ideation (SSI-part I) were used to assess suicidal ideation at baseline, 1 day after the first infusion (day 1), 1 day following the last infusion (day 13), and again 2 weeks post-infusion (day 26). For this purpose, plasma was obtained at baseline, day 13 and 26.

Results: The rates of antisuicidal response to ketamine were 61.7% (37/60), 81.7% (49/60), and 73.3% (44/60) at days 1, 13, and 26, respectively. The linear mixed model revealed significant time effects on suicidal ideation and pVEGF concentrations over time (all P s < 0.05). Antisuicidal responders did not have significantly altered pVEGF concentrations compared with non-responders on day 13 and day 26 (all P s > 0.05). No significant correlation was found between the baseline pVEGF concentration and suicidal ideation as measured by the SSI part 1, HAMD suicide item and MADRS suicide item on days 1, 13, and 26 (all p s > 0.05).

Conclusion: This preliminary finding does not support a role for VEGF in the antisuicidal effects of serial ketamine treatments in individuals with depression and suicidal ideation. Further research is needed to confirm and expand these findings.

Keywords: ketamine, VEGF, suicidal ideation, depression, response

INTRODUCTION

Approximately 0.8 million individuals worldwide die by suicide every year (1), which is becoming a substantial public health concern. Suicide is a complex and multifaceted phenomenon where numerous potential mechanisms could be implicated (2). Suicidal ideation is common in individuals with major depressive disorder (MDD) (3) and bipolar depression (BD) (4), especially among inpatients. Better therapy for suicidal ideation in MDD and BD is a critical target in preventing deaths due to suicide (5). However, very few treatments can rapidly alleviate suicidal ideation (6). Although accumulating evidence has indicated that treatment with dialectical behavioral therapy (7), cognitive behavioral therapy (CBT) (8, 9), and lithium (10) can effectively alleviate suicidal ideation, the onset of clinically relevant antisuicidal effects generally takes 2–4 weeks. Thus, novel pharmacotherapeutic approaches are urgently needed for subjects with depression and suicidal ideation.

As a non-selective *N*-methyl-D-aspartic acid receptor (NMDAR) antagonist, ketamine has shown quick and dramatic antisuicidal effects in randomized controlled trials (RCTs) (11, 12) and meta-analyses (13, 14) for MDD and BD. In addition to its rapid antisuicidal effects, ketamine at a single intravenous dose has a rapid effect in reducing the level of anhedonia (15–18) and ameliorating depressive symptoms (19, 20) in MDD and BD. After controlling for the effects of ketamine on depression, ketamine's antisuicidal ideation remained significant (13, 21). Antidepressant and antisuicidal responses to a single ketamine infusion could be prolonged with repeated ketamine infusions (22, 23). For example, a recent study found that the antisuicidal response rates increased from 57.0 to 65.1% after five additional infusions of ketamine in depressed patients experiencing suicidal ideation (22). However, a certain proportion of depressed patients experiencing suicidal ideation do not adequately respond to single or repeated ketamine infusions, but the reasons for this are unclear.

Vascular endothelial growth factor (VEGF), as an angiogenic cytokine, has been associated with the antidepressant response to electroconvulsive therapy (ECT) (24) and serotonin selective reuptake inhibitors (SSRIs) (25). Patients experiencing suicidal ideation had lower cerebrospinal fluid VEGF concentrations than healthy controls (26). In contrast, antidepressant therapy can induce hippocampal expression of VEGF (27). Recently, Deyama et al. found that the rapid antidepressant response to ketamine was associated with neuronal VEGF-Flk-1 signaling in the medial prefrontal cortex (mPFC) (28). Finding on the relationship between VEGF and ketamine's antidepressant effect in depressed patients were inconsistent (29, 30). For instance, McGrory et al. found that VEGF plays an essential role in the antidepressant action of ketamine (30). However, another study reported a negative finding (29). No study has yet reported on the association of plasma VEGF (pVEGF) concentrations and the antisuicidal effects of repeated-dose intravenous ketamine in Chinese subjects with depression who are experiencing suicidal ideation.

The aim of the current study was to: (1) detect the change in pVEGF concentrations after repeated-dose intravenous ketamine

in depressed patients experiencing suicidal ideation and (2) to demonstrate the relationship between pVEGF concentrations and the antisuicidal effects of repeated doses of intravenous ketamine. We hypothesized that pVEGF concentrations would be increased after six ketamine infusions, and pVEGF would play an important role in the antidepressant actions of ketamine in individuals with depression and suicidal ideation.

METHODS

Study Population and the Procedure

The data for this study were obtained from a single-center clinical trial (Registration Number: ChiCTR-OOC-17012239) in which unipolar and bipolar depressed patients received six ketamine infusions at the Affiliated Brain Hospital of Guangzhou Medical University from September 2016 to December 2017 (31, 32). All patients gave written informed consent and the study was approved by the Affiliated Brain Hospital of Guangzhou Medical University Institutional Review Board (Ethical Application Ref: 2016030). In the present study, we specifically report the association between pVEGF concentration and the effect of ketamine on suicidal ideation, focusing on depressed patients with suicidal ideation. The inclusion criteria were as follows: (1) sixty depressed patients were 18–65 years old with suicidal ideation as defined by the Beck Scale for Suicide Ideation (SSI)-part I ≥ 2 (33, 34); (2) patients fulfilling the diagnostic criteria listed in the DSM-5, for MDD or BD without psychotic symptoms; (3) each participant experiencing a major depressive episode of at least moderate severity, as defined by the 17-item Hamilton Depression Rating Scale (HAMD) ≥ 17 (35, 36); (4) full understanding of the study procedure. The exclusion criteria of the current study were consistent with those used in previous studies (31, 32). Briefly, participants diagnosed with other psychiatric disorders such as schizophrenia, substance use disorder or alcohol use disorder were excluded, but a comorbidity of obsessive compulsive disorder, anxiety disorder or eating disorder was permitted when it was not judged to be the primary presenting problem. All subjects received six intravenous infusions of ketamine at subanaesthetic doses over 12 days. During the study period, the participants continued their psychotropic medications.

Antisuicidal Response

The SSI part I, the Montgomery-Åsberg Depression Rating Scale (MADRS) suicide item, and the HAMD suicide item were used to evaluate the severity of suicidal ideation at baseline, 1 day after the first infusion (day 1), 1 day after the completion of six ketamine infusions (day 13), and at the 2-week follow-up after the completion of six ketamine infusions (day 26). Antisuicidal responses to repeated-dose intravenous ketamine at day 13 were defined by the SSI part I < 2 (22, 37).

Measurement of pVEGF Concentrations

A commercially available enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, USA) was used to examine the pVEGF concentrations according to the manufacturer's recommendations. The plasma was obtained at

baseline and then on days 13 and 26. The measurement of the pVEGF concentrations was in line with those used in a recent study (29).

Statistical Analysis

Data from this study were analyzed by using SPSS 24.0 statistical software. Significance was considered at $p < 0.05$. The demographic and clinical characteristics and pVEGF

concentrations at baseline were compared between the antisuicidal responders and the non-responders using the chi-squared test and/or Fisher's exact test for categorical variables and Student's *t*-test and/or the Mann-Whitney U test for continuous variables, as appropriate. Changes in the pVEGF concentrations and the suicidal symptoms evaluated by the HAMD suicide item, MADRS suicide item, and SSI part I over time and the subgroup differences (antisuicidal responders vs.

TABLE 1 | Baseline characteristics of antisuicidal responders and non-responders calculated by SSI part I scores on day 13.

Variables	Total sample (n = 60)		Antisuicidal responders (n = 49)		Antisuicidal non-responders (n = 11)		Statistics		
	N	%	N	%	N	%	χ ²	df	p
Male	27	45.0	22	44.9	5	45.5	— ^a	— ^a	1.00
Employed	23	38.3	21	42.9	2	18.2	— ^a	— ^a	0.18
Married	34	56.7	27	55.1	7	63.6	— ^a	— ^a	0.74
On ADs two or more	8	13.3	8	16.3	0	0	— ^a	— ^a	0.33
On APs	35	58.3	29	59.2	6	54.5	— ^a	— ^a	1.00
On mood stabilizers	16	26.7	13	26.5	3	27.3	— ^a	— ^a	1.00
On benzodiazepines	27	45.0	21	42.9	6	54.5	— ^a	— ^a	0.52
On anxiolytics	27	45.0	22	44.9	5	45.5	— ^a	— ^a	1.00
On anticholinergics	8	13.3	8	16.3	0	0	— ^a	— ^a	0.33
	Mean	SD	Mean	SD	Mean	SD	T/Z	df	p
Age (years)	35.3	12.4	34.8	12.0	37.4	14.4	−0.6	58	0.54
Education level (years)	12.2	3.5	12.5	3.4	10.7	3.9	0.8	58	0.14
BMI	22.2	3.5	22.1	3.3	22.8	4.5	−0.7	58	0.51
Illness duration (months)	91.5	80.0	81.5	69.1	135.9	110.2	−2.1	58	0.04
FLUeq (mg/day)	35.6	20.7	35.8	21.7	34.5	16.2	0.2	58	0.85
CPZeq (mg/day)	169.1	117.6	168.7	125.8	170.8	74.5	−0.5	— ^b	0.64
Baseline pVEGF concentrations (ng/ml)	38.4	55.7	44.5	59.7	11.6	15.7	−1.8	— ^b	0.07
Baseline SSI-part I scores	5.0	2.4	4.8	2.5	5.2	2.2	0.34	58	0.73
Baseline HAMD suicide item scores	2.2	0.8	2.2	0.8	2.5	0.8	−1.5	58	0.15
Baseline MADRS suicide item scores	2.9	1.3	2.8	1.2	3.5	1.5	−1.8	58	0.07

Bolded values are $p < 0.05$.

^aFisher's Exact Test.

^bMann-Whitney U test.

Ads, Antidepressants; APs, antipsychotics; BMI, body mass index; CPZeq, chlorpromazine equivalent milligrams; FLUeq, Fluoxetine equivalents equals; pVEGF, plasma vascular endothelial growth factor; df, degrees of freedom; HAMD, the Hamilton Depression Rating Scale; MADRS, the Montgomery-Åsberg Depression Rating Scale; SSI, the Beck Scale for Suicide Ideation; SD, standard deviation; TRD, treatment refractory depression.

TABLE 2 | Comparison of suicidal ideation scores and pVEGF concentrations between antisuicidal responders and non-responders in depressed patients with suicidal ideation using linear mixed model analysis.

Variables	Group-by-time interaction		Time main effect		Group main effect	
	F	p	F	p	F	p
HAMD suicide item scores	6.8	<0.001	33.2	<0.001	11.9	0.001
MADRS suicide item scores	4.6	0.004	30.1	<0.001	10.2	0.002
SSI-part I scores	4.1	0.008	28.8	<0.001	11.2	0.002
pVEGF concentrations (ng/ml)	0.6	0.55	3.5	0.04	0.3	0.57

Bolded values are $p < 0.05$.

pVEGF, plasma vascular endothelial growth factor; SSI, the Beck Scale for Suicide Ideation; MADRS, the Montgomery-Åsberg Depression Rating Scale; HAMD, the Hamilton Depression Rating Scale.

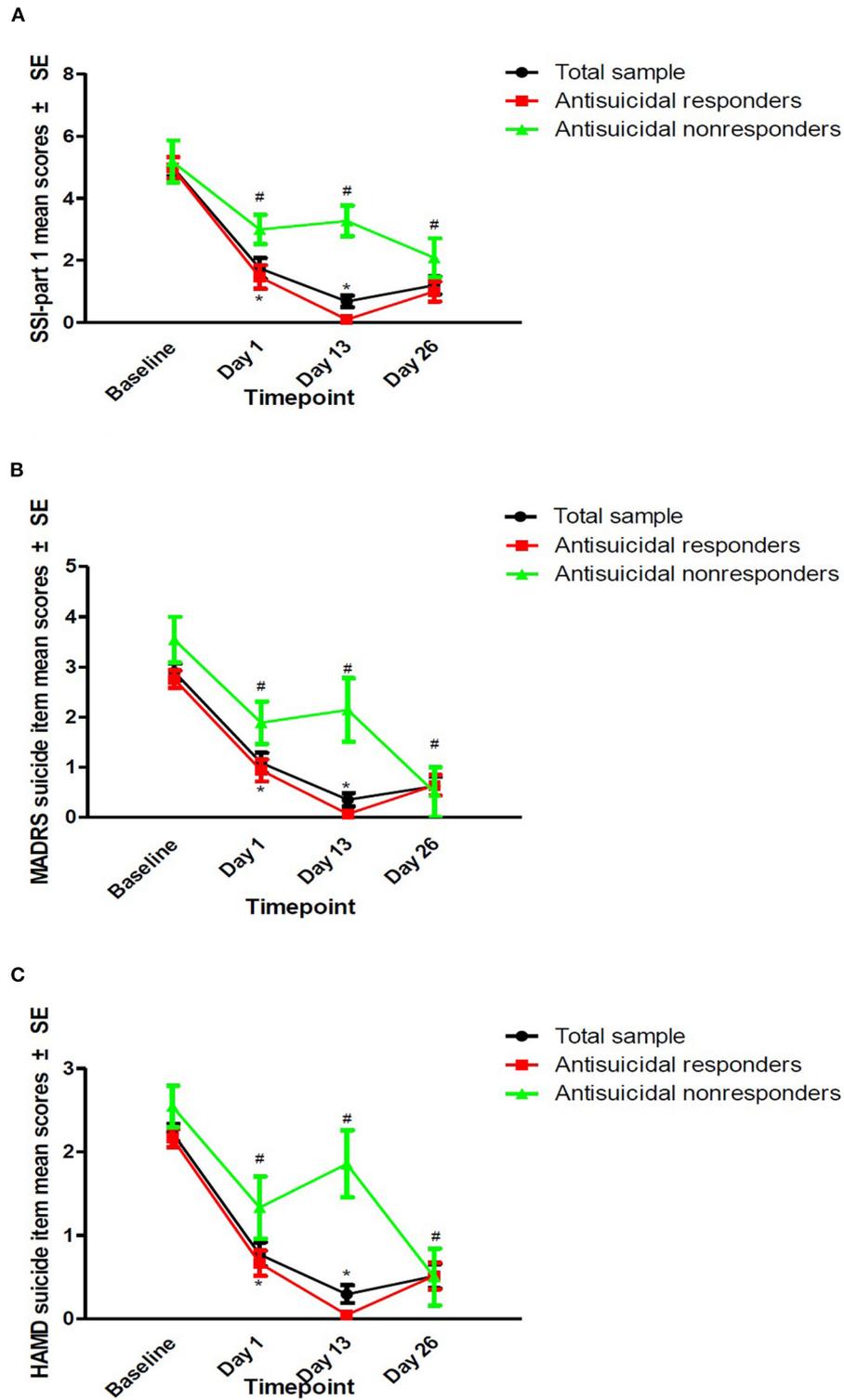


FIGURE 1 | The antisuicidal effects of ketamine were measured by SSI part I, the MADRS suicide item, and the HAMD suicide item. The antisuicidal effects of ketamine as measured by SSI part I (A), the MADRS suicide item (B), and the HAMD suicide item (C). #A significant difference was found compared to the baseline at the indicated times ($P < 0.05$). *A significant difference was found between antisuicidal responders and non-responders at the indicated times ($P < 0.05$). SSI, the Beck Scale for Suicide Ideation; MADRS, the Montgomery-Åsberg Depression Rating Scale; HAMD, the Hamilton Depression Rating Scale.

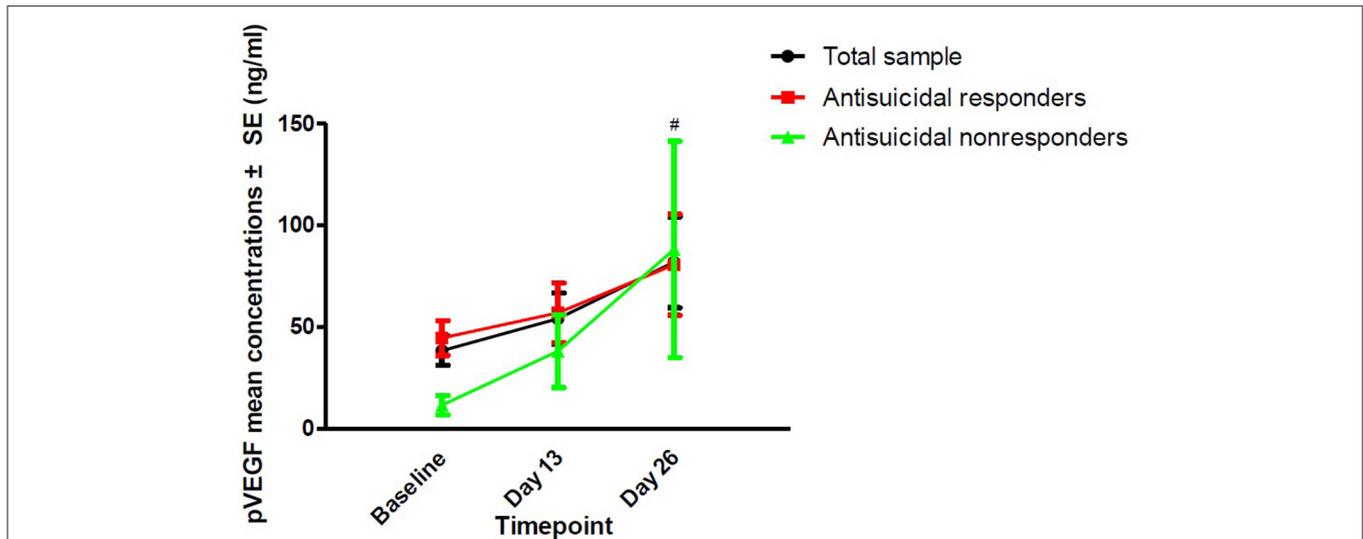


FIGURE 2 | The change in pVEGF concentrations in depressed patients with suicidal ideation at the indicated times. #No significant difference at the indicated times was found when compared to baseline ($P > 0.05$). No significant difference at the indicated times was found between antisuicidal responders and non-responders ($P > 0.05$). pVEGF, plasma vascular endothelial growth factor.

TABLE 3 | Correlation analysis between suicidal ideation and baseline pVEGF concentrations in depressed patients with suicidal ideation at the indicated times.

Variables	HAMD suicide item scores			MADRS suicide item scores			SSI-part I scores		
	Day 1	Day 13	Day 26	Day 1	Day 13	Day 26	Day 1	Day 13	Day 26
Baseline pVEGF concentrations (ng/ml)	$r = -0.07$	$r = -0.18$	$r = 0.16$	$r = -0.05$	$r = -0.19$	$r = 0.13$	$r = 0.17$	$r = -0.22$	$r = 0.24$
	$p = 0.62$	$p = 0.22$	$p = 0.30$	$p = 0.74$	$p = 0.19$	$p = 0.41$	$p = 0.20$	$p = 0.09$	$p = 0.07$

Variables	Change in HAMD suicide item scores			Change in MADRS suicide item scores			Change in SSI-part I scores		
	Day 1	Day 13	Day 26	Day 1	Day 13	Day 26	Day 1	Day 13	Day 26
Change in pVEGF concentrations (ng/ml)	$r = 0.10$	$r = -0.14$	$r = 0.09$	$r = 0.09$	$r = -0.10$	$r = 0.07$	$r = 0.10$	$r = -0.24$	$r = -0.02$
	$p = 0.53$	$p = 0.36$	$p = 0.54$	$p = 0.59$	$p = 0.51$	$p = 0.67$	$p = 0.53$	$p = 0.11$	$p = 0.91$

pVEGF, plasma vascular endothelial growth factor; r , Pearson coefficient of correlation; SSI, the Beck Scale for Suicide Ideation; MADRS, the Montgomery-Åsberg Depression Rating Scale; HAMD, the Hamilton Depression Rating Scale.

non-responders) were investigated using linear mixed models. The association of pVEGF concentrations with the antisuicidal effects of ketamine was examined by correlation analysis.

RESULTS

pVEGF concentrations were obtained from 60 patients suffering from depression and suicidal ideation. A comparison between the demographic and clinical characteristics of antisuicidal responders and non-responders is presented in **Table 1**. Antisuicidal responders had marginally significantly higher baseline pVEGF concentrations than antisuicidal non-responders ($P = 0.07$; **Table 1**).

The rates of antisuicidal responses to ketamine were 61.7% (37/60), 81.7% (49/60), and 73.3% (44/60) on days 1, 13, and 26, respectively. The linear mixed model with SSI part I, MADRS suicide items and HAMD suicide items showed a

significant main effect of time and group and a group-by-time interaction (all $P_s < 0.05$; **Table 2**). Antisuicidal responders had a significantly greater reduction in suicidal ideation than non-responders (as measured by the SSI part I, the MADRS suicide item and the HAMD suicide item) at days 1 and 13 (all $P_s < 0.05$; **Figure 1**). The linear mixed model with pVEGF concentrations showed a significant main effect of time ($P < 0.05$; **Table 2**) but not for the main effect of group and group-by-time interaction (all $P_s > 0.05$; **Table 2**). Although a significant change in pVEGF concentrations was found at day 26 as compared to baseline ($P < 0.05$), the antisuicidal responders compared to nonresponders did not have significantly altered pVEGF concentrations at day 13 and day 26 (all $P_s > 0.05$; **Figure 2**).

As depicted in **Table 3**, no significant association of baseline pVEGF concentrations and reductions in suicidal ideation following ketamine treatment (as measured by the SSI part I, the

MADRS suicide item, and the HAMD suicide item) were found on day 1, day 13, or day 26 (all P s > 0.05; **Table 2**).

DISCUSSION

The current study first illuminated the association of pVEGF concentrations with the effect of ketamine on suicidal ideation. Our findings indicate that antisuicidal responders had marginally significantly greater pVEGF concentrations at baseline than antisuicidal non-responders. Despite a significant reduction in suicidal ideation during serial ketamine infusions over time, the pVEGF concentrations were not significantly altered in antisuicidal responders compared with non-responders on day 13 and day 26. Similarly, no notable association was detected between the pVEGF concentrations and the effects of repeated-dose intravenous ketamine on suicidal ideation as measured by SSI part I, the MADRS suicide item, and the HAMD suicide item.

Accumulating evidence suggests that VEGF is associated with brain function, including neurogenesis, learning and memory, by regulating hippocampal synaptic activity and plasticity (38–41). Dysregulated VEGF concentrations have been involved in major mental disorders, such as MDD and BD (42). Low pVEGF concentrations are associated with a higher suicide risk among suicide attempters (43). Therapy with antidepressants such as SSRIs (27, 44) and ketamine (30) can increase the expression of VEGF. Consistent with previous studies (11–14), in this study, ketamine had a rapid and robust effect in reducing suicidal ideation. Repeated administration of intravenous ketamine (0.5 mg/kg) did not significantly increase pVEGF concentrations, even after a 2-week follow-up, corroborating the results of previous studies (45).

As reported by Deyama et al.'s study, the antidepressant-like and neurotrophic actions of brain-derived neurotrophic factor (BDNF) require VEGF signaling (44). Thus, VEGFR2 signaling appears to be indispensable for cellular and behavioral responses to antidepressant treatments (27). The findings of several animal trials support a role for VEGF in the biological actions of antidepressants (i.e., fluoxetine) (46) and mood stabilizers (i.e., lamotrigine) (47). Similarly, VEGF could mediate the antidepressant actions of electroconvulsive seizures (48, 49) and a single ketamine infusion (28) but not six ketamine infusions (29). However, in this study, we found that VEGF was not involved in the antisuicidal effects of repeated-dose intravenous ketamine in Chinese patients with depression and suicidal ideation, which should be confirmed by RCTs.

This study is associated with several limitations. First, the relatively small sample size is the first study limitation, partly accounting for the negative results. Second, the lack of a control group in the protocol of the present study was another limitation, affecting the interpretation and external validity of the findings. Third, when compared to the samples from controlled clinical trials, the sample of the current study based on a real-world design is potentially more heterogeneous. Furthermore, the pooling of subjects suffering from MDD and BD made the sample non-homogeneous. Fourth, although substance use disorder is a significant predictor of non-adherence among individuals

suffering from mood disorders (50), patients suffering from substance use disorder were excluded in this study. Finally, all subjects continued to receive psychotropic medications, which may have potentially affected their pVEGF concentrations and explained the contradictory findings between this study and previous studies (30, 45). Finally, as reported by Levy et al., blood VEGF concentrations may not be associated with VEGF concentrations in the brain (51). However, VEGF concentrations in the brain could not be directly detected in the current study.

CONCLUSIONS

This preliminary study does not support a role for VEGF in the antisuicidal effects of serial ketamine treatments in individuals with depression and suicidal ideation. Further research is needed to confirm and expand these findings.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Affiliated Brain Hospital of Guangzhou Medical University Institutional Review Board (Ethical Application Ref: 2016030). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Y-PN: study design. WZ, Y-LZ, C-YW, and X-FL: data collection. WZ and L-MG: analysis and interpretation of data. WZ: drafting of the manuscript. BZ and Y-PN: critical revision of the manuscript. All authors: approval of the final version for publication.

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