Original Article

A Higher Dose (0.8 mg/kg) of Ketamine Infusion for Treatment-resistant Depression: An Open-label Study in Taiwan

Mu-Hong Chen, M.D.[1,2,3], Wei-Chen Lin, M.D.[1,3], Cheng-Ta Li, M.D., Ph.D.[1,2,3], Tung-Ping Su, M.D.[1,2,3,4,5]**

Departments of [1]Psychiatry and [4]Medical Research, Taipei Veterans General Hospital, [2]Division of Psychiatry, Faculty of Medicine, National Yang-Ming University, [3]Institute of Brain Science, National Yang-Ming University, [5]Department of Psychiatry, Cheng Hsin General Hospital, Taipei, Taiwan

Abstract

Objective: Studies of the Caucasian population showed that the treatment response rate of 0.5 mg/kg ketamine infusion is as high as 70% in patients with treatment-resistant depression (TRD). By contrast, our earlier study has found a response rate of about 50% in Taiwanese patients with TRD, with much lower blood levels of ketamine and norketamine. In the current study, we intended to investigate whether a higher (0.8 mg/kg) dose of ketamine infusion can improve the treatment outcome. **Methods:** An open-label study with six TRD patients was done. Every participant received a single dose (0.8 mg/kg) of ketamine infusion and was followed up for two weeks for depressive symptoms. The blood levels of ketamine and norketamine were also assessed. We combined the data from the current open-label study and our previous randomized double-blind study (0.5 mg/kg, 0.2 mg/kg, and placebo) for further analyses. **Results:** The treatment response rate in the 0.8 mg/kg group was 66.7% at 240 min after ketamine infusion, which is higher than that in the 0.5 mg/kg group. A generalized estimating equation model indicated a group effect ($p < 0.001$), a time effect ($p < 0.001$), and a group*time effect ($p < 0.001$) for the trajectory of the total depression score among four groups. Ketamine and norketamine levels were dose related (0.8 mg/kg > 0.5 mg/kg > 0.2 mg/kg). Adverse effects, such as a floating feeling and dizziness, did not differ in subjects between the 0.8 mg/kg and 0.5 mg/kg groups. **Conclusion:** A single higher dose (0.8 mg/kg) of ketamine infusion was a safe and effective treatment strategy for Taiwanese patients with TRD. A 0.8 mg/kg ketamine infusion may achieve optimal blood levels of ketamine and norketamine and may have a superior treatment response in Taiwanese patients.

Key words: clinical trial, major depressive disorder, Taiwanese, treatment response
***Taiwanese Journal of Psychiatry* (Taipei) 2020; 34: 72-77**

Introduction

Major depressive disorder is a chronic mental illness and has been predicted to be the leading cause of disease burden by 2015. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study reported that up to 40% of patients with major depressive disorder do not achieve symptomatic remission after two trials of traditional antidepressants, defined as treatment-resistant depression (TRD). About one-third of the patients continues to experience depression after four trials of different antidepressant treatments, including combination therapy and augmentation therapy [1]. Without adequate and optimal treatment, the residual symptoms of major depressive disorder can lead to worsened clinical outcomes, such as high relapse rates, suicidality, as well as diminished quality of life and psychosocial functioning [2-4].

Recent studies showed that a single subanesthetic dose (0.5 mg/kg) of ketamine has a fast-acting antidepressant effect which occurs within 1 h and lasts for about 1–2 weeks [5-7]. Several studies with a similar study design investigating the therapeutic efficacy of 0.5 mg/kg ketamine in Caucasian patients with TRD demonstrated that the response rate in

[1]*Corresponding author. No. 201, Section 2, Shih-Pai Road, Taipei, 112, Taiwan.
*E-mail: Tung-Ping Su <tomsu0402@gmail.com> and Cheng-Ta Li <on5083@msn.com>

Received: Jan. 9, 2020 revised: Apr. 20, 2020 accepted: Apr. 30, 2020
date published: Jun. 26, 2020

Access this article online

Quick Response Code:

Website: www.e-tjp.org

DOI: 10.4103/TPSY.TPSY_19_20

How to cite this article: Chen MH, Lin WC, Li CT, Su TP. A higher dose (0.8 mg/kg) of ketamine infusion for treatment-resistant depression: An open-label study in Taiwan. Taiwan J Psychiatry 2020;34:72-7.

patients is as high as 70% [5-7]. For example, Wan et al. found that the overall antidepressant response rate, defined as a ≥ 50% improvement in the Montgomery–Åsberg Depression Rating Scale (MADRS), is 67% [6]. Murrough et al. reported that the likelihood of response in 24 h is greater with ketamine than with midazolam (odds ratio: 2.18), with response rates of 64% and 28%, respectively [5]. In a study by Zarate et al., 71% of 17 patients who received 0.5 mg/kg ketamine infusion have met the response criteria [8]. But in our previous study, we compared the treatment response in Taiwanese patients with TRD treated with 0.5 mg/kg ketamine, 0.2 mg/kg ketamine, or normal saline placebo infusion and found that the response rate after ketamine infusion is only 45.8% in the 0.5 mg/kg group [9]. By analyzing the serum ketamine and norketamine levels in our patients, we found that both ketamine (115.86 ng/mL vs. 204.13 ng/mg) and norketamine (33.39 ng/mL vs. 55.52 ng/mL) levels in 40 min after ketamine infusion are much lower in our patients than in Caucasian patients, which may indicate that the treatment efficacy of ketamine for TRD is limited in Taiwanese patients [7, 9].

In this study, we intended to determine an optimal dose of ketamine that improves the antidepressant response for TRD patients in Taiwan. With an open-label study design, we investigated whether a higher dose (0.8 mg/kg) of ketamine infusion has a higher antidepressant efficacy and assessed the potential adverse effects.

Methods

Inclusion criteria for cases

In this open-label clinical trial, we followed the inclusion criteria and procedure of our previous study, which investigated the treatment efficacy of a single dose of 0.5 or 0.2 mg/kg ketamine infusion in TRD. We recruited six patients who met *the DSM-IV* criteria for major depressive disorder, recurrent without psychotic features according to the Mini International Neuropsychiatric Interview [10], and who had failed to respond to more than two adequate antidepressant trials at the outpatient clinic of Taipei Veterans General Hospital in 2016.

Excluded were patients who had a history of bipolar disorder, psychotic symptoms, substance dependence other than nicotine, mild symptoms (MADRS score < 20 before study entry), or major medical illness (e.g., epilepsy and stroke). This study was approved by the institutional review board of Taipei Veterans General Hospital and the Department of Health of Taiwan (IRB protocol numbers = 2012-04-037B and 2016-02-001B, date of approval = April 20, 2012, and January 29, 2016) with the stipulation that the patients signed the informed consents before participating in the study.

Study design and procedure

This was an open-label study. Every participant received a single dose (0.8 mg/kg) of a 40-min intravenous R/S-ketamine hydrochloride (Ketalar, Pfizer Pharmaceuticals, Groton, Connecticut, USA) infusion on the test day (day 1). The MADRS was given in person before the initiation of the test infusions and 40, 80, 120, and 240 min later. Ratings were obtained through telephone on days 2-7 and 14 after ketamine infusion. For ketamine infusion test days, scores were evaluated in relation to the baseline. One consequence of this approach is that some MADRS measures (such as sleep) do not change during the test day. Subsequent assessments were based on the previous 24 h. To facilitate this, efforts were made to ensure that follow-up time points were consistent across test days. The primary outcome was the MADRS score. A ≥50% reduction of the total MADRS score was defined as a treatment response. We assessed dissociative effects of ketamine with the Clinician-Administered Dissociative States Scale (CADSS).

Plasma levels of ketamine

Plasma samples were obtained at the baseline and at 40, 80, 120, and 240 min after ketamine infusion through an intravenous line separate from the one for ketamine administration. The measurement of plasma levels of ketamine and norketamine was described in detail in our previous study [9].

Statistical analyses

To compare the treatment efficacy of 0.8 mg/kg ketamine infusion with 0.5 mg/kg or 0.2 mg/kg ketamine infusion, we combined the current open-label study data ($n = 6$ for 0.8 mg/kg ketamine) with our previous randomized placebo control study data (n = 24, 23, and 24 for 0.5 mg/kg ketamine, 0.2 mg/kg ketamine, and normal saline placebo) for further analyses. One-way analysis of variance (ANOVA) and Pearson's Chi-square tests were used to compare the continuous and categorical variables among groups, respectively.

A generalized estimating equation model with the autoregressive method for correlations of repeated measures for the same individual over time was used to assess the effects of ketamine on MADRS during the treatment period with the group (0.8 mg/kg, 0.5 mg/kg, 0.2 mg/kg, and placebo) as a between-subject factor, time (40, 80, 120, and 240 min on days 1-7 and 14) as a within-subject factor, and the baseline MADRS score as a between-subject predictor, as well as all possible interactions. We compared serum ketamine and norketamine levels between the groups and across time points.

All data processing and statistical analyses were done using the Statistical Package for the Social Science software version 17 software for Window (SPSS Inc., Chicago, Illinois, USA). The differences between groups were considered significant if two-tailed $p < 0.05$.

Results

The baseline characteristics, such as age, sex, duration of illness, body mass index, and baseline MADRS score, did not differ between the 0.8 mg/kg group in this study and the other three groups in our previous study (Table 1). A generalized estimating equation model indicated a group effect ($p < 0.001$), a time effect ($p < 0.001$), and a group*time effect ($p < 0.001$) for the trajectory of the total MADRS score among the four groups (Figure 1). Table 2 and Figure 1 showed that the 0.8 mg/kg group had a slightly greater reduction of the MADRS

score and a lower ratio than the 0.5 mg/kg group and had a significant reduction of the MADRS score and a lower ratio than the control group across each time point from 40 min to day 5 after ketamine infusion. The treatment response rate in the 0.8 mg/kg group was 66.7% at 240 min after ketamine infusion, higher than that in the 0.5 mg/kg group. The average CADSS score in the 0.8 mg/kg group was 1.17 ± 1.33 in 40 min after ketamine infusion and was not associated with the change of the total MADRS score at each time point (all $p > 0.1$). Adverse effects, such as a floating feeling, dizziness, and nausea, did not differ between the 0.8 mg/kg and 0.5 mg/kg groups (Table 3).

Figure 2 shows plasma ketamine and norketamine levels. Ketamine and norketamine levels were dose-related (0.8 mg/kg

Table 1. Demographic data and clinical characteristics of patients with treatment-resistant depression in fours dosage groups

	Open-label trial	Randomized, placebo-control trial		
	a. Ketamine (0.8 mg/kg) Mean ± SD (n = 6)	b. Ketamine (0.5 mg/kg) Mean ± SD (n = 24)	c. Ketamine (0.2 mg/kg) Mean ± SD (n = 23)	d. Placebo Mean ± SD (n = 24)
Age (years)	50.50 ± 10.84	48.46 ± 11.01	44.9 6 ± 12.31	48.63 ± 8.12
Female, n (%)	4 (66.7)	21 (87.5)	17 (73.9)	15 (62.5)
BMI (kg/m^2)	21.92 ± 2.30	24.21 ± 3.90	21.63 ± 3.51	23.62 ± 4.85
Duration of illness (years)	14.83 ± 13.70	13.17 ± 8.92	9.70 ± 8.68	10.85 ± 6.83
MADRS score at baseline	35.67 ± 1.37	33.96 ± 7.35	35.09 ± 6.66	34.96 ± 4.86

SD, standard deviation; BMI, body mass index; MADRS, Montgomery–Åsberg Depression Rating Scale

Table 2. Treatment outcomes of patients with treatment-resistant depression in four dosage groups

	Open-label trial	Randomized, placebo-control trial		
	a. Ketamine (0.8 mg/kg) (n = 6)	b. Ketamine (0.5 mg/kg) (n = 24)	c. Ketamine (0.2 mg/kg) (n = 23)	d. Placebo (n = 24)
MADRS changes, mean ± SD				
40 mins versus baseline**	−14.17 ± 8.35	−10.04 ± 9.47	−7.13 ± 7.56	−3.37 ± 4.75
80 mins versus baseline**	−16.33 ± 5.71	−11.21 ± 10.67	−6.96 ± 6.69	−4.58 ± 4.97
120 mins versus baseline***	−19.67 ± 5.32	−12.25 ± 10.69	−7.39 ± 7.09	−5.83 ± 5.07
240 mins versus baseline***	−18.83 ± 5.08	−13.54 ± 10.14	−7.78 ± 6.84	−5.63 ± 5.42
Day 2 versus baseline**	−18.67 ± 6.12	−13.67 ± 9.49	−9.74 ± 7.63	−6.67 ± 7.36
Day 3 versus baseline*	−15.67 ± 6.38	−11.54 ± 9.78	−10.35 ± 8.27	−6.04 ± 6.02
Day 5 versus baseline*	−12.33 ± 10.44	−11.96 ± 9.90	−9.13 ± 9.38	−5.21 ± 5.31
Day 7 versus baseline	−6.17 ± 10.59	−9.54 ± 9.29	−7.70 ± 8.27	−4.38 ± 5.93
Day 14 versus baseline	−7.67 ± 9.69	−9.50 ± 11.67	−8.00 ± 8.18	−4.88 ± 5.77
MADRS decreasing ratio (%)				
40 mins versus baseline*	−39.31% (22.89)	−29.57% (26.05)	−24.01% (29.15)	−10.93% (14.70)
80 mins versus baseline*	−45.62% (15.27)	−32.36% (29.69)	−23.85% (27.92)	−13.43% (15.09)
120 mins versus baseline**	−54.92% (13.64)	−35.59% (29.93)	−25.20% (28.86)	−17.71% (16.49)
240 mins versus baseline**	−52.61% (12.98)	−40.26% (28.10)	−26.14% (27.37)	−17.26% (17.90)
Day 2 versus baseline**	−52.13% (16.18)	−40.65% (26.81)	−29.59% (24.24)	−20.26% (23.46)
Day 3 versus baseline*	−43.88% (17.30)	−34.06% (27.34)	−31.77% (27.98)	−17.97 (17.71)
Day 5 versus baseline	−34.75% (29.15)	−34.09% (25.77)	−28.79% (30.13)	−15.79% (16.63)
Day 7 versus baseline	−17.02% (29.09)	−26.74% (25.68)	−23.06% (25.55)	−13.08% (18.19)
Day 14 versus baseline	−21.04% (26.18)	−25.33% (32.75)	−23.80% (25.75)	−14.41% (18.19)
Response rate, n (%)				
40 mins	2 (33.3)	6 (25.0)	5 (21.7)	2 (8.3)
80 mins	2 (33.3)	7 (29.2)	4 (17.4)	2 (8.3)
120 mins*	4 (66.7)	7 (29.2)	4 (17.4)	3 (12.5)
240 mins*	4 (66.7)	9 (37.5)	4 (17.4)	3 (12.5)
Day 2	3 (50.0)	11 (45.8)	6 (26.1)	3 (12.5)
Day 3	2 (33.3)	5 (20.8)	6 (26.1)	2 (8.3)
Day 5	2 (33.3)	8 (33.3)	6 (26.1)	2 (8.3)
Day 7	1 (16.7)	5 (20.8)	2 (8.7)	2 (8.3)
Day 14	1 (16.7)	6 (25.0)	4 (17.4)	1 (4.2)

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ using one-way analysis of variables or Pearson's Chi square test if appropriate.
SD, standard deviation; MADRS, Montgomery–Åsberg Depression Rating Scale

> 0.5 mg/kg > 0.2 mg/kg) (Figure 2a and b). They also varied significantly by time point (both $p < 0.001$), but there were no significant differences by responder status.

Discussion

Our findings showed that a single higher (0.8 mg/kg) dose of ketamine infusion was a safe and effective treatment strategy for Taiwanese patients with TRD. The blood levels of ketamine and norketamine in Taiwanese patients who received 0.8 mg/kg ketamine infusion were similar with the blood levels in Caucasian patients who received a single dose of 0.5 mg/kg ketamine infusion. Furthermore, 0.8 mg/kg ketamine infusion can achieve a higher response rate (as high as 66%), similar to the response rate in Caucasian patients treated with 0.5 mg/kg ketamine infusion, in Taiwanese patients with TRD. But the treatment response rate of 0.8 mg/kg ketamine infusion group was not significantly superior on days 2, 3, 5, 7, and 14, compared with other three groups, which may be owing to the small sample size of 0.8 mg/kg ketamine infusion group (Table 1).

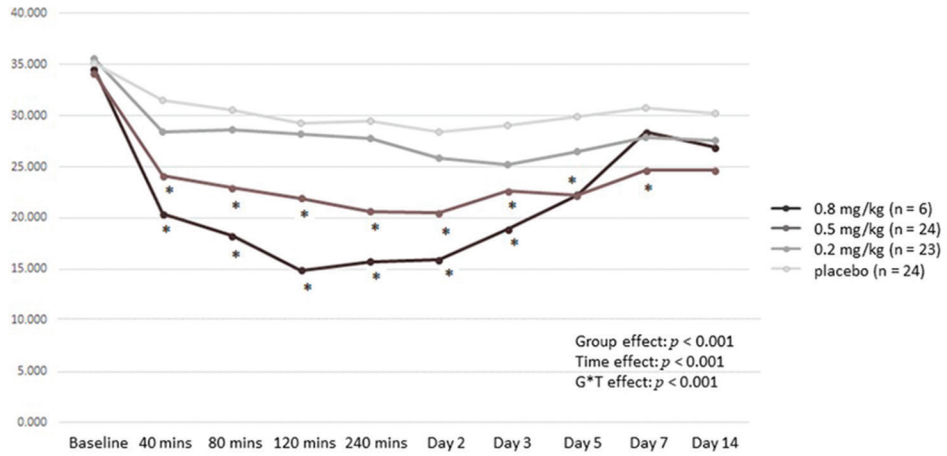

Figure 1. Montgomery–Åsberg Depression Rating Scale scores at baseline and each time point of postketamine infusion. *Significantly different compared to the placebo group.

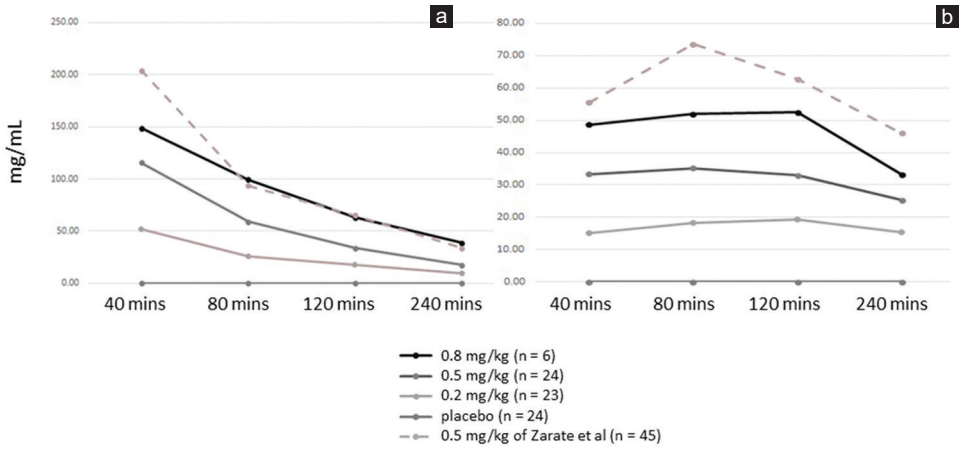

Figure 2. (a) Ketamine blood levels and (b) Norketamine blood levels at 40 min, 80 min, 120 min, and 240 min of postketamine infusion.

Table 3. Adverse effects of patients with treatment-resistant depression in fours dosage groups

Adverse effects, *n* (%)	Open-label trial a. Ketamine (0.8 mg/kg) (*n* = 6)	Randomized, placebo-control trial		
		b. Ketamine (2/.5 mg/kg) (*n* = 24)	c. Ketamine (0.2 mg/kg) (*n* = 23)	d. Placebo (*n* = 24)
Dizziness	2 (33.3)	10 (41.7)	6 (26.1)	3 (12.5)
Nausea	0 (0)	2 (8.3)	4 (17.4)	0 (0)
Chest tightness	0 (0)	3 (12.5)	2 (8.7)	0 (0)
Drowsiness	1 (16.7)	4 (16.7)	0 (0)	1 (4.2)

As mentioned in the introduction, Taiwanese patients with TRD are less responsive to a single dose of 0.5 mg/kg ketamine infusion compared with Caucasian patients [9]. One possible reason for this finding is the lower blood levels of ketamine and norketamine that 0.5 mg/kg ketamine infusion has provided in Taiwanese patients [9]. In this study (Table 2), we suggest that 0.8 mg/kg ketamine infusion may be more effective for increasing ketamine and norketamine levels in Taiwanese patients with TRD, achieving a treatment response rate of about 70%. Considering our current and previous data together, we found that a single dose of 0.8 mg/kg or 0.5 mg/kg ketamine infusion is more effective than that of 0.2 mg/kg ketamine or placebo infusion in TRD patients (Table 2).

As for patients who responded poorly to a single dose of either 0.5 mg/kg or 0.8 mg/kg ketamine infusion, further studies are required to clarify whether a higher dose (1 mg/kg) of ketamine infusion may be another treatment choice with a superior treatment outcome. But previous animal studies demonstrated that a much higher dose of ketamine infusion increases depression- and anxiety-like behaviors in rats [11]. Therefore, the benefits and risks of a higher dose of ketamine infusion for TRD should be considered first.

Here, we attempt to offer three hypotheses to explain why 0.8 mg/kg ketamine may be an optimal dose for TRD in the Taiwanese population:

- Ketamine is biotransformed in the liver by cytochrome P450 (CYP) enzymes, including CYP3A4, CYP2B6, and CYP2C9, into norketamine through *N*-demethylation [12]. The genetic diversity of CYP enzymes between Caucasians and Asians may influence the pharmacokinetics, pharmacodynamics, and blood levels of ketamine and norketamine [13, 14]. Guan et al. reported that the frequencies of common CYP2B6 allelic variants in Chinese and other Asians are markedly different from those in Caucasians [15]. An *in vitro* study suggested that CYP2B6 may play an important rôle in the metabolism of ketamine, but an *in vivo* study has not validated this finding [16].
- The functional balance between CYP2B6 and CYP3A4, such as compensation through CYP3A4 in the presence of the less efficient CYP2B6, should be considered for ketamine metabolism [12]. We propose that ketamine metabolism is faster in Taiwanese patients than in Caucasian patients, leading to lower blood levels in Taiwanese patients [12-16]. Therefore, 0.8 mg/kg ketamine may be the optimal dose for TRD patients in Taiwan. Increasing evidence suggested that BDNF and its polymorphisms (i.e., rs6265) play a rôle in the treatment response to ketamine infusion [17, 18]. A clinical study of Caucasian patients with depression showed that the mean change of depressive symptoms is 20% for Met carriers and 40% for Val carriers at 240 min after ketamine administration [17]. A study of mice demonstrated that expression of the BDNF Met allele results in basal synaptic deficits and block synaptogenic and antidepressant actions of ketamine in the prefrontal cortex [18]. But the Met allele occurs at a 40%-50% frequency within the Asian population, which is higher than the 20%-30% frequency in the Caucasian population [19]. The higher prevalence of the Met allele in the Asian population, including Taiwanese, may imply that a higher dose (i.e., 0.8 mg/kg) of ketamine infusion is necessary for Asian and Taiwanese patients with TRD. However, our previous study fails to find an association between BDNF Val66Met polymorphism and the treatment response to ketamine infusion [9]. Further studies are required to investigate the rôle of BDNF in the antidepressant efficacy of ketamine in the Asian populations.

Study limitations

Our current findings should not be generalized to include TRD patients of other races, because our study has three major limitations.

- The current study on the antidepressant effect of 0.8 mg/kg ketamine infusion was an open-label study, and the case number was small. A randomized, double-blind study with a larger sample size would be necessary to validate our findings
- Although the adverse effects did not differ between 0.8 mg/kg and 0.5 mg/kg ketamine infusion based on our current and previous studies, potential dose-dependent adverse effects, such as hypertension and dissociation, should be investigated
- The rates of ketamine and norketamine metabolism may differ between races.

Summary

A single higher (0.8 mg/kg) dose of ketamine infusion was a safe and effective treatment strategy for Taiwanese patients with TRD. A 0.8 mg/kg ketamine infusion may achieve optimal blood levels of ketamine and norketamine and a higher treatment response (as high as 66%) in Taiwanese patients with TRD. For treating TRD patients in Taiwan, 0.8 mg/kg ketamine infusion may offer an improved outcome compared with 0.5 mg/kg ketamine infusion, which may have only a limited effect. But whether the exact treatment efficacy of 0.8 mg/kg ketamine infusion compared with 0.5 mg/kg or 0.2 mg/kg ketamine infusion would need the further randomized, double-blind, placebo-control trial to validate the results.

Acknowledgment

None of the funding organizations had any rôle in the study design, data collection, analysis, interpretation of result, writing of the report, and the ultimate decision to submit the paper for publication.

Thank all research assistants, physicians, pharmacist, and nursing staff at D020 Unit of Taipei Veterans General Hospital for their assistance during the study.

Financial Support and Sponsorship

The study was supported by grants from Ministry of Science and Technology, Taiwan (101-2314-B-010-060, 102-2314-B-010-060) as well as the Kun-Po Soo Medical Foundation.

Conflicts of Interest

None of the authors in this study have any conflicts of interest to declare.

References

1. Howland RH: Sequenced treatment alternatives to relieve depression (STAR*D). part 2: Study outcomes. *J Psychosoc Nurs Ment Health Serv* 2008; 46: 21-4.
2. Dignam P: Treatment-resistant depression. *Aust N Z J Psychiatry* 2009; 43: 87.
3. Fekadu A, Wooderson SC, Markopoulo K, et al.: What happens to patients with treatment-resistant depression? a systematic review of medium to long term outcome studies. *J Affect Disord* 2009; 116: 4-11.
4. Little A: Treatment-resistant depression. *Am Fam Physician* 2009; 80: 167-72.
5. Murrough JW, Iosifescu DV, Chang LC, et al.: Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *Am J Psychiatry* 2013; 170: 1134-42.
6. Wan LB, Levitch CF, Perez AM, et al.: Ketamine safety and tolerability in clinical trials for treatment-resistant depression. *J Clin Psychiatry* 2015; 76: 247-52.
7. Zarate CA Jr., Brutsche N, Laje G, et al.: Relationship of ketamine's plasma metabolites with response, diagnosis, and side effects in major depression. *Biol Psychiatry* 2012; 72: 331-8.
8. Zarate CA Jr., Singh JB, Carlson PJ, et al.: A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* 2006; 63: 856-64.
9. Su TP, Chen MH, Li CT, et al.: Dose-related effects of adjunctive ketamine in Taiwanese patients with treatment-resistant depression. *Neuropsychopharmacology* 2017; 42: 2482-92.
10. Sheehan DV, Lecrubier Y, Sheehan KH, et al.: The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998; 59 (Suppl) 20: 22-33.
11. Li N, Lee B, Liu RJ, et al.: mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science* 2010; 329: 959-64.
12. Andrade C: Ketamine for depression, 5: potential pharmacokinetic and pharmacodynamic drug interactions. *J Clin Psychiatry* 2017; 78: e858-61.
13. Mizutani T: PM frequencies of major CYPs in Asians and Caucasians. *Drug Metab Rev* 2003; 35: 99-106.
14. Myrand SP, Sekiguchi K, Man MZ, et al.: Pharmacokinetics/genotype associations for major cytochrome P450 enzymes in native and first- and third-generation Japanese populations: comparison with Korean, Chinese, and Caucasian populations. *Clin Pharmacol Ther* 2008; 84: 347-61.
15. Guan S, Huang M, Chan E, et al.: Genetic polymorphisms of cytochrome P450 2B6 gene in Han Chinese. *Eur J Pharm Sci* 2006; 29: 14-21.
16. Rao LK, Flaker AM, Friedel CC, et al.: Role of cytochrome P4502B6 polymorphisms in ketamine metabolism and clearance. *Anesthesiology* 2016; 125: 1103-12.
17. Laje G, Lally N, Mathews D, et al.: Brain-derived neurotrophic factor Val66Met polymorphism and antidepressant efficacy of ketamine in depressed patients. *Biol Psychiatry* 2012; 72: e27-8.
18. Liu RJ, Lee FS, Li XY, et al.: Brain-derived neurotrophic factor Val66Met allele impairs basal and ketamine-stimulated synaptogenesis in prefrontal cortex. *Biol Psychiatry* 2012; 71: 996-1005.
19. Hashimoto K: A BDNF Val66Met polymorphism and ketamine-induced rapid antidepressant action. *Clin Psychopharmacol Neurosci* 2012; 10: 59-60.