Advances in Pharmacology and Therapeutics Journal
Shahid Sadoughi University of Medical Sciences, Yazd, Iran

SHAHID SADOUGHI UNIVERSITY OF MEDICAL SCIENCES

Original Article

Ketamine as a novel treatment protocol for treatment-resistant major depressive disorder

Running Title: Ketamine and resistant depression

Atena Fallah Tafti[1], Seyed Mojtaba Yasini[2], Fatemeh Saghafi[3], Reza Bidaki[2,4*], Hossein Jafari[5], Mahmoud Vakili[6]. Yekta Rameshi[7]

[1]Psychiatry resident, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
[2]Professor of Psychiatry, Research Center of Addiction and Behavioral Sciences, Shahid Sadoughi University Of Medical Sciences, Yazd, Iran.
[3] Faculty of Pharmacy, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
[4]Diabetes Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
[5]Anesthesiologist, Infertility Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
[6]MD, MPH, Associate Professor in Community Medicine, Monitoring of Health Research Center, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iranences , Yazd , Iran.
[7]Pharmaceutical Sciences Research Center, School of Pharmacy, Shahid Sadoughi University of Medical Sciences and health services, Yazd, Iran.

ARTICLEINFO

Received: 10/11/2021
Accepted: 12/28/2021

Corresponding author
Research Center of Addiction and Behavioral Sciences, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
Tel/Fax: +98-9121955521
E-mail
reza_bidaki@yahoo.com

Abstract

Aims: Major depressive disorder (MDD) has devastating effects on patient's quality of life (QOL). It seems that the use of ketamine in the treatment of MDD is an easy and less invasive technique compared with invasive methods, such as electroconvulsive therapy (ECT). As there were few studies in this regard, especially in Yazd province, the current study aimed to evaluate the therapeutic effect of repeated injected ketamine on patients with MDD and resistant to treatment.

Methods: This hospital-based open-label prospective study was conducted from September 2017 to May 2019 at Comprehensive Psychiatric Center, Taft,Yazd, Iran. In this pre-and post- trial, 18 patients with a diagnosis of MDD were recruited. The patients were diagnosed with MDD based on Diagnostic and Statistical Manual of Mental Disorders (5e) text revision Adapted from American Psychiatric Association (DSM 5). The patients aged between 18 to 70 years. Patients were eligible to participate in this study if they did not have history of physical or mental comorbidity. After completing Hamilton Depression Rating Scale (HDRS), the patients received 0.5 mg/kg ketamine infusion over 40 minutes with vital signs monitoring. After 2.5 hours of infusion, the HDRS was re-completed. The patients, who responded to treatment (≥50% reduction in HDRS score), received the treatment on days 3, 5, 7, 9, and 11 after the start of the study. Patients were re-evaluated after receiving the last dose of ketamine.

Results: After the first ketamine infusion, 13 of 18 (72%) patients responded to treatment. A significant decrease was seen between the mean depression score before (21.6 ± 8.5) and 2.5 hours after the first injection (9.7 ± 4.8) in responded patient ($p<0.001$). In addition, a significant decrease was seen in all of 13 patients who continued ketamine until the 11th day (6.3 ± 4.0) ($p<0.001$).

Conclusion: Findings suggested that ketamine injection was efficacious in reducing the severity of depression in patients with MDD. Due to the decrease in the average of HDRS score and the absence of significant side effects, it seems that repeated ketamine infusion therapy can be offered as a new therapy protocol for TRD.

Keywords: Ketamine; Major depressive disorder; Psychiatry; Treatment-resistant

Citation: Fallah Tafti A, Yasini SM, Saghafi F, Bidaki R, Jafari H, Vakili M, Rameshi Y. Ketamine as a novel treatment protocol for treatment-resistant major depressive disorder. Adv Pharmacol Ther J. 2021;1(2): 89-97. https://doi.org/10.18502/aptj.v1i2.8674

DOI: https://doi.org/10.18502/aptj.v1i2.8674

Introduction

Treatment-resistant depression (TRD) is defined as failure to respond adequately to at least two types of antidepressant drugs given in an adequate dose for sufficient time, and is a turbulence in the field of psychiatry (1- 3). Major depressive disorder (MDD) is the third reason of death in people aged between 39 up to 78 years old. It also has destructive effects on patient quality of life and is associated with high health care costs (4-6).

Pharmacotherapy, psychotherapy, ECT, or a combination of them are common modalities for MDD managment (7). Neverthelse, most of the time, low efficacy, adverse effects, and the association of these treatments with patient adherence problems lead to more negative attitudes towards their prescription (8). Only 33-63 % of patients with major depression respond to the first-line antidepressants, while the rest of them do not show clinical improvement in depressive symptoms and become resistant to treatment (9).

Ketamine hydrochloride, a noncompetitive antagonist for the N-methyl d-aspartate glutamate (NMDA) receptors, is used as an anesthesia medicine and for the treatment of chronic pain (10, 11). Given that the mechanism of ketamine in the improvement of depression has not been clarified fully yet, it is not mediated by known mood-modulating pathways. It is thought that ketamine blocks the NMDA receptor on GABA interneurons and activates the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor. AMPA receptor enhances brain-derived neurotrophic factor (BDNF) production and tropomyosin receptor kinase B (TrkB) stimulation. As a result, TrkB activates both mammalian target of rapamycin complex 1 (mTORC1) and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling, resulting in depression improvement (12).

Developing new drugs with the capability of producing rapid-onset and profound antidepressant effects is essential for patients with TRD. Evidence on the relationship between neurotransmitter glutamate and the development of depression makes researchers investigate alternative antidepressant therapies. The antidepressant effect of ketamine was first proposed by Berman et al., just over a decade ago. Since then, the effects of ketamine on MDD, TRD, bipolar depression, and shock therapy have been investigated (13, 14). The side effects of ketamine are low, and it si well tolerated by the patients (15).

However, the results of studies in this regard are uncertain and questionable. Therefore, considering the possibility of using ketamine therapeutic effect before implementing final invasive interventions such as ECT through simple and less invasive methods. The current study was performed to evaluate the effect of intravenous ketamine infusions on patients MDD.

Materials and methods

This hospital-based open-label prospective study was conducted from September 2017 to May 2019 at Comprehensive Psychiatric Center, Taft, Yazd, Iran. Written informed consent was obtained from all he patients participated in the study. Sociodemographic and clinical data of the patients were obtained. In addition, Hamilton Depression Rating Scale (HDRS) was usd to assess the patients' depression severity. HDRS is a multiple-item questionnaire, which is used to provide an indication of MDD and a guide to evaluate MDD recovery (16-18). This study aimed to determine the effectiveness of intravase (IV) ketamine in the management of MDD patients who were resistant to treatment and referred to Comprehensive Psychiatric Center in Yazd province.

Study design

This study was a pre-and post- intervention research.

Patient selection

From September 2017 to May 2019, all MDD patients who were resistant to treatment and referred to Comprehensive Psychiatric Center of Taft were included. In total, 18 patients with a diagnosis of MDD based on Diagnostic and Statistical Manual of Mental Disorders (DSM-5) were selected.

Inclusion criteria

-Diagnosis of MDD

-Willingness to participant in the study

-Aged between 18to 70 years

Exclusion criteria

-Negative history of physical and psychiatric comorbidities.

-Lack of willingness to participate.

-A significant and persistent drug-induced complication.

-Substance abuse.

-Pregnancy or lactation.

-History of other psychiatric comorbidity disorders.

Study procedure

After completing the written informed consent form by the patient or his/her caregiver, the study was initiated. HDRS was filled by a psychiatry resident using all available data from the patient report as well as information provided by a caregiver, pharmacy, and medical records. HDRS was completed for each patient before and 2.5 hours after ketamine prescription. The patients received intravenous ketamine (0.5 mg/kg) administered over 40 minutes. If the patients experienced systolic blood pressure (SBP) >161 or <89 mmHg, diastolic BP (DBP) > 110 or <40 mmHg, heart rate <40 or >130 beats/min, respiratory rate <10 or >30 per minute, O2Sat <90%, loss of consciousness, or irrational behavior, hallucination, or agitation, ketamine infusion was discontinued (19).

During the intravenous infusion of ketamine, patients' vital signs were monitored. HDRS was evaluated at baseline and 2.5 hour following the infusion. In case of responding to treatment, ≥50% reduction in HDRS score, the patients

 DOI: https://doi.org/10.18502/aptj.v1i2.8674

underwent re-infusion for further 5 sessions on the 3rd, 5th, 7th, 9th, and 11th day. After administering the last dose of ketamine, HDRS was completed for all the patients.

Statistical Analysis

The quantitative and qualitative variables were reported as mean ± standard deviation (SD) and number (frequency), respectively. Kolmogorov-Smirnov test was run to assay the normality of the data. The distributed quantitative variables were compared between groups by using the independent sample t-test. Moreover, paired T-test was used to compare changes of HDRS score over 2.5 hours and at the last infusion. Chi-square and Fisher's exact tests were used to compare qualitative variables. All the statistical analysis was conducted by Statistical package for social science (SPSS) version 23, and two-tailed P-values < 0.05 were considered statistically significant.

Results

A total of 18 patients were enrolled, among whom were 9 men (50%). The patients' mean (SD) age was 40.6 (11.4) years old. The mean (SD) HDRS score at the baseline was 22.1 (7.3). HDRS score of 13 patients (72%) reduced at least 50%, suggesting that they responded to the first dose of ketamine so ketamine treatment was continued for them. Six men and seven women responded to the first dose. No significant difference was observed between gender and response to treatment (p>0.05) (**Table 1**).

Table1. Details on patients' HRSD score at baseline, after 2.5 hour, and day 11th

Patient (No.)	Sex	Age (year)	HRSD score at the base	HRSD score after the first infusion	HRSD score after the last infusion
1	M	45	27	24	-
2	F	50	18	9	6
3	M	24	26	18	-
4	M	37	46	23	17
5	F	40	21	10	6
6	M	44	27	14	12
7	M	40	10	4	2
8	M	57	18	5	4
9	F	26	17	7	5
10	F	42	15	7	3
11	M	32	20	10	6
12	F	26	23	9	8
13	M	50	19	7	5
14	F	50	24	12	5
15	M	45	20	16	-
16	F	28	22	17	-
17	F	30	22	19	-
18	F	65	24	10	4
Meen (SD)	40.6	22.1 (7.3)	9.7 (4.8)	6.3 (4.0)	

			(11.4)	

No: Number; M: Male; F: Female; HDRS: the Hamilton depression rating scale; SD: standard deviation

A significant decrease was seen between the mean depression score before (21.6 ± 8.5) and 2.5 hours after the first injection (9.7 ± 4.8) in responded patients (p<0.001). In addition, a significant decrease was seen in all of 13 patients who continued ketamine until the 11th day (6.3 ± 4.0) (p<0.001). Details on the mean differences of HDRS score are shown in **Table 2**.

Table 2. Comparison of HDRS score means

Variable		Comparing	Between-time Difference (95% CI)	*P-value*
HDRS score, Mean	Before	After 2.5 hours	9.89	<0.001
		After the last infusion	15.78	<0.001

Discussion

This study was carried out to determine the effect of repeated ketamine infusion on MDD patients who were resistant to treatment. Previous findings suggested that ketamine injection was efficacious in reducing the severity of depression in patients with MDD. Due to the decrease in the average HDRS score and the absence of significant side effects, a combination of ketamine and conventional maintenance treatments can be offered as a new therapeutic protocol for TRD.

Szymkowicz et al., revealed that three patients with major depression responded to ketamine treatment and experienced no significant side effects following ketamine administration (20). In addition, a significant antidepressant effect of ketamine (24 hours after the first dose) was reported by Murrough et al (21). In another study, six patients with MDD received ketamine. Fifty percent of them experienced a significant improvement of depressive symptoms in the short and long term following ketamine infusion (22). A significant change in the symptoms of depression following ketamine infusion was also reported by Messer et al., using Beck Depression Inventory (BDI) (23).

No cognitive decline was seen in the current study as well as Paslakis et al. study (24). In a case study, depressive symptoms were assessed by HDRS and BDI and a significant clinical improvement in depressive symptoms was detected on the second day post ketamine administration. The improvement was reported 25 minutes after ketamine infusion; however, persistent antidepressant effects of ketamine were seen throughout the subsequent 7 days. In particular, a profound improvement of depressive symptoms was reported on the second day after the first infusion of ketamine, while the second infusion was less effective (25). In another case study, one patient did not respond to both intravenous and subanesthetic intravenous ketamine infusions, while the other patient complained about rapid antidepressant side effects on the first and third days. However, the side

 DOI: https://doi.org/10.18502/aptj.v1i2.8674

effects did not last up to the sixth day. Both patients experienced psychiatric side effects during administration (26). In line with these studies, our study confirmed the efficacy of ketamine in reducing depression using a larger sample. In the present study, 5 of 18 patients did not respond to ketamine as an antidepressant agent. Nevertheless, the significant effect of ketamine on the reduction of depression was observed and confirmed in the remaining 13 patients. In another study, a montgomery asberg depression rating scale (MADRS) was used and a significant improvement was achieved post ketamine therapy in patients with TRD (27). Based on the findings of the aforementioned studies and the present study, it seems that ketamine has a rapid and persistent antidepressant effect on patients with TRD. Similar to the current study, all other studies in this field confirmed the rapid and persistent antidepressant effects of ketamine on TRD (6, 15, 21-23, 26, 28-31). Therefore, it can be concluded that ketamine can be a new and promising pharmacological option for the treatment of major depression and TRD in comparison with current antidepressants delaying therapeutic effects and requiring several weeks to exert their effects. Rapid improvement in depression symptoms, in most patients after the first infusion, was the most benefit of ketamine treatment compared with previous anti-depressants (32). We observed a significant decrease in the mean depression scores only 2.5 hours following the first infusion of ketamine.

In a double-blind randomized placebo-controlled trial, 64% of patients responded to ketamine treatment (10). Similarly, 23.27% of our patients responded to treatment, which confirmed the findings reported by Murrough et al. Therefore, the efficacy of ketamine in depression attenuation scores in our study could be due to the proposed mechanism.

The ketamine dosage in two studies was 0.5 mg/kg. However, the duration of patients' follow-up after the infusion was different. In a clinical controlled trial study, the follow-up lasted up to two months after the last infusion (33). One of the differences between our study and others was the percentage of reduction in depression scores. In most studies, the scores were less than 50; whereas, in this study, the percentage of reduction in depression scores following ketamine administration was greater than 50. This difference can be due to this fact that other studies used a single infusion of ketamine but we used repeated infusions of ketamine. However, we discovered that the rate of depression score reduction was less than 50% in our study, which was consistent with similar studies. In an 8-week trial, memantine was not effective in treating MDD at doses of 5-20 mg/day (34). The oral administration of this drug was less efficient than a single dose of ketamine. The therapeutic outcomes of our study after the first infusion were better than those of that study. Therefore, it seems that the use of antagonists with a high affinity for NMDA receptors to produce an antidepressant effect is needed.

A placebo-controlled double-blinded trial was performed to evaluate the effect of ketamine on seven patients with TRD. Seventy-two hours follow-up revealed a significant decrease in the patients' depression scores (4), which was

consistent with our findings. Zarate et al., also investigated the efficacy of ketamine infusion in reducing TRD. They found that 29% of patients did not respond to this treatment. However, they observed a significant decrease in the depression scores after ten minutes following ketamine administration in other patients. This statistically significant decrease in depression scores was also apparent one-week post-infusion (6). In our study, 38.4% of patients did not respond to ketamine treatment, which was higher than the percentage reported by Zarate et al.

In a review study, the effects of ketamine and other glutamate receptor regulators were evaluated. A significant short-term effect of ketamine was revealed in comparison with other similar compounds. However, a significant difference was not reported in the long-term follow-up (35). In line with the aforementioned study, we showed that ketamine significantly reduced depression scores 2.5 hours after infusion. In their study, Shirawi et al., examined the efficacy of oral ketamine in reducing treatment-resistant depression in 22 patients. They discovered that 18% of patients had a 50% reduction in BDI score , 14% experienced a minor reduction in depression symptoms, 23% experienced more severe symptoms of depression, and 45% did not respond to ketamine treatment (36). In our study, intravenous administration of ketamine was used and better therapeutical outcomes were achieved. Diamond et al., evaluated the effect of ketamine infusion on the treatment of 28 patients with TRD, and showed that only 11% of the patients responded to treatment within six hours after the infusion (37). Consequently, our study revealed a better response to ketamine treatment. Theoretically and according to practical results, it seems that ketamine could play an important role in treating TRD.

Conclusion

Considering the rapid and profound efficacy of ketamine in reducing the mean of depression scores and the absence of significant complications, a combination therapy consisting of ketamine and other conventional therapies can be applied as a new therapeutic protocol to reduce the symptoms of TRD.

List of abbreviations

MDD: major depression disorder/ QOL: quality of life/ ECT: Electroconvulsive therapy/ DSM IV: diagnostic and Statistical Manual of Mental Disorders 4th edition/ HDRS: Hamilton Depression Rating Scale/ mg/kg: milligram per kilogram/ NMDA: N-methyl d-aspartate glutamate/ SPSS: Statistical package for social science/ BDI: Beck Depression Inventory/ MADRS: Montgomery Asberg Depression Rating Scale/ BDS: Beck Depression score/ PFC: Prefrontal cortex.

Ethical Code

This study received the Ethics ID (IR.SSU.MEDICINE.REC.1396.31) by the Ethics Committee of Yazd University of Medical Sciences.

Conflict of interests: The authors declare that there is no conflict of interest.

 DOI: https://doi.org/10.18502/aptj.v1i2.8674

Funding: The manuscript was financially supported by a grant from the Research and Technology Department of Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

Acknowledgments: This article was derived from the thesis "Ketamine as a new treatment protocol for treatment-resistant major depressive disorder" supervised and submitted by Professor Reza Bidaki, the Faculty of Medicine of Shahid Sadoughi University of Medical Sciences, Yazd, Iran, in partial fulfillment of the requirements for the Degree of general practitioner (GP) of Atena FallahTafti.

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 DOI: https://doi.org/10.18502/aptj.v1i2.8674