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Original Article

The Effect of Intravenous Ketamine on Suicidal Ideation in Depressed Patients: A Randomized Clinical Trial

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Abstract

Background: Major depressive disorder (MDD) generally occurs together with depression in patients with no history of manic, mixed, or hypomanic episodes. The suicidal ideation in MDD patients is very common and can potentially be considered an emergency circumstance in many cases. Among the developed drugs and medicines, ketamine (KET) is a potential option to treat patients with MDD. This study aims at investigating the effect of KET on the treatment of suicidal ideation and the reduction of the intensity of symptoms in patients suffering from MDD.

Materials and Methods: This randomized double-blind clinical trial was performed on 30 patients who suffered from MDD and had suicidal ideation at Ibn Sina Hospital, Bandar Abbas, Iran, during 2016-2017. The patients were divided into two groups: the KET group which received 0.5 mg/kg of intravenous (IV) KET diluted in 500 mL of normal saline over 30 minutes and the control group which received 500 mL of normal saline without KET over 30 minutes.

Results: According to the statistical analysis, 24 hours after the intervention, suicidal ideation score reached 2.53 and 20.6 in the KET and control groups, respectively. In fact, KET caused a significant reduction in the score of the suicidal ideation (SSI) (SSI < 4) in comparison with the control group ($P < 0.001$).

Conclusion: It was observed that KET can play a key role in the treatment of depression disorders, especially severe and life-threatening forms that require immediate intervention, such as the use of electroconvulsive therapy.

Keywords: Depressive disorder, Ketamine, Suicidal ideation, Injection, Double-blind study

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Introduction

Depression is a serious common disease characterized by mood disorders, with an approximate prevalence of 15%-25%. In the past, depression was considered a short-term issue, but today it is a disease with a high recurrence rate in many patients. The probability of the second occurrence of major depression after the first one is about 50%, and this probability increases from 80% to about 90% in the next episodes (1).

Major depressive disorder (MDD) occurs during the periods of depression with no recorded history of mixed or hypomanic episodes (2). This disorder can lead to severe functional disorder, disability, and relapse and sometimes can cause a chronic disorder, with a 15% risk of suicide (3). The prevalence of suicidal attempts and self-harm in this disorder is relatively high, reaching 47% in patients who refer to emergency departments of hospitals. Interestingly, this number increased from 0.8 to 1.5 per 1000 people in 2012 in the United States.

Suicidal ideation in MDD patients is an emergency and serious clinical condition that must be carefully considered and immediately treated (4, 5). The importance of this issue has been reflected in a recent study conducted on the effect of ketamine (KET) on suicidal ideation in patients with MDD. In this study, 74 cases of patients had a very short-term decision-making ability. Moreover, recognizing and treating the risk factors were found to be the key factors in preventing suicide (6). Because most of the patients were young and elderly (but in their active years of life), the rate of mortality was high (7). Over the past five decades, the drugs and medicines developed to cure depression required a long time to be effective (minimum of 2 to 4 weeks) and for most of the patients, it was not possible to tolerate the symptom of these drugs. Considering the ineffectiveness of the treatment with those drugs, further

research was required to develop some new alternatives or treatment procedures (8). Among the developed drugs and medicines, KET is an option which can be used to treat patients with MDD and may have further applications in some cases compared to electroconvulsive therapy (8). KET is an intravenous anesthetic that can create a condition known as dissociative anesthesia with the characteristics of catatonia, amnesia, and analgesia without loss of consciousness (9,10).

Pharmacologically speaking, KET is an N-methyl-d-aspartate (NMDA) receptor antagonist. It is widely used for the induction of anesthesia in the USA. At subanesthetic doses, KET was found to increase glutamate levels (3). This is because glutamate regulation and expression are altered in patients with MDD. Studies have also identified an abnormal glutamate–glutamine–gamma-aminobutyric acid cycle in patients with suicidality (11). Furthermore, KET has also been shown to affect nicotinic and opioid receptors (11). Despite the continuous research to find a suitable alternative medicine and identify the full mechanism of action of KET, no other class of antidepressant medication has been found yet. It is worth saying that although the properties of KET as a rapid-acting anti-suicidal and antidepressant medication are not fully understood, it could still be a prototype for the development of other medication(s) that retain the mechanism of action with more favorable qualities and fewer adverse effects. However, studies on the effect of KET revealed some promising results in the treatment of depression.

In the present work, an effort was made to assess the effect of KET on the treatment of the depression, thereby planning to investigate the effect of KET on suicidal ideation and reduction of the severity of symptoms in patients with MDD.

Materials and Methods

This randomized double-blind clinical trial (identifier: IRCT2015030921397N1; https://www.irct.ir/trial/18764) was performed on 30 patients who suffered from MDD and had suicidal ideation at Ibn Sina Hospital, Bandar Abbas, Iran, in 2016-2017. The patients suffered from MDD (based on DSM –IV criteria), had suicidal ideation, and also were hospitalized in Ibn Sina hospital. Patients included in the study did not receive any antidepressant drug in the past month and had major depression based on the DSM-IV criteria. They were above 18 years old with suicidal ideation or suicide attempts before being admitted to the hospital. Patients with bipolar disorder (type 1 and type 2), cyclothymia, psychosis (referred to as "psychotic disorders"), obsessive–compulsive personality disorder, schizoaffective disorder, alcoholism, pregnancy, breastfeeding, chronic medical diseases, and illnesses causing depression in the patients were excluded from the study.

An independent researcher performed permuted block randomization with a fixed block size of 4 and 1:1 allocation using a computer-generated random allocation with sequentially numbered, opaque sealed envelopes.

The KET group received 0.5 mg/kg intravenous (IV) KET diluted in 500 mL of normal saline over 30 minutes. The control group received 500 mL of normal saline without KET over 30 minutes. The patients were interviewed by a psychiatrist and assessed using Beck Depression Inventory (BDI) and Beck Scale for Suicidal Ideation (BSSI). All patients were monitored for one hour in a quiet room at Ibn Sina hospital. Patients were examined before receiving the drug and re-examined 2, 24, and 72 hours after receiving the drug. Then, the appropriate treatment protocol for patients (medication or electroconvulsive therapy) was performed. It was found that the scale for suicidal ideation (SSI) ≥ 4 is a meaningful suicidal ideation while the SSI < 4 is a meaningless suicidal ideation.

All statistical analyses were performed using SPSS version 26.0 (IBM Corporation, Chicago, IL). For describing qualitative data, frequency (n) and percentage (%) and for quantitative data, mean and standard deviation (SD) were applied. The Shapiro-Wilks test was used to test the normality of BDI and BSSI scores. Related-samples Friedman's two-way ANOVA by rank test was applied to compare BDI and BSSI scores in the control and KET groups. In addition, using GraphPad Prism version 9, we compared BDI and BSSI in a graph. Additionally, Mann-Whitney test was applied to compare the mean difference in vital signs before and after receiving the treatment. A *P* value of less than 0.05 was considered statistically significant.

Results

The mean age of the patients in the KET and control groups was 28.66 ± 12.33 and 28.33 ± 11.31 years, respectively ($P = 0.939$). In the KET group, 10 patients (66.7%) and in the control group, 9 patients (60%) were female ($P = 0.701$). Ten patients (33.3%) were married, 15 patients (50%) were single, and 5 patients (16.7%) were divorced (Table 1).

Table 2 shows the BDI scores at various time intervals. At the beginning of the study, before the intervention, BDI scores in the two groups were not significantly

Table 1. Characteristics of Patients in the Ketamine and Control Groups

Characteristics		Ketamine (n = 15)	Control (n = 15)	*P* Value
Gender, n (%)	Male	5 (33.3)	6 (40)	0.764
	Female	10 (66.7)	9 (60)	
Marital status, n (%)	Married	4 (26.6)	6 (40)	0.083
	Single	11 (73.3)	9 (60)	
Age (year), mean ± SD		28.67 ± 12.24	28.33 ± 11.32	0.939

n = the number of patients.

different and both groups were severely depressed (score = 30 to 64). Two hours after the intervention, KET did not significantly influence the severity of depression in comparison with the control group and despite the treatment, both groups of patients had severe depression (score = 30 to 64).

Additionally, 24 hours after the intervention, the mean depression score in patients who received KET was 23.80 ± 12.23 and in the control group, it was 35.80 ± 7.17, with a significant difference between the two groups ($P = 0.002$). Since the mean depression score reduced by 50% in comparison with the baseline value (from 50.47 to 23.8), it can be stated that KET had a significant effect on the severity of depression after 2 hours. This significant difference was also observed 72 hours after the injection ($P < 0.001$). Figure 1 presents the rate of depression in the studied patients at different time points. As can be seen, the highest reduction in the depression score was seen in the KET group (2 hours after the injection) and the effect continued up to 72 hours. In general, the results of the Friedman test showed that with the increase of the intervention time, the depression score significantly decreased ($P < 0.001$).

Table 3 shows the results of a rough comparison of the mean suicidal ideation scores at various times in both groups. The results of the Mann-Whitney test showed that the mean suicidal ideation score at the beginning of the study (before intervention) was 17.53 ± 10.17 in the KET group and 19.93 ± 6.08 in the control group, with no significant differences between the groups ($P = 0.653$). Considering the fact that the score of suicidal ideation in both groups was higher than 4, the severity of suicidal ideation in both groups was significant (SSI ≥ 4). After 2 hours, however, the KET group showed a significant reduction in suicidal ideation ($P < 0.001$). In other words, suicidal ideation was significant in the control group (SSI > 4); however, it was not significant (SSI < 4) in the KET group. This effect of KET continued and was identifiable 24 and 72 hours after the injection. In general, the results of the Friedman test showed that with the increase of the intervention time, the suicidal ideation score significantly decreased ($P < 0.001$).

Figure 2 presents the rate of suicidal thoughts at different time points in the KET and the control groups. As can be seen, the highest reduction in suicidal ideation was observed 2 hours after the injection of KET.

According to the results of Mann-Whitney test presented in Table 4, there was no significant difference between the two groups in terms of the vital signs of the patients such as blood pressure, respiratory rate, heart rate, and arterial oxygen saturation before and also after receiving the treatment ($P > 0.05$). It was indicated that the intervention had no effects on the vital signs of the patients.

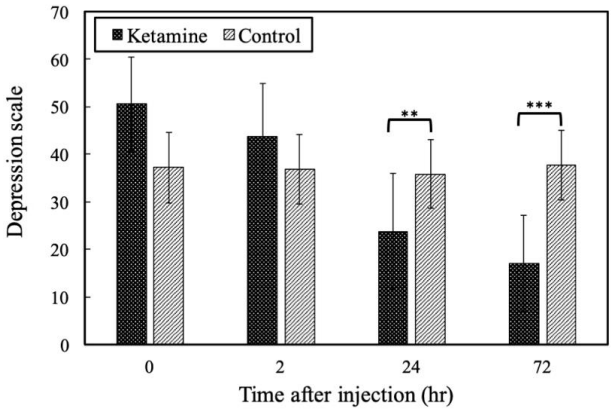

Figure 1. Assessment of Depression at Different Time Points after the Injection in the Ketamine and Control Groups (** and *** are *P* values of 0.003 and 0.001, respectively).

Table 2. Comparison Between the Ketamine and Control Groups in Terms of Depression at Four Time Points after Injection

Group		Time After Injection (h) Mean ± SD				Related-Samples Friedman's Two-Way ANOVA by Rank	
		0	2	24	72	Test Statistics	*P* Value
Ketamine		37.479.97	31.6711.27	23.8012.23	17.0710.10	42.125	< 0.001
Control		37.137.43	36.807.22	35.807.17	37.737.30	9.209	0.029
Mann-Whitney U	Test statistics	103	139.5	184.5	214.0		
	P value	0.713	0.267	0.002	< 0.001		

SD: Standard deviation.

Table 3. The Comparison of between the Ketamine and Control Groups in Terms of Suicidal Ideation at Four Time Points after Injection

Group		Time After Injection (h) Mean ± SD				Related-Samples Friedman's Two-Way ANOVA by Rank	
		0	2	24	72	Test Statistics	*P* Value
Ketamine		17.5310.17	6.278.72	2.534.92	2.335.30	24.29	< 0.001
Control		19.936.08	19.805.37	20.605.35	21.005.02	6.95	0.073
Mann-Whitney U test	Test statistics	124	194.5	219.0	222.0		
	P value	0.653	< 0.001	< 0.001	< 0.001		

SD: standard deviation

Table 4. Comparison of Mean Difference of the Vital Signs in the Ketamine and Control Groups

Variable	Group	Mean ± SD	*P* Value
Heart rate	Ketamine	-3.33 ± 8.15	0.803
	Control	-2.67 ± 6.20	
Respiratory rate	Ketamine	-2.20 ± 1.52	0.139
	Control	-1.40 ± 1.35	
Systolic blood pressure	Ketamine	-4.60 ± 9.40	0.821
	Control	-3.93 ± 6.28	
Diastolic blood pressure	Ketamine	-4.00 ± 7.84	0.868
	Control	-3.47 ± 9.49	
Arterial oxygen saturation	Ketamine	-0.07 ± 0.70	0.631
	Control	0.07 ± 0.79	

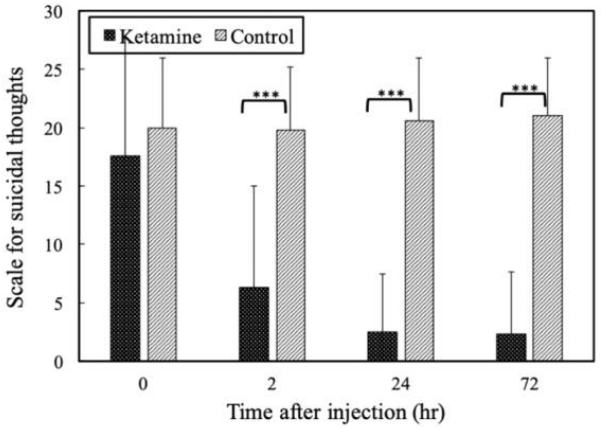

Figure 2. Assessment of Suicidal Ideation at Different Time Points after the Injection in the KET and Control Groups (*** is *P*-value of 0.002).

Discussion

This study showed that the infusion of low-dose KET can reduce the symptoms of depression in terms of suicidal ideation 24 hours after the infusion. Although KET is a high-affinity NMDA receptor antagonist, it has less tendency to attach to the μ-opioid receptor and also has a weak antagonistic activity on dopamine transmission. Likewise, NMDA receptors may have a secondary effect on mood by influencing the monoamine and opioid systems (11). Hence, in the present study, an effort was made to identify a suitable treatment for depression by reducing the rate of suicidal attempts in MDD patients. In some of the previous studies conducted by Reinstatler and Youssef (12), Liebrenz et al (13), Kollmar et al (14), Stefanczyk-Sapieha et al (15), Machado-Vieira et al (16), Phelps et al (17), Ibrahim et al (18), Salvadore et al (19), Mathew et al (20), and Aan het Rot et al (21), a dose of 0.5 mg/kg over 40-60 minutes was applied to the patients; however, Correll and Futter (22) used an intravenous dose of 0.27-0.3 mg/kg/h for 5 days. Goforth and Holsinger (23) used 1.5 mg/kg intramuscular injection. Glue et al (24) also administered an intramuscular dose of 0.5-1 mg/kg. Considering the aforementioned studies, a dose of 0.5 mg/kg of KET over 30 minutes was selected and used in the present study. It is worth saying that a single dose of KET had no effect on depression until 2 hours after infusion but it decreased the mean score of BDI 24 and 72 hours after the injection. In a study conducted by Aen het Rot et al, (21), a continuous infusion of KET was administered for 5 days. The response rate of KET varied from 25% to 85% 24 hours after the infusion and varied from 14% to 70% 72 hours after the infusion. Zarate et al (6) showed that the antidepressant efficacy of KET in bipolar depression was observed from 40 minutes to day 2. Additionally, based on the BDI scale, it continued up to 10 days after injection. Berman et al (25) demonstrated that a significant reduction in the severity of depression can occur until 72 hours after the start of KET infusion (in comparison with the placebo). Kheirkhah et al (7) showed that the mean depression scores decreased significantly after the injection of KET in comparison with the baseline score. In fact, a single dose of KET injection decreased the scores by 30% and 45% after 2 and 7 days, respectively. Moreover, 2 and 7 days after the drug injection, 20% and 40% of the patients responded appropriately to the treatment with KET, respectively. Comparing the current study with those already published in the literature, we can conclude that the effect of KET on depression begins 24 hours after the injection and continues for at least 72 hours after the injection. Besides, the antidepressant effect of KET is different from patient to patient.

It is worth saying that the half-life of KET is about 2 hours and that of norketamine is 5 hours, and the secondary metabolites of KET are 7-10 times less effective than KET. However, since KET not only is a strong NMDA receptor antagonist but also has some affinity to bind to the μ-opioid receptors and a relatively weak antagonistic activity on the dopaminergic system. It can be concluded that KET has the potential to affect mood through its secondary effects on the monoaminergic and opioid systems. Recent studies have demonstrated that KET has a rapid effect on rapamycin signaling pathway by increasing the synaptic protein signal and also enhancing the number and performance of the new synapses in the frontal cortex of mice. Hence, KET can decrease the effect of stressor-induced decreased synapsis in mammalians (26).

In our study, a significant decrease in the suicidal ideation score (SSI < 4) 24 and 72 hours after the injection was observed; however, the first sign of the effectiveness of the drug was observed in the first two hours of the infusion. Reinstatler and Youssef (12) also showed that the rapid decline in suicidal ideation began 40 minutes after KET injection and lasted for an average of 3 days. In another study performed by Zigman and Blier (27), the rate of suicidal ideation after 40 minutes decreased from 9/10 to 0/10 (after 40 minutes) and continued up to 8 days. These results were also confirmed by a study conducted by Zarate et al (4), in which there was a significant reduction in

suicidal ideation in patients. This effect started 40 minutes after the injection and continued until 3 days after the injection based on the Montgomery–Asberg Depression Rating Scale (MADRS) scale, indicating that the SSI score in these patients decreased from 3.9 to 0.6 in 40 minutes. The study conducted by DiazGranados et al (11) showed that the SSI score significantly reduced in 40 minutes. These studies suggest that the onset of KET effect on suicidal ideation is 40 minutes after the infusion.

In another study by Kudoh et al (28), 70 patients with major depression were studied for medicines suitable for anesthesia. The first group of patients received propofol, fentanyl, and KET and the second group received propofol and fentanyl. The results showed that low doses of KET used in the first group reduced the severity of depression in postoperative patients. This finding was confirmed by the results of the previous studies, showing that KET can produce a significant antidepressant effect, which is also justified by the pharmacological properties of KET. It is worth noting that MK-801, which is a non-competitive NMDA antagonist, and Ap7, which is a competitive NMDA antagonist, showed antidepressant-like activity. MK-801 has been found to have similar anti-depressant effects without producing hypotonic effects as KET does (28).

In a study conducted by Stone et al (29), KET was reported to induce perceptual and behavioral responses similar to the positive and negative psychotic symptoms of schizophrenia. It was found that the occurrence of the negative symptoms of using KET is largely due to the direct antagonistic effect of KET on the NMDA receptor, while the positive symptoms were possibly due to another unknown biochemical pathway (11).

In the present study, the effects observed with a single dose of KET injection, as a strong NMDA receptor antagonist, were not observed with other weak or moderate antagonists of NMDA (e.g., oral memantine), as reported in the literature (7). This further suggests that there may be a need to develop new drugs with high-affinity antagonistic effects against the NMDA receptor. It is noteworthy that pharmacokinetics plays a key role here, as the injection form of the drug might be more effective than the oral form. From a pharmacologic point of view, KET, unlike memantine, has a higher affinity for NMDA and its inhibitory effect is more gradual. KET is a full antagonist of NMDA, while memantine is a partial antagonist. Furthermore, in addition to NMDA, KET influenced the AMPA and this could also contribute to the anti-depressant effects observed with KET (7).

Conclusion

In conclusion, considering the ease of administration of KET, the fast onset of effects, and negligible side effects, it is recommended that combination therapy, including KET in combination with conventional treatments be considered as a new, effective, and beneficial therapeutic protocol for improving the symptoms associated with severe depression. To investigate this hypothesis, further studies with larger groups and longer follow-ups compared with placebo group are required. It is also suggested that in future studies, different doses of KET and different prescribing methods should be assessed.

The current study lacks the determination of the exact onset and duration of the effect of KET. Therefore, the accurate evaluation of these properties of KET should be experimentally conducted. Likewise, a proper comparison will be conducted on various depression scales to identify a suitable benchmark for decision making regarding the selection of drugs.

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Authors' Contribution

Study conceptualization and experiment design: FM, AM, SHN, and SHS; data handling: FM and HMZ; data analysis: SHT and SHN; draft preparation: AM and SHS; supervision: FM and AM; statistical analysis: SHT; provision of study materials and equipment: HMZ and SHS; study supervision: SHS and AM.

Competing Interests

The authors declare that they have no conflict of interest.

Ethical Approval

This study was approved by the Ethics Committee of Hormozgan University of Medical Science (IR.HUMS.REC.1393-11-7/4) and confidentiality of the data was ensured.

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Informed Consent

Informed consent was obtained from all patients.

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