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Original Article

A Comparison between Single and Double-Dose Intravenous Ketamine Administration in Bipolar Mood Disorder: A Double-Blind Controlled Clinical Trial

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Abstract

Objective: As glutamatergic system dysfunction is involved in bipolar depression pathophysiology, the glutamate receptor modulators such as Ketamine have been applied as complementary medication for mood stabilizers. While the treatment is currently just the intravenous injection of a single dose, and there is no robust conclusion on Ketamine effectiveness or its side effects in bipolar patients, this study aimed to consider single- and double-dose intravenous injections of Ketamine in bipolar patients compared to the placebo.

Method: In a randomized, double-blind controlled clinical trial, 30 patients diagnosed with bipolar I and II disorders according to DSM-IV-TR (SCID-I) were randomly divided into three groups: the first group received an intravenous injection of Ketamine (0.5 mg/kg) and placebo with a three-day interval, the second group received two doses of Ketamine (0.5 mg/kg) in the same interval, and the third group received two placebo injections. Patients were assessed for depression, anxiety, and mania at various time points, including before the injection, 60 minutes after the injection, on the first, third, fifth, seventh, and 14th day, as well as at the end of the first month using the Hamilton Depression Rating Scale, Beck Anxiety Inventory, and Young Mania Scale, respectively. Data were analyzed using ANOVA and Repeated measure tests.

Results: The mean age of patients was 36.8 ± 7.9 years, with 18 females (60%) and 12 (40%) males. Depression and anxiety showed significant differences in both the single- and double-dose Ketamine groups over time ($P < 0.01$). Moreover, mania displayed significant changes during the study time in the single- and double-dose Ketamine groups, as well as the in the control group. However, during the study time, there were no significant differences observed in depression, anxiety, and mania among the three groups ($P = 0.198$, $P = 0.416$, and $P = 0.540$, respectively). Patients did not indicate any side effects during the study.

Conclusion: Intravenous Ketamine administration may relieve depressive manifestations in bipolar patients. The findings suggest that a double dose of Ketamine does not lead to greater improvement than a single dose.

Key words: *Bipolar Disorder; Depressive Disorder; Ketamine; Randomized Controlled Trial*

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Bipolar I disorder has been identified as one of the most severe psychiatric illnesses, ranking among the top ten debilitating diseases characterized by episodes of depression and elevated mood referred to as mania or hypomania, based on its severity (1, 2). Many patients during the major part of the sickness period suffer from symptoms of depression, which make this illness underdiagnosed (3). Unfortunately, a lack of response to treatment procedures in the depression phase would complicate the condition. Failure to relieve the symptoms of depression can lead to a more significant disability in patients and affect their lives (4). Therefore, research on effective treatments for depressive symptoms in bipolar patients has to be continued (5).

Recent evidence has introduced glutamate and N-methyl aspartate (NMDA) receptors as involved factors in bipolar disorder pathogenesis (6). Preliminary studies on patients with mood disorders have shown changes in the amount of glutamate in both the cerebrospinal fluid and serum. Although the stimulatory effects of glutamate have been proven, excess levels could be neurotoxic. The glutamatergic hypothesis proposes that excess glutamate accompanied by hypercortisolemia associated with abnormalities such as impaired cognitive functions and atrophic changes, which have been reported in chronic and recurrent depressive patients (7). The glutamate dysfunction in patients with mood disorders is complex and involves a decrease in levels in some areas, such as the occipital, while an increase is observed in other brain regions, such as the cingulate cortex (8). Previous studies have considered some medications like L-Carnosine and Palmitoylethanolamide in combination with citalopram to improve the symptoms of the disease (9, 10).

Most patients who experience a depressive phase characterized by symptoms such as disinterest and lack of pleasure, changes in appetite and sleep patterns, agitation or slowed mental or physical movement, loss of energy, feelings of worthlessness, and eventually recurrent thoughts about death and suicide (11-13), need immediate attention and treatment (14). However, over the past half-century, the delayed pharmacological effects of antidepressants, with a remarkable lag in their beginning of action typically taking about two to four weeks, resulted in the lack of compliance and an intolerable condition for patients during this period, thus encouraging researchers to seek other faster treatments (15). Moreover, periods of relapse occurring in bipolar depression are even more frequent compared to major depression, necessitating prompt attention for these patients (16-19), which makes Ketamine a strikingly useful drug that may improve depression faster than any other therapy (20, 21). Ketamine is a potent antagonist for NMDA receptors and has been investigated for managing major depressive and bipolar disorders, indicating evidence of its rapid efficacy in relieving depressive symptoms (22). Research-based evidence suggests that Ketamine also inhibits GABAergic neurons, which leads to increased presynaptic glutamate levels. Furthermore, it is believed that Ketamine could increase AMPA receptors function and decrease NMDA activity. The high ratio of AMPA to NMDA activation may also be involved in Ketamine's antidepressant properties (23, 24), resulting in a faster response to medication and improved acceptance of treatments by patients. Various investigations have shown rapid and significant responses within the first hours after Ketamine injection (15, 25).

In many of the previous studies, only one injection of Ketamine has been evaluated and the follow-up period in these investigations has been limited to two weeks (26), and the duration of the therapeutic effects of Ketamine injection for a long time has not been measured. It must also be clarified if this treatment can put the patients in the manic phase (6). Therefore, a randomized, double-blind, placebo-controlled trial was conducted to address these challenges and aimed to compare single- and double-dose intravenous Ketamine administrations in bipolar-depressed patients for one month.

Materials and Methods

Study Population

The sampling method used in this study was non-probabilistic. Patients diagnosed with bipolar disorder (either type I or II) and depressive episodes, aged between 18 and 60 years, were selected from either outpatients or those hospitalized in Ibn-E-Sina Hospital. A structured interview based on DSM-IV-TR (SCID-I) was performed by a psychiatrist with both the patients and their families to confirm the diagnosis.

Inclusion and Exclusion Criteria

In the past two weeks, patients who had not experienced a significant change in their medication regimen (such as an increase in the dose of current medications to 1.5 times the previous dose or starting a new mood stabilizer) were enrolled in the study. For a history of substance use, patients without a positive history of substance use and dependence in the past month were selected.

Patients with severe physical illnesses, especially hypertension, were not included in the study. Additional tests were performed to rule out physical illnesses after considering the medical history, physical examination, electrocardiogram, as well as in cases where there was suspicion of such illnesses. Patients with active psychotic and PTSD symptoms were not included in the study as Ketamine has demonstrated to exacerbate these symptoms. In case of any side effects, such as hypertension, the patient was excluded from the study. Patients with a mixed episode based on DSM-IV criteria were excluded from the study as well as those with severe depression (Hamilton score above 23) or severe suicidal ideation and a high risk of suicide because it is not permissible to delay treatment in these patients. For

patients in the first week of enrollment, there was no significant change in medication regimen (such as initiation of a new mood stabilizer, antidepressant, atypical antipsychotic, and an increase of more than 1.5 times of the mood stabilizer), and patients who required any immediate intervention or immediate change of medications were excluded from the study.

Study Procedure

Patients were randomly divided into three groups: Group 1 received one dose of Ketamine and one placebo injected three days apart; Group 2 received two doses of Ketamine injected three days apart, and Group 3 received two placebo injections. Patients were assigned to groups based on a table of random numbers by an anesthesiologist (coworker); neither the evaluator nor the patients knew the treatment group. The Ketamine group received an intravenous injection at 0.5 mg/kg body weight, while vital signs and pulse oximetry were monitored. Patients were monitored until full consciousness, and their health was confirmed by physical and mental examination before discharge. Those in the placebo group received 0.9% saline injection. The injection was given by an anesthesiologist technician under the supervision of a psychiatrist and an anesthesiologist.

Patients were evaluated at 60 minutes after injection and on days 1, 3, 5, 7, 14, and 30 after injection using the Hamilton Depression Inventory, Beck Anxiety Test, and Young Mania Scale (to measure a sudden change in patient status to mania). These assessments were conducted on different days by a trained psychologist, supervised by a psychiatric assistant, who was unaware of the patients' group. Moreover, the statistician was blinded to the treatment group for each patient.

Instruments

Structured Clinical Interview for Axis I Disorders in DSM-IV (SCID-I):

One of the most comprehensive structured interviews available is a new, wide-ranging tool closely linked to the DSM-IV decision formats for psychiatric diagnosis. This tool has good validity and reliability for diagnosing mental disorders. The kappa coefficient of 0.60 has been reported as the reliability coefficient between the evaluators for SCID. Sharifi *et al*. translated it into Persian with an accurate intercultural methodology based on the route suggested by the World Health Organization and then validated it in a large study and showed the reliability and validity of its feasibility (27).

Hamilton Depression Rating Scale:

This test measures depression severity and has 17 symptoms of depression that are scored in a range of 3 or 5 degrees. There are eight symptoms related to physical complaints, five symptoms related to behavioral problems, two to cognitive complaints, and finally, two to changes in patients' emotions. The reliability of the test has been reported to be 0.89 in the Iranian population. The reliability of the Iranian version was 0.89 (28).

Beck Anxiety Inventory (BAI):

This is a self-report measure of anxiety severity in adolescents and adults. Its internal consistency coefficient is 0.92. Its validity also varies by 0.75 with a retest method, and its correlation varies from 0.30 to 0.76. A validity coefficient of about 0.72, a one-month test-retest coefficient of 0.83, and Cronbach's alpha of 0.92 have been reported in the Iranian population (29).

Young Mania Scale:

It consists of 11 items completed according to the mental report of clinical condition in the past 48 hours, including increased mood, increased motor activity and energy, sexual desire, sleep, irritability, amount of speech, language-thinking disorder, content, destructive and aggressive behavior, appearance, and insight. Each item is graded from zero to 4 and some from zero to 8, with a maximum score of 50. The concurrent validity of the Yang scale with the Comprehensive International Diagnostic Questionnaire was 0.87. Based on the results of the differentiation study, a cut-off point of 17.14 and a sensitivity of 98.4% have been reported (30).

Statistical Analysis

Depending on the assessment of the normality test, the normal and non-normal continuous variables were examined using the ANOVA and Kruskal-Wallis tests, respectively, between the three groups. The categorical variables were analyzed using the chi-square or Fisher's exact tests. The general linear model for repeated measures, followed by the Bonferroni post hoc test, was used to compare groups during the study. Data were analyzed using SPSS v16 (IBM, USA), and a P-value less than 0.05 was considered significant.

Ethics

The study was approved by the Ethics Committee of Mashhad University of Medical Sciences under the reference number 1400/118584. All subjects were native Iranians, and the informed consent form was signed by patients and their guardians. The study was conducted under the latest revision of the Declaration of Helsinki. The clinical trial code was IRCT20101130005280N58.

Results

Demographic Characteristic

In this study, 30 patients were enrolled (Figure 1), including 18 females (60%) and 12 males (40%) with a mean age of 36.87 ± 7.98 years. And duration of disease of 19.58 ± 1.81.

As shown in Table 1, the distribution of sex, marital status, education and occupation did not show a significant difference among the three groups (P = 0.659). The mean age of the participants was similar between groups -35.10 ± 5.80, 35.50 ± 9.85, and 40.00 ±7.62 in the control, one-dose, and two-dose Ketamine groups, respectively (P = 0.323). Moreover, there was no significant difference in duration of disease between groups.

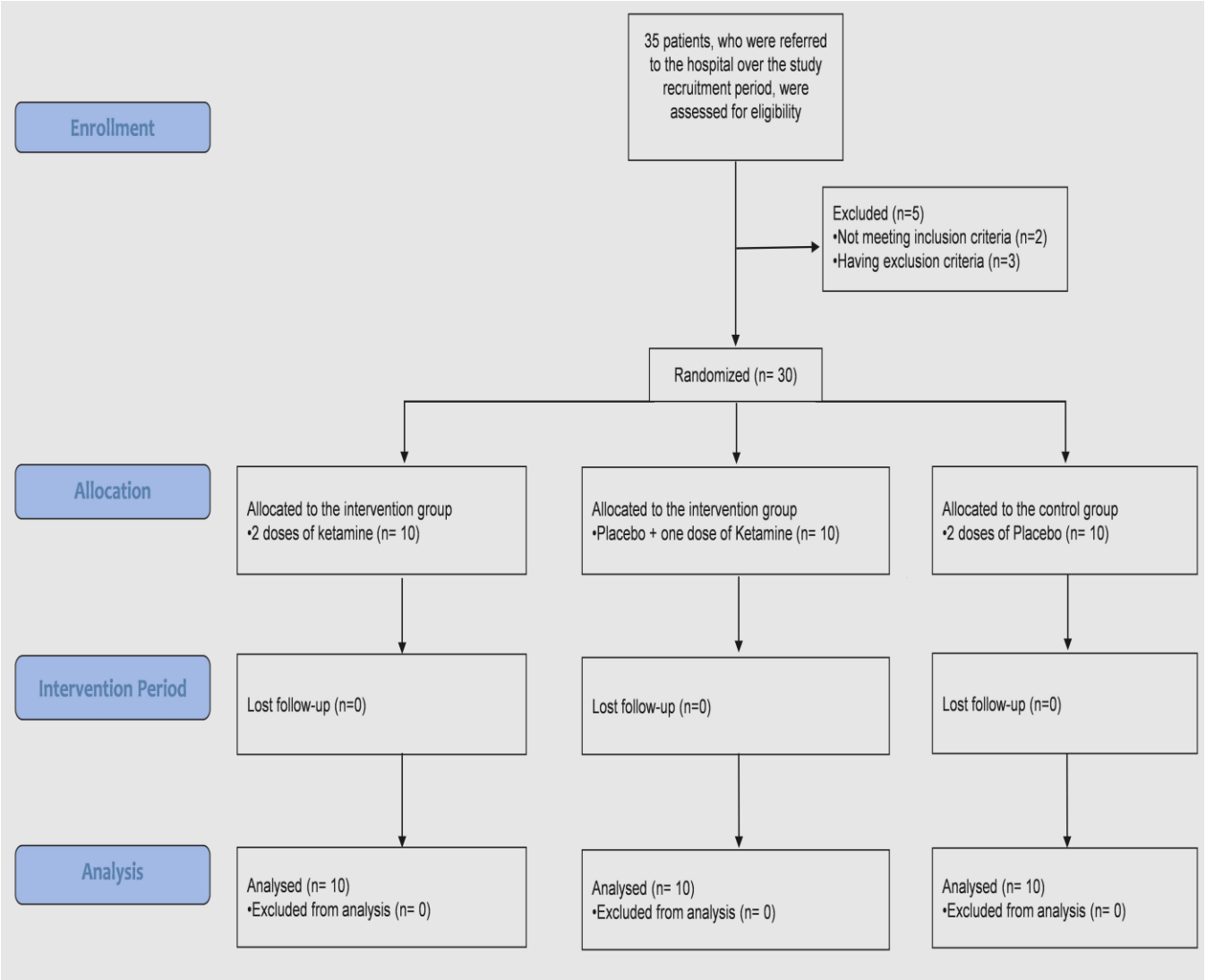

Figure 1. CONSORT Flow Diagram for a Randomized Controlled Trial to Investigate the Effects of Single and Double-Dose Intravenous Ketamine Administration in Bipolar Mood Disorder

Table 1. Comparing the Study Population Characteristics between Control, One Dose, and Two Doses of Ketamine Groups

Characteristics		Control	One Dose	Two Dose	P-Value
Age (Year)		35.10 ± 5.80	35.50 ± 9.85	40.0 ± 7.62	0.323
Duration of disease (Month)		20.0 ± 1.88	19.0 ± 2.16	19.7 ± 1.33	0.464
Sex	Male	4 (40%)	3 (30%)	5 (50%)	0.659
	Female	6 (60%)	7 (70%)	5 (50%)	
Marital status	Single	3 (30%)	3 (30%)	5 (50%)	0.563
	Married	7 (70%)	7 (70%)	5 (50%)	
Education	Non-academic	5 (50%)	4 (40%)	6 (60%)	0.659
	Academic	5 (50%)	6 (60%)	3 (30%)	
Occupation	Non-employee	2 (20%)	3 (30%)	4 (40%)	0.621
	Employee	8 (80%)	7 (70%)	6 (60%)	

Outcomes

The mean HAM-D scores were 20.40 ± 3.83, 22.20 ± 2.82, and 22.10 ± 3.28 in the control, one-dose, and two-dose Ketamine groups, respectively, at the beginning of the study. A significant difference was not observed between the three groups (P = 0.411). The results are shown in Table 2. The mean HAM-D score indicated a significant difference in times between the one-dose and two-dose Ketamine groups (P < 0.001). However, comparing the depression scores revealed no significant difference between the groups (P = 0.198) and one-dose and two-dose Ketamine groups (P = 0.827). The results are shown in Figure 2.

Table 2. Comparison of Hamilton Depression Test Scores between Control, Single Dose, and Double Doses of Ketamine Groups

Time	Hamilton Depression Rating Scale			P-Value**
	Control	One Dose	Two Dose	
Baseline	20.40 ± 3.84	22.20 ± 2.82	22.10 ± 3.28	0.411
60 Min	26.00 ± 5.98	33.70 ± 7.86	30.70 ± 5.76	0.064
Day 1	25.20 ± 8.51	30.00 ± 9.54	27.60 ± 5.89	0.430
Day 3	25.30 ± 7.62	25.10 ± 11.54	19.70 ± 5.91	0.279
Day 5	25.50 ± 9.71	22.40 ± 9.74	18.00 ± 4.76	0.153
Day 7	26.60 ± 4.93	18.60 ± 8.57	20.80 ± 3.01	0.016
Day 14	26.80 ± 4.44	18.50 ± 5.89	22.10 ± 2.81	0.002
Day 30	27.67 ± 4.67	17.70 ± 4.57	24.00 ± 2.45	< 0.001
P-value*	0.364	< 0.001	< 0.001	

* Between times in each group
** Between groups each time

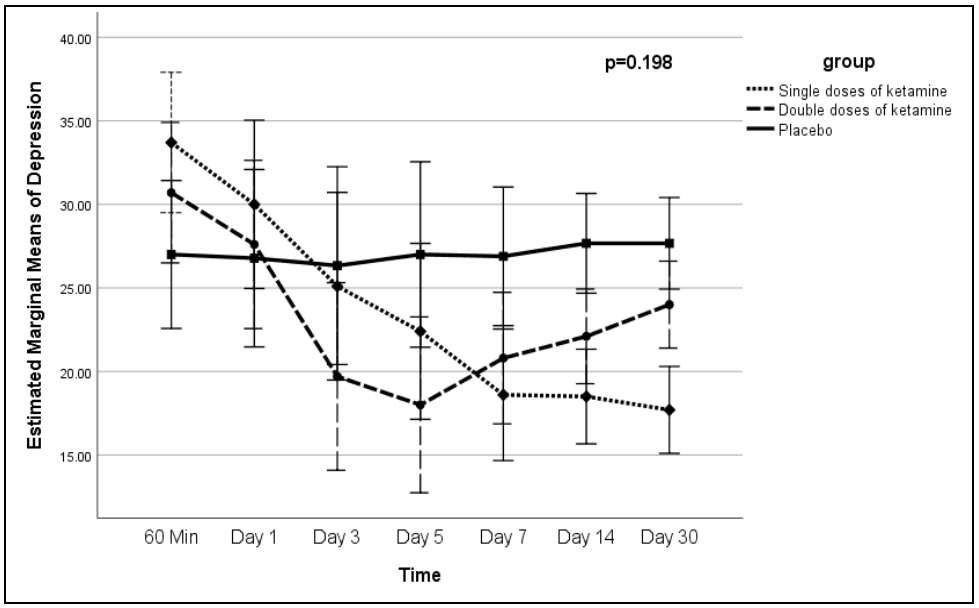

Figure 2. The Trend of Changes in the Depression on Different Days in Control, Single-Dose and Double-Dose Ketamine Groups

The baseline means of anxiety were 43.60 ± 12.92, 41.50 ± 15.81, and 39.60 ± 8.50 in control, one-dose, and two-dose Ketamine groups, respectively. Like the depression score, anxiety was similar among the three groups (P = 0.784). The results are shown in Table 3. While the anxiety scores changed over time in all groups, no significant difference was observed between them (P = 0.416). Moreover, single- and double-dose Ketamine groups were similar in anxiety scores (P = 0.375), the results of which are displayed in Figure 3.

Table 3. Comparison of Beck Anxiety Inventory between Control, Single-Dose, and Double-Dose Ketamine Groups

Time	Beck Anxiety Inventory			P-Value**
	Control	One Dose	Two Dose	
Baseline	43.60 ± 12.92	41.50 ± 15.81	39.60 ± 8.50	0.784
60 Min	44.60 ± 13.37	43.50 ± 17.88	40.40 ± 8.83	0.783
Day 1	37.60 ± 13.32	40.10 ± 14.24	31.80 ± 12.56	0.377
Day 3	34.90 ± 13.19	35.90 ± 11.59	27.90 ± 11.44	0.290
Day 5	41.10 ± 14.86	34.20 ± 8.42	29.80 ± 9.91	0.101
Day 7	41.90 ± 15.61	36.30 ± 12.60	29.50 ± 9.30	0.113
Day 14	40.40 ± 17.45	35.80 ± 14.23	31.60 ± 8.20	0.377
Day 30	40.90 ± 16.29	35.50 ± 12.02	34.00 ± 11.47	0.538
P-Value*	0.631	0.005	0.004	

*Between times in each group
**Between groups each time

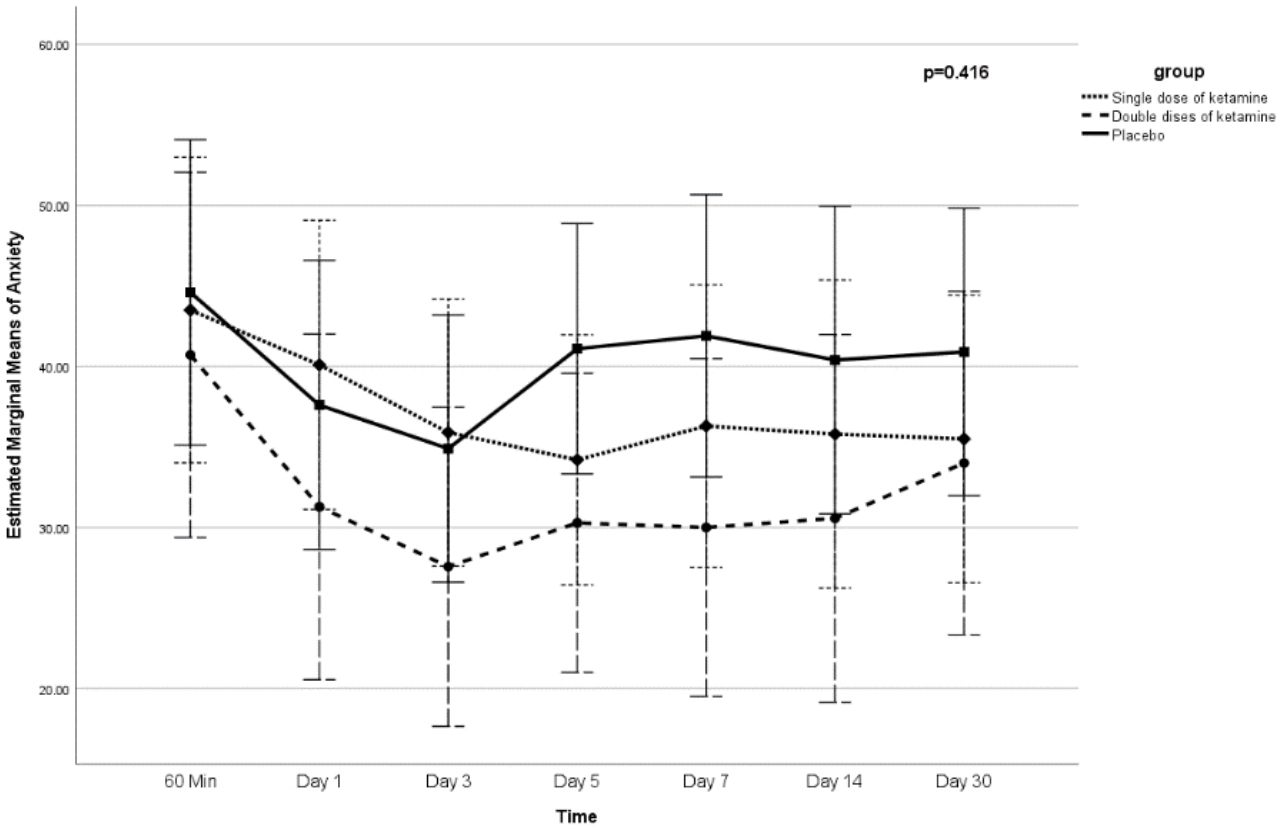

Figure 3. The Trend of Changes in Anxiety on Different Days in Control, Single Dose and Double Doses of Ketamine Groups

The mean score of YMRS was 0.70 ± 1.89, zero, and zero in control, single- and double-dose Ketamine groups, respectively, at the beginning of the study (P = 0.290). The results are shown in Table 4. Although the YMRS indicated significant changes over time in the control, single- and double-dose Ketamine injection

groups, it was similar between the three groups (P = 0.540). The results are shown in Figure 4.

Table 4. Comparison of Young Mania Scores between Control, Single-Dose, and Double-Doses Ketamine Groups

Time	Young Mania Scale			P-Value**
	Control	One Dose	Two Dose	
Baseline	0.70 ± 1.89	0.00 ± .00	0.00 ± .00	0.290
60 Min	0.80 ± 2.20	0.00 ± .00	0.00 ± .00	0.303
Day 1	1.80 ± 2.62	1.10 ± .88	4.33 ± 5.92	0.153
Day 3	4.10 ± 1.97	2.00 ± 2.87	3.67 ± 4.39	0.342
Day 5	4.70 ± 1.64	2.44 ± 3.74	5.78 ± 5.61	0.206
Day 7	4.10 ± 2.85	2.89 ± 4.01	5.89 ± 5.21	0.311
Day 14	3.60 ± 3.06	3.33 ± 3.32	6.22 ± 4.44	0.193
Day 30	4.22 ± 3.20	4.89 ± 4.57	4.80 ± .84	0.915
P-Value*	< 0.001	0.006	0.006	

* Between times in each group
** Between groups each time

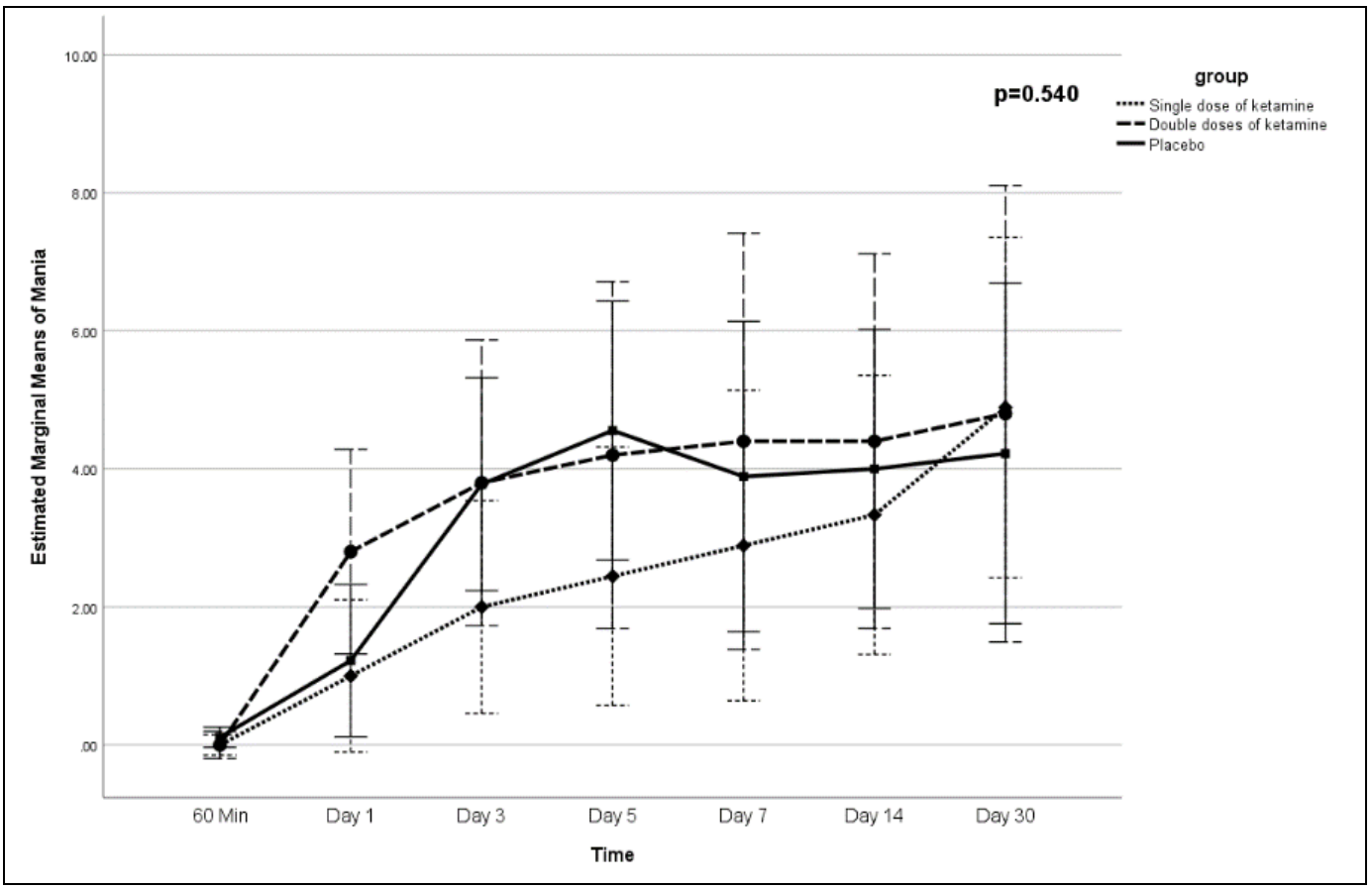

Figure 4. The Trend of Changes in Mania on Different Days in Control, Single-Dose and Double-Dose Ketamine Groups

Adverse Events

Evaluating the side effects of administrating the single and double doses of Ketamine revealed no severe adverse events in all patients.

Discussion

This double-blind, placebo-controlled research aimed to clarify the effectiveness of single and double doses of Ketamine on depression, anxiety, and manic features in

bipolar patients. The results demonstrated an antidepressant response to single or double Ketamine intravenous injections in these patients. Although there are findings mentioned above regarding the swift outcome of a single dose of Ketamine injections in these patients (26, 31), an extra and new observation indicated that a similar response occurred in the double administration of Ketamine compared to a single infusion.

Although Ketamine blocks NMDA receptors, it leads to increased neuroplasticity. Translational neuroscience studies have indicated that Ketamine blocks GluN2B-containing NMDA receptors, inhibiting eEF2 by phosphorylation. The lack of eEF2 phosphorylation causes an increase in BDNF production and leads to the AMPA receptors being transferred to the synapse. This process enhances synaptic connectivity and plasticity (32) (33). Moreover, animal studies have demonstrated that the restriction of glutamate release could underlie the antidepressant potential of Ketamine. BDNF release increases, followed by the induction of Ketamine release by glutamate and stimulation of AMPA glutamate receptors. Then, the TrkB receptor is stimulated and causes mTORC1 activation and motivates the synthesis of dendritic spines that share a temporal profile with antidepressant effects (34). These observations highlight the efficiency of Ketamine as a potential antidepressant medication.

In our study, depression elevated immediately after the injection of Ketamine. However, five days after receiving a single dose, the baseline score decreased for one month. However, after the second dose injection of Ketamine, the depression score increased two days after administration, and tended to elevate up to day 30. This finding indicates that the subjects' condition does not remain constant for a long time, and the effect of Ketamine decreases during the next weeks. However, no significant difference was observed between the cases receiving two doses and those receiving one dose of Ketamine.

Similar to our study, one investigation evaluating treatment-resistant bipolar depression found significant improvement in depressive symptoms after the injection of Ketamine in these patients (31). Another study on major depressive patients also indicated a rapid decrease in depressive symptoms 230 minutes after injection (22). Moreover, an investigation comparing single doses of Ketamine plus midazolam with six Ketamine injections revealed a greater reduction of depression induced by serial doses; however, a significant difference was not observed between the groups (35). On the other hand, based on a meta-analysis study, repeated doses have antidepressant potential (36). Administered intravenously, Ketamine improved symptoms in resistant bipolar depressive or major depressive patients, and its effect could continue in some patients up to one week after injection. Moreover, Ketamine administration is important, especially in people who need to respond quickly throughout their treatment. The influence of Ketamine on synaptic connections between neurons could enhance the synaptic signals and improve the neurons' relevancy. Therefore, appearance and maintenance improvement in symptoms within 7 to 10 days after the injection of this drug in some cases is not unexpected (20). In addition, its metabolites can create and hang on delayed responses, which are effective in treating depressed patients (26, 37).

Other trials on glutamatergic agents have also indicated that adding L-Carnosine and Palmitoylethanolamide to citalopram positively impacted subjects with major depressive disorder. These studies indicated a significant decrease in depression scores during six weeks. However, these studies differed from the current study in terms of the constant decreasing trend observed in the depression score (9, 10).

In this study, anxiety did not significantly increase immediately after injection. It then significantly decreased over time in the single and double doses of Ketamine without any significant difference between the groups. Consistent with our data, previous investigations have reported that Ketamine could improve anxiety in major depressive or bipolar patients with treatment-resistant depression (38, 39). Moreover, it was observed that Ketamine injection, compared to saline infusion, improved social anxiety; however, it did not influence the reduction of anxiety symptoms on the visual analog scale (40). Despite the number of injections, these findings suggest that Ketamine is an alternative medication for major depressive and bipolar patients presenting anxiety symptoms.

In the present study, while the mania score increased significantly over time in all groups, manic symptoms were not observed. Based on a previous report, Ketamine was well tolerated, and a small percentage of patients experienced manic symptoms. Cortical excitation and glutamate release can occur in mania symptoms in patients with bipolar depression after Ketamine administration. However, in some studies, this effect has been found to be transient and insignificant (41, 42), which could illustrate the safety of this drug as an antidepressant in curing these individuals.

Limitation

This study had several strong points. Firstly, patients were hospitalized for an average of one week before the onset of the investigation to provide adequate time to characterize the patients, assess their situation, and record evidence of stable depression or suicidal symptoms. Secondly, the study had a randomized design and a placebo-controlled group was considered. However, several methodological limitations might affect our findings. Due to the particular conditions of the patients, the most important limitation was the inability to increase the small sample size. Moreover, we had to exclusively investigate moderate and major depression due to the low number of patients.

Conclusion

Although the single and double doses of Ketamine have been shown to influence depression and anxiety, no evidence indicating the significant influence of repeated injections compared to the single dose of Ketamine was identified. Moreover, manic symptoms were not observed after the injection of Ketamine. Nevertheless, the results of this study further confirmed previous findings illustrating the fast-acting and safe properties of Ketamine as a suitable alternative for treating patients in the acute phase of bipolar depression. However, it should be noted that two injections of Ketamine do not lead to greater improvement compared to a single dose.

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Conflict of Interest

None.

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