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# The Efficacy of Ketamine Augmentation on Treatment-Refractory Obsessive-Compulsive Disorder: A Double-Blind Placebo-Controlled Clinical Trial

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## Abstract

**Introduction:** Abnormalities occurring in the glutamatergic system during obsessive-compulsive disorder, as a debilitating mental health condition, have been thus far illustrated. However, open-label and clinical trials of ketamine augmentation in limited subjects with treatment-refractory Obsessive-Compulsive Disorder (OCD) have not documented very persistent anti-OCD effects. Therefore, this controlled trial was conducted on patients with treatment-refractory OCD to evaluate the therapeutic efficacy of ketamine augmentation, as a non-competitive N-methyl-D-aspartate receptor antagonist.
**Method:** In this prospective, double-blind, placebo-controlled clinical trial, a total number of 30 subjects with treatment-refractory OCD were randomly assigned to either the group with the intravenous infusion of ketamine 0.5 mg/kg or the one receiving a dose of midazolam 0.045 mg/kg as an active placebo over 40 min. The OCD Visual Analog Scale (OCD-VAS) and the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) were also performed at mid-infusion, 1 h later, and on the 1st, 3rd, 5th, 7th, 14th, 21st, and 28th days following it.
**Results:** The mean OCD-VAS score in the group taking ketamine was lower than the value in the group receiving midazolam during the treatment. Even though these differences were not significant, the trend of changes in each study group was considerable (P=0.001). Response to treatment in the ketamine group was significantly higher than the midazolam group on the third day of treatment (P=0.042).
**Conclusion:** According to the findings of the present study, it can be stated that the adjuvant therapy with ketamine could bring significant positive effects on the third day of the treatment.

**Keywords:** Glutamate, Ketamine, Midazolam, Obsessive-Compulsive Disorder, Clinical Trial

## Introduction

Obsessive-Compulsive Disorder (OCD), as a debilitating mental health condition, causes suffering and even reduces the quality of life in affected patients [1]. Reportedly, 10-40% of patients with OCD are described as treatment-refractory [2]. Although Serotonin Reuptake Inhibitors (SSRIs) have been so far recommended by the United States Food and Drug Administration (FDA) for OCD therapy, there has been little improvement in their manifestations, and at least 6-10 weeks is needed to observe patients' response to treatment [3]. The therapeutic efficacy of antipsychotics as adjuvant first-line therapy in

treatment-refractory OCD have been further proven in several double-blind studies [4, 5]. However, many side effects of such medications have been reported. Disruptions in the glutamatergic system may be also involved in the pathogenesis of OCD [6, 7].

Besides, stress has been documented to alter the levels of glutamate in rodents, and, indeed, patients with anxiety disorders have displayed abnormal levels of glutamate and glutamate receptors [8]. In recent years, glutamate has been shown to play an important role in repetitive behaviors [7, 9]. Animal studies have also revealed that the hyper-activation of cortical-limbic glutamatergic neurons in transgenic mice could lead to OCD-like stereotypic behaviors and tics [9]. Genetic studies have further confirmed a role for the glutamatergic system during OCD. In such studies, the relationship between obsession and gene-expressed proteins contributing to glutamatergic transmission (namely, the solute carrier family 2, facilitated glucose transporter member 1 [SLC2A1] gene and glutamate ionotropic receptor N-methyl-D-aspartate [NMDA] type subunit 2B [BGRIN]) have been established [10, 11]. Gene variants in the glutamatergic system have been also associated with specific alterations in brain imaging studies, including lower concentrations of glutamate in the anterior cingulate connected with GRIN2B, and higher glutamate concentrations in the caudate nuclei of pediatric patients affected with OCD [12, 13]. In addition, Magnetic Resonance Spectroscopy (MRS) studies in OCD have found reduced glutamate concentrations in the anterior cingulate of patients with OCD [7, 14, 15]. Likewise, there is strong preclinical evidence that drugs reducing glutamatergic neurotransmission induce fast antidepressant and anxiolytic effects in animals and humans [16, 17].

Ketamine as a non-competitive antagonist of the N-methyl-D-aspartate receptor (also known as the NMDA receptor or NMDAR) has recently become a research target for its antidepressant effects within the hours of sub-anesthetic doses [18]. Ketamine has even shown to mitigate anxiety symptoms in adults with treatment-refractory generalized anxiety disorder [19, 20]and social anxiety disorder (SAD), with reported increased social engagement on subsequent days [21]. In another case, the anti-anxiety effects of ketamine had also become evident in treatment-refractory GAD and SAD patients that had persisted until one week after infusion [22]. Moreover, there is clinical evidence that glutamate-modulating drugs can be utilized to treat OCD patients [23]. However, mixed results have been thus far reported in patients with OCD. In this sense, a single ketamine infusion (0.5 mg/kg) in a randomized controlled crossover trial had further caused fast and prolonged (for at least one week) clinically relevant relief of OCD symptoms [24], while a negative outcome had been reported in an open-label study [25]. Multiple intravenous ketamine have also been used in 14 patients with treatment refractory OCD [26]. Their findings showed that one patient had a drop in the Y-BOCS to 0 and two patients had a partial response, while none of the other 11 patients showed a significant clinical improvement. Due to insufficient evidence on the efficacy of ketamine augmentation on OCD, this double-blind placebo-controlled trial was conducted on treatment-refractory OCD patients to evaluate the therapeutic effects of ketamine, as a non-competitive antagonist of the NMDAR.

## Method

This study was a prospective, double-blind, placebo-controlled clinical trial conducted at Zare Hospital located in the city of Sari, Iran. It was also approved by the Local Ethics Committee of Mazandaran University of Medical Sciences, Sari, Iran. All the research procedures were further authorized by the Psychiatry and Behavioral Sciences Research Center of Mazandaran University. . The samples were included in the study by census. The number of samples based on the study Sharma (26) with the formula, was calculated at least 15 people in each group. The patients were included based on their clinical referrals, and only after obtaining their written informed consent to participate in the trial. These subjects were of adult age with treatment-refractory OCD and a diagnosis of this mental health condition at least for one year, with reference to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), and the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score > 6 [19]. They were also required to have a stable dosage of psychiatric medications without any changes in dosage four months before the treatment. These subjects were medically and neurotically healthy based on their medical history, physical examinations, and medical laboratory assessment results. They were excluded if they were pregnant or nursing and even suffered from other mental health conditions such as psychotic, mood, and eating disorders or if they had prominent suicidal thoughts. No one had substance dependency for three months. The patients who had received psychotherapy over the past eight weeks were also excluded. Moreover, those suffering from depressive disorders with reference to the Hamilton Depression Rating Scale (HDRS-17) score > 25 [27] could not participate in this study. There were no other changes in psychotropic medications during the trial.

Formula of calculating sample size is:

$n = 2\ (Z\alpha + Z\ [1-\beta])^2 \times SD^2 / d^2$

$Z\alpha = 2.56$, $Z\ (1-\beta) = 2.28$, $SD = 15$, $d$ (effect size) $= 20$

So $n = 2\ (2.56 + 2.28)^2 \times 15^2 / 20^2 = 15/50$

Fifteen individuals in each group should be recruited in the study.

The parallel groups of 30 patients with treatment-refractory OCD were randomly assigned to either the group with a single Intravenous (IV) infusion of ketamine (0.5mg/kg) over 40 min after an overnight fast (n=15) or midazolam (0.045 mg/kg) under the same conditions (n=15). Based on the results of the previous study [24], the sample size was also calculated. Allocation sequences were further determined based on simple randomization, which was not stratified. As well, 30 envelopes were prepared in a covered package, of which 15 cases were group A and 15 cases were group B. At the beginning,

after baseline assessments, each subject removed an envelope from the box so that they remained unaware. Randomization was further carried out by an independent person, who also assigned the subjects. Midazolam (as an anesthetic agent) was provided in place of a control condition to mimic ketamine in terms of nonspecific behavioral effects (viz. sedation, disorientation, etc.) with no well-known anti-obsessive effects. An anesthesiologist and a nurse were also present all the time during this procedure and for at least 1 h after the infusion. Moreover, the vital signs were monitored every 15 min until 1 h following the infusion. After baseline screening, OCD severity, as well as the potential side effects of ketamine/midazolam augmentation, was assessed at mid-infusion, 1 h later, and on the 1st, 3rd, 5th, 7th, 14th, 21st, 28th days after it. Throughout the study, the assessments were performed by a psychiatric assistant, blinded to the interventions. All the subjects were also unaware of the intervention type. Furthermore, a statistician blinded to the treatment analyzed the data.

The OCD-VAS was applied as a self-rating scale to assess the rapid change trends during obsessions and compulsions. In this sense, an OCD-VAS score of 10 represented constant intrusive obsessions-compulsions and zero denoted no obsessions-compulsions. An independent researcher, blinded to the treatment, also evaluated the patients at each assessment stage using the Y-BOCS with Cronbach's alpha coefficient of 0.89. The response to treatment was additionally defined as >35% improvement in the OCD symptoms. Besides, depression comorbidity was assessed by the HDRS-17 with Cronbach's alpha coefficient of 0.7 [27]. The Clinician-Administered Dissociative State Scale (CADSS) with Cronbach's alpha coefficient of 0.94 [28] was further employed to evaluate the potential dissociative side effects. Manic and psychotic symptoms as a potential side effect of ketamine/midazolam augmentation were subsequently evaluated by the Young Mania Rating Scale (YMRS) with Cronbach's alpha coefficient of 0.93 [29] and the Brief Psychiatric Rating Scale (BPRS) with Cronbach's alpha coefficient of 0.69 [30].

The baseline data were presented in accordance with descriptive indices such as percentage and mean. Linear mixed-effects were also used to assess the impact of the treatment on each outcome measure (viz. OCD-VAS and HDRS-17). The OCD-VAS was then analyzed in a piecewise linear manner from baseline to mid-infusion, mid-infusion to 1-h later, and 1-28 days after it. These analyses assessed the differences between ketamine and midazolam augmentation using contrasts within each mixed-effect linear regression model. The same model was further utilized to examine depression severity (at baseline and days 1-28 post-infusion) via the HDRS-17. Effect sizes were additionally calculated via the estimates divided by the baseline Standard Deviation (SD) for each outcome. In addition, the binary treatment response was defined as greater than or equal to a 35% reduction in the Y-BOCS score between baseline and days post-infusion. Moreover, the IBM SPSS Statistics for Windows, version 21, was used. All the tests were two-sided with a significance level of $P<0.05$.

## Results

In this study, 30 patients with treatment-refractory OCD were selected, and then randomly assigned to two groups of 15 (namely, ketamine and midazolam groups). The demographic and clinical characteristics of the subjects are shown in Table 1. There were no statistically significant baseline differences between the two groups regarding the frequency of gender (P=0.68), age (P=0.55), OCD duration (P=0.35), OCD severity, and depressive symptoms established by the Y-BOCS (P=0.355), OCD-VAS (P=0.48), and HDRS-17 (P=0.675).

Fisher's exact test results also showed no response to treatment (>35% reduction in the Y-BOCS score) during the infusion and 1 h later in both groups. Despite higher rates of response to treatment in the group taking ketamine from the first day (four subjects in the ketamine group vs. no one in the group receiving midazolam), a statistically significant difference between the two groups was observed only on the third day after the infusion (five patients in the ketamine group vs. no cases in the group taking midazolam) (P=0.042).

As depicted in Figure 1, the mean OCD-VAS score in the group with ketamine augmentation was lower than that in the midazolam group during the treatment (5.6±0.77 in the ketamine group vs. 6.6±0.48 in the group taking midazolam). Although these differences were not significant (P>0.05), the change trends in each group were noteworthy (P=0.001).

**Table 1.** Demographic, Clinical, and Baseline Data of OCD Patients

| | | Group 1 | Group 2 | P |
|---|---|---|---|---|
| **Age** | | 34.9±36.7 | 37.13±12.24 | 0.55 |
| **Gender** | Male | 20% | 33.4% | 0.68 |
| | Female | 80% | 66.6% | |
| **OCD duration** | <10 yr | 46.7% | 66.7% | 0.35 |
| | 11-20 yr | 26.6% | 26.7% | |
| | >20 yr | 26.7% | 6.6% | |
| **Y-BOCS** | | 23.2 | 21.29 | 0.355 |
| **OCD-VAS** | | 6.6 | 6.92 | 0.728 |
| **HDRS-17** | | 11.53 | 12.47 | 0.675 |

Based on the HDRS-17 score, there was a 31.5% reduction in depression severity in the ketamine group (P=0.956) and a 21.5% drop in the group taking midazolam (P=0.713) after the treatment, compared with the baseline data, which was not significantly different. The mean HDRS-17 scores in the ketamine and midazolam groups were also respectively equal to 8.07±2.6 and 12.02±.44 after the treatment, which was not significantly different (P=0.206).

Figure 2 illustrates the rate of positive psychotic, manic, and dissociative symptoms in the study subjects. The mean BPRS score for psychotic complications in the ketamine group was not significantly different from the midazolam one (viz. 26.45±1.22 vs. 29.74±1.22, respectively, P=0.179). Three subjects in the group receiving ketamine also reported manic symptoms, whereas no one affirmed such symptoms in the midazolam group. This figure was also not significant (P=0.126). The mean CADSS scores were also equal to 22.5 and 8.5 in the ketamine and midazolam augmentation groups, respectively (P<0.001). This side effect was mainly seen at mid-infusion in the ketamine group (11.86 vs. zero in the midazolam group). Moreover, one out of five patients reported mild systemic side effects such as dyspnea (P=0.32), dry mouth (P=0.15), epigastric pain (P=0.15), tachycardia (P=0.32), vomiting (P=0.32), and weakness (p=0.082), which was not significantly different between both groups. Significant neurological side effects included drowsiness (14 patients in the midazolam group vs. five subjects in the group taking ketamine at mid-infusion (P<0.001)), vertigo (seven patients in the ketamine group vs. no cases in the group receiving midazolam at mid-infusion (P=0.003)), and five cases in the ketamine group vs. no patient in the group taking midazolam on the first day [P=0.018]). In addition, two patients in the ketamine group reported the re-experience of dissociative symptoms during the infusion on the first and third days after it.

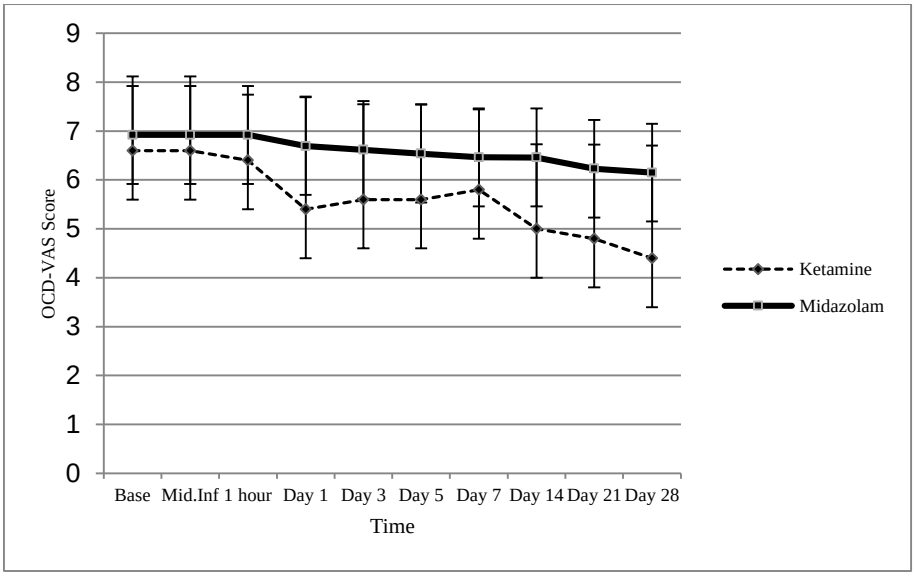


**Figure 1.** Change trend in the OCD-VAS scores during the treatment.

## Discussion

In this trial, the efficacy of the adjuvant therapy with ketamine augmentation compared with midazolam (as the placebo) was studied in treatment-refractory OCD patients. Although SSRIs can improve OCD symptoms, this type of response might occur after a few weeks [3]. Besides, 10-40% of the patients do not respond to these medications [2]. Since the disruptions in the glutamatergic system are involved in the pathogenesis of OCD, this hypothesis has been suggested that glutamate receptor inhibitors such as ketamine may bring therapeutic effects in these patients. In the present study, treatment-refractory subjects responded to this intervention on the third day after ketamine infusion. In this line, in the study by Rodriguez et al. 50% of the patients had responded to treatment with ketamine augmentation, while none of them had done so with saline [24]. In another open-label trial on 10 treatment-refractory patients, Bloch et al. had further reported that none of them had responded to treatment despite the 11% reduction in the severity of the symptoms [25]. In the present double-blind controlled study, this difference was not statistically significant although the moderate severity of OCD symptoms based on the OCD-VAS score in the ketamine group was relatively less than that in the group taking midazolam at all times. However, a significant reduction was observed in the OCD symptoms in the ketamine group on the 7th, 14th, and 21st days after infusion. In a previous controlled crossover study, Rodriguez et al. had found significantly lower to moderate levels of obsession at mid-infusion and 230 min after it up to seven days in the ketamine group compared to the control group that had received saline. They had further reported transient psychotic symptoms in the ketamine group. The findings in the present study showed that ketamine augmentation did not increase the risk of long-term psychotic, manic, and other systemic effects over the follow-up period. These findings suggested that ketamine was safe in the short term for OCD patients when administered at a dose of 0.5 mg/kg over 40 min. However, the results of this trial were not

consistent with the outcomes reported by Rodriguez et al. using a crossover clinical trial. In addition to recruiting a larger sample size (30 vs. 15 patients), a psychoactive agent similar to ketamine (i.e., the anesthetic benzodiazepine midazolam) was thus applied as a control condition to design a double-blind study since saline was a neutral agent. Midazolam might also induce transient psychoactive effects to enhance blinding. Meanwhile, it could be utilized as a placebo (devoid of specific antidepressant and anti-obsession effects). Otherwise, the antidepressant effect of ketamine has been shown to be smaller as compared with midazolam [31]. This can be one of the reasons for the differences between the recent study and that by Rodriguez et al. [24]. Another discrepancy between both trials was that all subjects in the above mentioned study were drug-free before the treatment. The failure of the Y-BOCS and the OCD-VAS to measure obsessions and compulsions accurately at the moment and in a short time might be the source of bias in both studies. Indeed, there was a short interval between the assessments at the first hour after the infusion when the subjects were feeling sleepy. In addition, many compulsions, such as arrangement and washing could be state-dependent. Therefore, the assessments in the present study as well as the previous ones may not provide sufficient validity. This issue had been considered in the open-label trial by a previous study [25], in which they had slightly modified the Y-BOCS to account for the compressed temporal context of the assessments. It might be the reason why the response to treatment was detected on the third day and not before it due to possible drowsiness during and after the infusion. Therefore, it is suggested to apply appropriate measures for the assessment of existing obsessions and compulsions in future investigations. In contrast to the trial by Rodriguez et al. wherein two out of 15 subjects (20%) had comorbid depression, 22 out of 30 subjects (73.3%) had comorbid depression in the present study. This difference in the prevalence rate of comorbid depression might be one of the reasons for the discrepancy in the findings between these two studies. Actually, OCD patients with comorbid depression that are also amotivational and hopeless possibly fail to take the measures accurately.

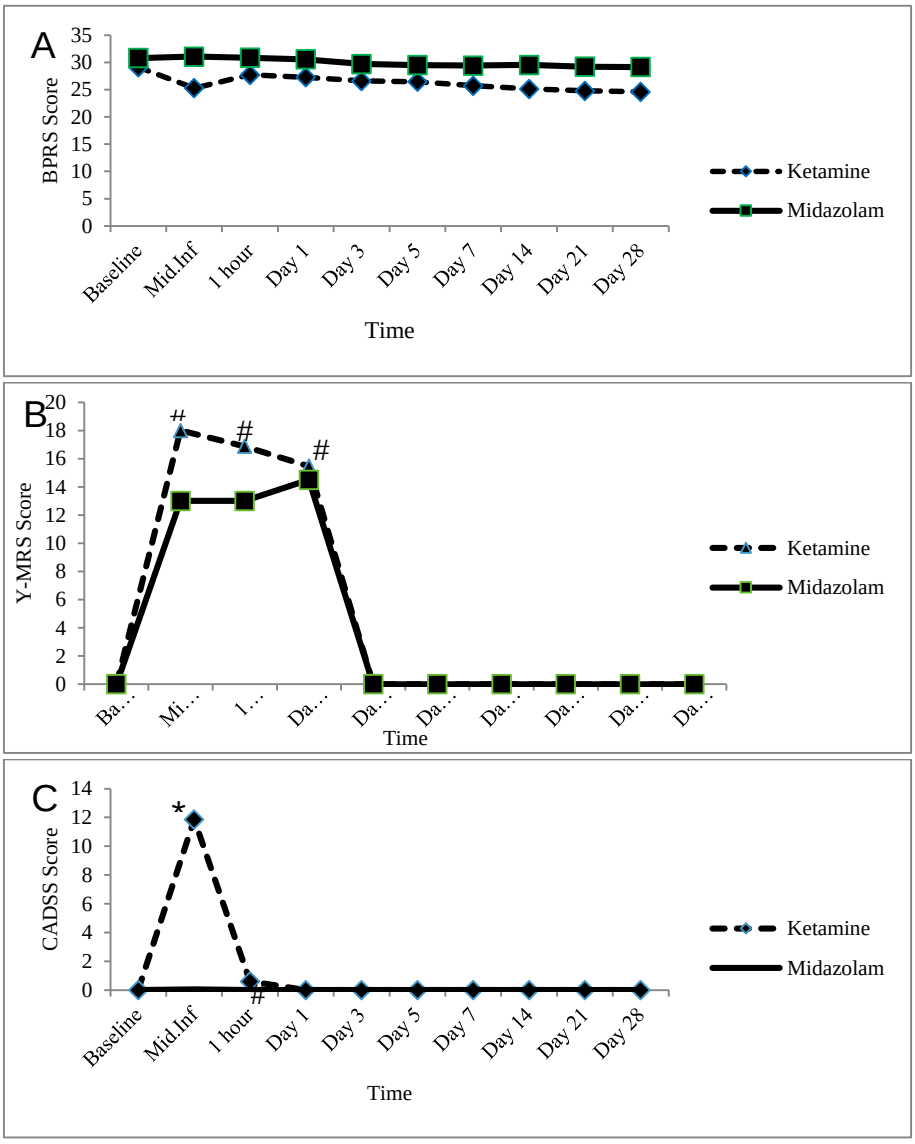


**Figure 2.** Change trends during infusion complications (psychotic [2A], manic [2B], and dissociative [2C] symptoms) over 28-day post-infusion. *P<0.05 and #P>0.05

Some limitations should be considered in interpreting the findings of the present study. First, all the patients were receiving a stable dosage of anti-OCD medications from one month before the treatment. Therefore, it does not seem to be a confounding factor. Whereas concomitant medications might affect the clinical input of NMDA channel blockers, it would be better to involve drug-free patients for future studies. Second, as mentioned earlier, midazolam augmentation was used as an active placebo to design a double-blind study. Although no dissociative effects were detected in the midazolam group, there was a case report of OCD induced by midazolam [32]. This should be considered that the possible effect of midazolam on OCD could affect non-significant differences between the two groups in the present study. Another active placebo should be further considered in future trials. Third, some study subjects described their experience as overall positive, and one of them requested ketamine infusion once again. Therefore, the psychoactive effects and abuse liability of ketamine should be taken into account, and it seems necessary to exclude patients with a history of substance abuse in other studies. Fourth, the subjects in this trial were a treatment-refractory subgroup of OCD patients who had various obsessions and compulsions. As neurobiological and pharmacological responses may be different during various bursts of obsessions and compulsions, according to Rodriguez et al. it is better to involve subjects with near-constant and similar obsessions or compulsions. Fifth, since different environments and situations may shape obsessions and compulsions, it would be better to implement treatments and follow-ups at a constant place such as a hospital.

## Conclusion

A dose of 0.5 mg/kg of ketamine augmentation in treatment-refractory OCD patients is well tolerated. In the present study, treatment-refractory OCD subjects responded to the adjuvant therapy with ketamine 0.5 mg/kg on the third day after ketamine infusion but it had no long-term anti-OCD impacts. The moderate severity of OCD symptoms based on the OCD-VAS score in the ketamine group was relatively less than that in the group taking midazolam at all times, although this difference was not statistically significant. Also, the trend of changes in each study group based on the OCD-VAS score was considerable. There were also no long-term complications when ketamine was administered at a dose of 0.5 mg/kg over 40 min.

## Conflict of Interest

The authors declare no conflicts of interest.

## Ethical Approval

In this research, ethical principles were considered. Patients were informed about the purpose of the research and they were included after obtaining their written informed consent. It was also approved by the Local Ethics Committee of Mazandaran University of Medical Science.

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