Original Article

A Comparison of the Anti-Anxiety Effects of Oral Ketamine and Fluvoxamine in Children with Separation Anxiety Disorder Manifesting as School Refusal

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Abstract

Background: Children suffer from a high prevalence of anxiety problems that require prompt treatment. It has been demonstrated that ketamine offers rapid anti-anxiety effects. This study aimed to evaluate ketamine's anti-anxiety impact in the treatment of children with school-refusal separation anxiety disorder.

Materials and Methods: In this open-labeled randomized clinical trial, 71 children (6-10 years) diagnosed with school refusal separation anxiety disorder were randomly assigned to two groups; a case group, who received ketamine at a weekly rising dose of 0.1 to 1 mg/kg; the control group treated with Fluvoxamine (25 mg/day), which could increase to 200 mg/day if necessary. The SCARED and CATS questionnaires were used to assess anxiety before treatment, at the 8th and 16th weeks of intervention. The data were analyzed using repeated-measures analysis of covariance.

Results: The mean anxiety scores in the eighth week (19.7 ± 16.1) were significantly lower in the ketamine group than before (31.5 ± 10.8). Until the sixteenth week (19.4 ± 14.6), there was no further decrease in scores in the ketamine group, in the fluvoxamine group, pre-treatment scores (36.3 ± 16.5) and eighth week (36.9 ± 16.6) were not significantly different, but scores decreased significantly in a sixteenth week (26.2 ± 12.5).

Conclusion: In first eight weeks of treatment, ketamine was more successful than fluvoxamine at reducing anxiety disorder, considering the emergence of this disorder and the lack of major adverse effects of ketamine, it seems to be beneficial in early phases of treatment. Due to the quick onset of ketamine in future trials, their combination therapy is recommended during the initial weeks of treatment.

Keywords: Anxiety, children, fluvoxamine, ketamine, separation anxiety disorder

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Introduction

Anxiety disorders with a longevity prevalence of >20% are among the most widespread psychiatric disorders.[1] Among anxiety disorders in children, we can refer to Separation Anxiety Disorder which makes children avoid schools. The long-term consequences of this disorder encompass fewer opportunities for attending educational settings, occupational and social problems, and a high risk of affliction by subsequent psychiatric diseases.[2]

Studies estimate that the outset of Separation Anxiety Disorder manifesting as school refusal occurs in about 5% of all school-aged children, affects girls and boys equally, and frequently arises between ages 6 and 10.[3] Many

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available medications used for treating anxiety disorders take several weeks to reveal their therapeutic goals; however, we need immediate treatments in such cases considering the consequences of this disorder. Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist examined by many studies for curing some infections like depression and suicide but limitedly probed for treating anxiety disorders, while ketamine has demonstrated immediate anti-depression effects on treatment-resistant depression (TRD).[4-12] Ketamine has been also effective in treating Post-Traumatic Stress Disorder (PTSD).[13] The decline of suicidal thoughts and attempts has been examined in different studies, such that past research has revealed that intravenous ketamine (0.5 mg/kg) is influential in the recession of suicidal thoughts and ideas in emergency conditions; nonetheless, treatment with adjuvant drugs is suggested due to the temporary and short-term effect of this medication.[14,15] Different studies have reported the anti-anxiety effects of this medication on children and adults. In New Zealand, Glue *et al*.[16,17] (2017 and 2019) investigated the anti-anxiety effect of ketamine on treatment-resistant patients with Social Anxiety Disorder (SAD) and Generalized Anxiety Disorder (GAD). In these double-blind studies, 12 patients were assigned into two groups. The first was treated with incremental 0.25, 0.5, and 1 mg/kg doses of ketamine in weekly intervals for 5 weeks, and the second, as the control group, received midazolam (0.01 mg/kg). The results showed the immediate anti-depression effects of ketamine. Shadli *et al.* (2018) examined the effect of ketamine on the electroencephalogram (EEG) of under-treatment patients with SAD and GAD. In their study, 12 patients suffering from SAD and GAD were assigned into two groups in a double-blind and random manner. One group received 0.25, 0.5, and 1 mg/kg doses of ketamine, while the other received midazolam (0.01 mg/kg). Ten minutes before and 2 hours after drug reception, the EEGs of the patients were recorded. The results revealed that ketamine decreased the theta waves in the right frontal lobe and reflected the anti-depression effects of ketamine.[18] Other studies also confirmed the anti-depression effects of ketamine in reducing the anxiety and irritability of adults with mood disorders.[19,20] Several studies have investigated the effect of ketamine on reducing the anxiety of children before surgical and diagnostic operations and showed that the medication is effective in decreasing the anxiety of children and their faster separation from their parents before some surgeries such as hernia surgery and diagnostic actions as imaging and audiometry.[21-25] The implemented studies have not so far reported any severe side effects of ketamine. Thus, considering its immediate anti-anxiety and anti-depression effects reported in past research, this study aimed to investigate the anti-anxiety effect of ketamine and compared it with fluvoxamine as standard therapy in anxiety disorders.

Materials and Methods

This research was an open-labeled randomized clinical trial whose sample was selected from outpatients referring to the child and adolescent psychiatric subspecialty clinics in Isfahan city during the September 2020-December 2020 period. The sample included children with an age range of 6-10 that suffered from school refusal Separation Anxiety disorder according to DSM-5 and the approval of a child and adolescent subspecialist psychiatrist. They did not possess any serious suicidal thoughts or plans, and they and their parents disclosed their consent to enter the study. Patients suffering from psychiatric comorbid disorders, Patients receiving medication or psychotherapy for anxiety, and possessing low IQ were not included. Likewise, those having treatment intolerance, not promptly referring for their treatment completion, tending to leave the study for any reason and at any time, drugs and substances abuse, exhibiting drug reactions or allergy to the examined medications during the treatment, and experiencing any treatment-interfering psychosis or medical disease were excluded. The Screen for Child Anxiety Related Disorders (SCARED) questionnaire, with a total score range of 0-82, a cutoff point of 25 for children, a validity of 0.7-0.9, and reliability of 88%, and the Child's automatic thought scale (CATS) scale with a total score range of 0-160, the cutoff point of 21 for children, the validity of 0.8, and reliability of 75%, both enjoying suitable validity and reliability,[26-33] were used for measuring children's anxiety. Questionnaires were filled by patients or with the help of families. Furthermore, demographic information, including age, gender, education, report-based academic learning level, disorder duration, and familial history of psychiatric disorders, was collected by questionnaires. All children possessing the inclusion criteria and suffering from the school refusal Separation Anxiety disorder were entered into the study, and they and their families were adequately explained the study procedure. The informed consent was acquired according to Helsinki declaration on ethical principles for medical research involving human subjects. Then, the patients were randomly selected and assigned to the intervention and control groups via double randomized blocks. The first (intervention) group was treated with ketamine, and the other (control) group underwent fluvoxamine therapy. Ketamine treatment began with a 0.1 mg/kg dose, which increased to a maximum dose of 1 mg/kg in weekly visits according to the tolerance level of the patient. The patients were controlled for 40 minutes at the hospital, and their blood pressure, heart rate, and respiration were checked. Due to the unavailability of oral ketamine, a vial of ketamine was dissolved in fruit juice and given to the patients based on the approval of a pharmacologist. Notably, the effect of this medication does not change in this way, according to past studies.[34-38] The treatment of fluvoxamine began with a 25 mg/day dose, which increased to a maximum dose of 200 mg/day if necessitated according to the opinion of the child subspecialist psychiatrist. All patients were followed up for 16 weeks, and the questionnaires which formed the basis of the evaluations were administered before the treatment and on weeks 8 and 16. The repeated measure ANCOVA run in the SPSS 20 software was used for data analysis.

Results

The main purpose of this research was to investigate and compare the anti-anxiety effect of oral ketamine and fluvoxamine on treating children with Separation Anxiety Disorder manifesting as school refusal. The respective data were collected from the intervention (oral ketamine) and control (fluvoxamine) groups by two SCARED and CATS questionnaires in three phases (before the treatment, week 8, and week 16). In this regard, we present first the descriptive information and then the inferential results, i.e., the assumptions needed for analyzing the hypotheses.

Describing demographic characteristics

The average age of the participants was 8.5 years. Table 1 represents the demographics of 71 children with school refusal Separation Anxiety Disorder.

The results of Table 1 show that boys with a <1-year disorder duration comprised a large number of fluvoxamine-receiving patients, and girls with a 1-2-years disorder duration majorly constituted the patients receiving oral ketamine. Many participants in both groups did not have familial psychiatric disorder histories.

The anxiety scores of both groups were not significantly different before and after the treatment based on their age, gender, disorder duration, and familial history; thus, the patients in both groups were homogeneous in terms of the mentioned variables ($\alpha > 0.05$ with a confidence level of 95%).

The research witnessed an attrition rate of 12 in the ketamine group and 17 in the fluvoxamine group due to the families' non-adherence to the treatment for different reasons, including remoteness and the patients' and their families' disinclinations to continue the treatment despite being justified.

Requisite assumptions

Repeated measure ANOVA should be used for determining if the fluvoxamine- and oral ketamine-receiving groups are different in their levels of anxiety. To apply this test, we need to examine the assumptions of normality, homogeneity of variances, and variance-covariance matrix homogeneity. An examination of data normality with the Shapiro-Wilk test showed that the CATS and SCARED scores were normally distributed in both the fluvoxamine and ketamine groups. Moreover, the assumption of the homogeneity of variances was checked and confirmed. The homogeneity of variances in both groups and the homogeneity of the variance-covariance matrix were investigated and confirmed before the treatment and in weeks 8 and 16 about to the CATS and SCARED tests.

Table 1: General demographics of participants

	Fluvoxamine ($n=33$)	Oral Ketamine ($n=38$)
Gender		
Girl	12 (16.9%)	20 (28.2%)
Boy	21 (29.6%)	18 (25.4%)
Disorder duration *n* (%)		
<1 year	15 (21.1%)	16 (22.5%)
1-2 years	13 (18.3%)	17 (23.9%)
>2 years	5 (7%)	5 (7%)
Familial psychiatric disorder history		
Without familial history	29 (40.8%)	24 (33.8%)
With familial history	4 (5.6%)	14 (19.6%)

Inferential analysis of the main hypothesis

This section analytically presents the data associated with every research hypothesis by examining the assumptions of the normality of variables, homogeneity of variances, and homogeneity of the variance-covariance matrix for the CATS and SCARED tests.

Hypothesis: The anti-anxiety effects of oral ketamine and fluvoxamine on children with school refusal Separation Anxiety disorder are different about the CATS and SCARED tests.

Results of research variables

Table 2 represents the group-separated mean and standard deviation values for research variables. The results of this table show that, according to the CATS test, the mean score of anxiety in week 8 (19.16 ± 7.1) has considerably decreased in the ketamine group compared to the participants' pretreatment mean score (31.10 ± 5.8). However, no extra recession is observed in the anxiety scores of the ketamine group until week 16 (19.4 ± 14.6). The mean scores of the fluvoxamine group were not significantly different before the treatment (36.3 ± 16.5) and week 8 (36.9 ± 16.6). However, a decline was observed in the anxiety scores of this group in week 16 (26.2 ± 12.5). According to the SCARED test, the mean anxiety scores of both groups in week 8 equally decreased relative to their pretreatment scores, and this effect was slightly higher in week 16 in the fluvoxamine group.

To the results in Table 2, the significance value for the time-effect variable (before the treatment, week 8, and week 16) was larger than 0.05 ($\alpha>0.05$). Thus, oral ketamine did not have any over-time effect on the anxiety scores (CATS and SCARED) during the treatment of children with separation anxiety disorder, and concerning the mean values, the anxiety of patients has not changed significantly over time. The significance value for the interaction effect of group (ketamine and fluvoxamine) and time was smaller than 0.05 ($\alpha <0.05$), i.e., oral ketamine impacted and decreased the mean score of patients with separation anxiety disorder. Hence, the research hypothesis formulating that the anti-anxiety effects of oral ketamine and fluvoxamine on children with school refusal separation anxiety disorder are different is confirmed with a 95% confidence level based on the CATS and SCARED tests.

Figure 1 illustrates the anxiety rate in the time/group state and indicates that, according to the CATS test, the mean separation anxiety of the ketamine group experienced a descending slope from the pretreatment phase to week 8 and then proceeded to week 16 with a relatively horizontal line. The mean anxiety

Table 2: Within-subject effects of anxiety

	Fluvoxamine (n=33) (Mean±S.D)	Oral ketamine (n=38) (Mean±S.D)	Time effect P	Interaction effect P	Treatment effect P
CATS					
Before treatment	36.3±16.5	31.5±10.8			
Week 8	36.9±16.6	19.7±16.1	0.997	0.002	0.108
Week 16	26.2±12.5	19.4±14.6			
SCARED					
Before treatment	30.06±11.7	26.9±10.1			
Weak 8	25.4±9.2	23.4±8.1	0.117	0.001	0.467
Weak 16	24.3±8.2	24±8.3			

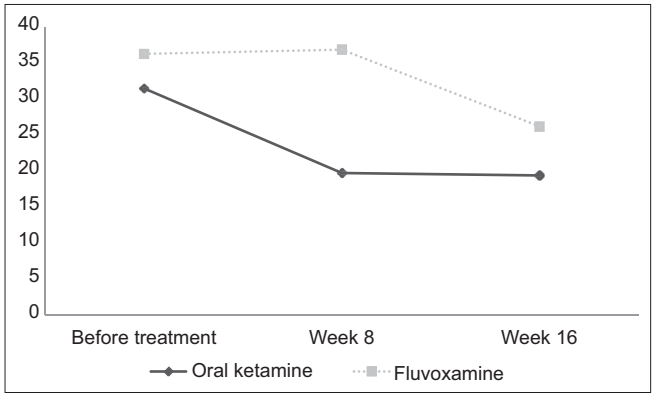

Figure 1: Anxiety mean (CATS test) in different periods vs. group

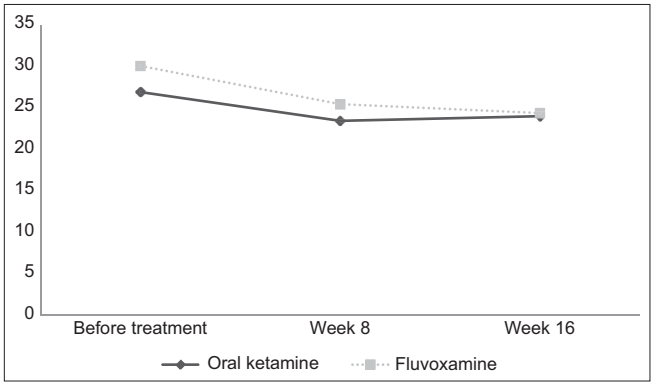

Figure 2: Anxiety mean (SCARED test) in different periods vs. group

scores of the fluvoxamine group are not different in the pretreatment phase and week 8; however, a steep descending slope is observed from week 8 to week 16.

Figure 2 illustrates the anxiety rate in the time/group state and indicates that, according to the SCARED test, the separation anxiety mean of the ketamine group has experienced a steep descending slope from the pretreatment phase to week 8 and then a mild ascending slope until week 16. In the fluvoxamine group, the mean separation anxiety score mildly descended from the pretreatment phase to week 8 and then experienced a steeper descending slope than ketamine until week 16.

Discussion

As mentioned, anxiety disorders are of extreme significance due to their high prevalence. School refusal separation anxiety disorder is an emergency condition among children and necessities immediate intervention and treatment since the long-term consequences of this disorder, such as few opportunities to attend educational settings, occupational and social problems, and a high risk of affliction with other psychiatric diseases, provide children with many intricacies.[2] A bulk of treatments so far identified for anxiety disorders commence with slow impacts and require several weeks to reach their therapeutic objectives. Present anxiety-treating medications, among which are Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), bring about some side effects, take time to produce therapeutic responses, and cater to a high degree of relative response and low degree of long-term recovery in patients.[39] Furthermore, the current psychotherapy methods of anxiety treatment are highly costly and time-consuming. This study investigated the anti-anxiety effect of ketamine in comparison with fluvoxamine. According to the CATS test, the mean scores of the ketamine group were significantly different in the pretreatment phase and week 8, indicating the faster effect of ketamine than fluvoxamine. Likewise, since the anxiety scores of children did not change significantly over time, we can conclude that both medications equally reduce children's anxiety in the long run.

Different studies have so far probed and confirmed the anti-anxiety and anti-depression effects of ketamine.[4-24] Several studies have also investigated the effect of ketamine on reducing the pre-surgery anxiety of children, such as hernia operations, and diagnostic actions, like imaging or audiometry, and showed that the medication was effective in decreasing the anxiety of children. In these studies, ketamine with a 5-6 mg/kg dose was applied before surgeries and diagnostic actions.[21-25] In New Zealand, Glue *et al*.[16,17] (2019 and 2019) investigated the anti-anxiety effect of ketamine on treatment-resistant patients suffering from SAD and GAD. In these double-blind studies, 12 patients were assigned into two groups. The first group was treated with incremental 0.25, 0.5, and 1 mg/kg doses in weekly intervals for 5 weeks, and the second group received midazolam (0.01 mg/kg). While the results have revealed immediate anti-anxiety effects of ketamine, this

study has addressed >18-year patients, compared ketamine with midazolam, which is a non-standard treatment in curing anxiety disorders, and not considered longer follow-up periods for patients. Our study applied ketamine with 0.1-1 mg/kg doses for 6-10-years-old children, compared this medication with standard anxiety treatment, i.e., fluvoxamine, and heeded a longer follow-up period. Talor *et al*.[40] (2018) compared the results of a ketamine injection (0.5 mg/kg) with those of a Placebo among 18 adult patients with SAD and reported the effectiveness of ketamine on anxiety reduction. In a review study, Banov *et al*.[39] (2020) emphasized the immediate anti-anxiety effect of ketamine. This review study referred to the role of ketamine in decreasing suicidal thoughts and argued that ketamine changed synaptic connections by developing a hyperglutamatergic condition and helped synaptogenesis by raising the BDNF level (Brain-Derived Neurotrophic Factor). Meanwhile, patients with PTSD showed a fast decline of symptoms 24 hours after the injection. Lattie *et al*. (2021) treated 24 patients with anxiety disorders with three incremental subcutaneous doses of ketamine (0.25, 0.5, and 1 mg/kg) in weekly intervals and later with a maintenance dose of 1 mg/kg for a month. They compared patients with the control group treated with midazolam and revealed the immediate and dose-dependent effect of ketamine.[41] In Dutton *et al*.'s (2022) study, 32 patients with chronic suicidality experienced continuous reductions in their anxiety and stress after being treated with oral ketamine (0.5.3 mg/kg) for 6 weeks.[42] The results of these recent studies are in line with our findings. Similar to these studies, which have not so far reported any serious side effects for ketamine, our patients did not convey any severe indisposition for ketamine, except for the usual and prevalent side effects, including vertigo (23%), headache (13%), and nausea (15%). However, this treatment should be cautiously applied to high-risk patients, such as those suffering from psychosis, substance abuse, or health problems that are intensified due to ketamine consumption, e.g., uncontrolled blood pressure, aneurysm, or Increased Intracranial Pressure (ICP).[39] Past studies also sought efficacious treatments to cure anxiety disorders. For example, due to the time-consuming nature of different psychotherapeutic methods in curing anxiety disorders and the high cost of these treatments, Karbasi *et al*. (2018) employed Internet-based Cognitive-Behavioral Treatment (CBT) to reduce costs and shorten the treatment time of patients. To the results of this study and ours, if ketamine is combined with CBT in future studies, CBT will be more effective with the immediate impact of ketamine on concentration.[43] Furthermore, other studies have confirmed the effect of internet-based CBT on curing anxiety disorders.[44-46] Karbasi *et al*. (2018) examined the effect of parent CBT on the rise of self-confidence and fall of anxiety symptoms in children with Attention Deficit Hyperactivity Disorder (ADHD) and suggested mixing CBT with ketamine therapy in ADHD-suffering children with anxiety disorders.[47] Karbasi *et al*. (2010) examined the effect of group CBT held fully and partially in person on the reduction of anxiety symptoms among adolescent girls,[33] and Islami *et al*. (2015) sought to immediately cure children with Nyctophobia (fear of the dark) by designing a mechatronic simulator, though this disorder is not an emergency disorder in psychiatry.[48] In the present study, we pursued to discover efficacious pharmaceutical methods for curing emergency anxiety disorders in children.

Research limitations

Similar to other studies, the present study suffers from some limitations that should be considered during the data description. The participants were evaluated by self-report questionnaires. Although they are valid and suitable scales for anxiety measurement, they may not be adequately appropriate for obtaining accurate data since anxiety is an internal disorder. Therefore, it is better to combine them with objective methods, such as Functional Brain Assessment. The results should also be cautiously generalized since this study has examined children in Isfahan city. It is also suggested that future studies replicate this research by considering longer follow-up periods and larger sample sizes.

Conclusion

About the emergency nature of school refusal separation anxiety disorder among children and its long-term consequences, we need immediate treatments in the initial weeks of diagnosis. As mentioned, recent studies have displayed the immediate anti-anxiety and anti-depression effects of ketamine. In the current research, ketamine revealed a faster effect initially but an equal effect to fluvoxamine in the long run. Furthermore, no serious side effects were reported for this medication. Thus, ketamine is suggested in the first weeks of treating emergency cases of anxiety, like school refusal and separation anxiety disorder. Likewise, considering the immediate initial impact of ketamine and its similar effect to fluvoxamine after several weeks, we suggest future studies apply a combination treatment of ketamine and fluvoxamine in the initial weeks and stop prescribing it after the therapeutic impact of fluvoxamine commences several weeks later.

Ethics code

IR.MUI.MED.REC.1399.1161.

Clinical trial code

IRCT20211004052670N3.

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Conflicts of interest

There are no conflicts of interest.

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