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RESEARCH ARTICLE

Coadministration of ketamine with conventional antidepressants in animal models of depression

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ABSTRACT

Background: Mental health has become one of the thrust areas for research given the complexity of the human mind and paucity of treatment strategies to handle its dysfunction effectively. The mental disorders gain prominence due to the damage they can cause to the individual themselves, the people who are in contact with them and to the society at large. Depression is a mental disorder which is encountered frequently and needs immediate attention. Conventional antidepressants such as selective serotonin reuptake inhibitor and tricyclic antidepressants are used in the management of depression. These drugs have a poor safety profile, take time for therapeutic response and have issues with patient compliance as a concern. Hence, it is postulated that concurrent administration of ketamine with conventional antidepressants would relieve the effects of depression more rapidly, would lower the dose of the later and would be more efficacious. **Aims and Objectives:** To study the antidepressant effect of coadministration of ketamine with conventional antidepressants in animal models of depression. **Materials and Methods:** The study was a randomized controlled animal study done on 36 male albino BALB/c mice divided into six groups, namely, Group A distilled water i.p., Group B imipramine 10 mg/kg (i.p.), Group C ketamine 10 mg/kg, Group D escitalopram 5 mg/kg (i.p.), Group E imipramine 10 mg/kg (i.p.) and ketamine 10 mg/kg (i.p.), and Group F escitalopram 5 mg/kg (i.p.) and ketamine 10 mg/kg (i.p.), respectively. The animal model used was the forced swim test. The reduction in immobility time was taken as the guide for the antidepressant effect. **Results:** The data were analyzed with the one-way ANOVA test using SPSS version 18. The results showed a significant reduction in immobility time and a statistical significance between the groups ($P = 0.017$). A *post-hoc* test showed that all the groups, i.e., B, C, D, E, and F significantly reduced the immobility time in comparison with the control Group A. **Conclusion:** The above results support the fact that coadministration of ketamine can be a treatment modality for the management of depression with the advantage of quicker onset of action.

KEY WORDS: Ketamine; Forced Swim Test; Escitalopram; Antidepressant; Imipramine; Coadministration

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INTRODUCTION

Depression is a common mental disorder, characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, and feelings of tiredness and poor concentration.[1] Almost 1 million lives are lost yearly due to suicide, which translates to 3000

suicide deaths every day. It is estimated that by the year 2020 if current trends for demographic and epidemiological transition continue, the burden of depression will increase to 5.7% of the total burden of disease and it would be the second leading cause of disability-adjusted life years.[2] A recent large population-based study from South India, which screened more than 24,000 subjects in Chennai, using patient health questionnaire-12 reported overall prevalence of depression to be 15.1% after adjusting for age using the 2001 census data.[3]

Conventionally used antidepressants are selective serotonin reuptake inhibitor and Selective norepinephrine reuptake inhibitor.[4] It is suggested that chronic stress activates the hypothalamic pituitary adrenal axis (HPA) in certain susceptible people producing changes in central monoamines and increased levels of stress decreased neurogenesis in dentate gyrus of the hippocampal region, thus producing abnormalities in the HPA axis. It is also well documented that the high level of glucocorticoid and glutamate receptors on such central neurons is postulated as mediating the alterations.[5] Targeting the antiglutaminergic effects of ketamine would yield a possible antidepressant effect.[6] Ketamine is classified as an dose of an N-methyl-D-aspartate (NMDA) receptor antagonist. Clinical studies suggest that acute administration of ketamine ameliorates depressive symptoms in patients suffering from major depression.[7]

From the above review of research data available we postulate that concurrent administration of ketamine with conventional antidepressants would relieve the depression effects more rapidly and would be more efficacious than treated with a single drug. Another reason for this study is that the conventionally used antidepressant take a longer time to act and whether coadministration can have a faster onset of action will be analyzed. This study is just an initiation of the above said ideas and confirmation of the study has to be done on a larger scale and with human trials.

There are very few studies which have been done with coadministration of ketamine with other drugs and with antidepressants in particular. Hence, in this study, the effect of coadministration of ketamine with conventional antidepressants in animal models of depression was studied, and the relationship between antiglutaminergic agents and depression was analyzed.

MATERIALS AND METHODS

Animals

This study was an experimental animal study. Adult male albino mice of 14–20 weeks each weighing 20–30 g were used for this experiment and were equally divided into six groups. Laboratory-bred adult male albino mice (BALB/c strain) were used for this study. They were kept in the animal house (SMVMCH, Puducherry, India) and maintained on a standard pellet diet and water *ad libitum* throughout the experimental period. Experiments were conducted within the guidelines of CPCSEA. The experimental study was approved by the Institutional Animal Ethics Committee.

Drugs and Apparatus

- Drugs: Ketamine, imipramine, escitalopram.
- For drug administration: Distilled water.
- Antidepressant effect: Forced swim test apparatus.

Methods

Evaluation of antidepressant activity using forced swim test. 36 albino BALB/c male mice were used. They were divided into six groups of 6 animals in each group based on the drug which was given.

Forced Swim Test

The test was done in a cylindrical plastic apparatus of size 10 cm in diameter and 25 cm in height. It has a water column to the height of 10 cm.[8,9]

The animals were made into six groups, each having 6 animals.

- Group A - control was provided with 0.25 ml of distilled water i.p to counteract the placebo effect.
- Group B - drug 1 was given imipramine of 10 mg/kg (i.p.).
- Group C - ketamine 10 mg/kg.
- Group D - drug 2 was given escitalopram 5 mg/kg (i.p.).
- Group E - coadmin 1 was given imipramine of 10 mg/kg (i.p.) and ketamine of 10 mg/kg (i.p.).
- Group F - coadmin 2 was treated with escitalopram of 5 mg/kg (i.p.) and ketamine of 10 mg/kg (i.p.), respectively.

The cylinder was filled with water up to 10 cm of height; the temperature of the water was maintained at 25°C.[9] Each animal from the group was administered with drug 20 min earlier and then subjected to the forced swim test. The usual procedure to test each mouse involves only 6 min session in which the activity of mouse in the initial 2 min was discarded and the period of immobility for the remaining 4 min was analyzed. The mice were individually forced to swim inside the tank, then removed and allowed to dry before returning them to the home cage. The observation of immobility was made in such a way that there can be little and finer movements, for the mouse to keep its head out of the surface of water.[10] This state of immobility provides the state of depression of the animal. The immobility time obtained from the various groups was then compared. Antidepressants decrease the period of immobility.

RESULTS

The data were analyzed statistically using one-way ANOVA followed by *post-hoc* analysis with SPSS software 18. Video recording was done for all the sessions on the forced swim test as 6 min duration for each encounter. Each animal was allowed only one encounter as experiment naïve mice were only used. The immobility time was recorded using a stopwatch, and the recording was not made by the principal investigator to avoid bias. Statistical analysis was performed using one-way ANOVA with SPSS software 18.0.

Mean duration of immobility [Figures 1 and 2] in the control Group (A) was observed to be 175 ± 22.99 seconds, whereas it was about 130 ± 15.10 seconds in the Group (B) treated with imipramine 10 mg/kg. The ketamine only Group (C) showed a mean immobility time of 127 ± 28.09 seconds and the coadministered Groups (E and F) had 107 ± 38.63 and 105 ± 51.94 seconds, respectively. The escitalopram Group (D) clocked 114+39.77 s of immobility. All values denoted as a mean ± standard deviation.

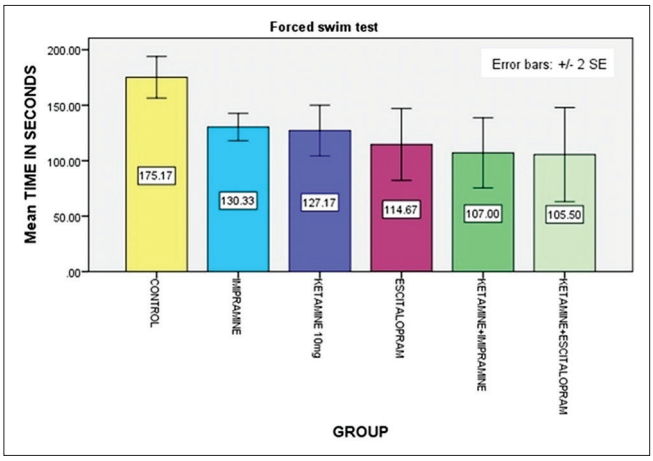

Figure 1: Mean duration of immobility indifferent groups

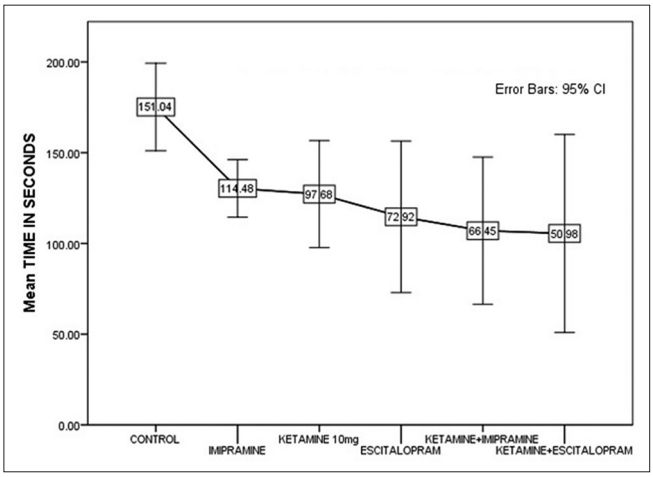

Figure 2: Trendline of mean immobility time

As can be seen in Table 1, in the forced swim test ANOVA revealed a significant overall difference between all the Groups (F [5, 30] = 3.29, $P < 0.05$) on the period of immobility time. A least significant difference *post-hoc* analysis was performed [Table 2] to assess the difference more specifically. The control group A was compared with the various other groups, i.e., individual drugs (imipramine, escitalopram, and ketamine) and coadministered drugs (ketamine plus imipramine and ketamine plus escitalopram). All the groups showed a significant decrease in immobility time in comparison with the control group. The various p values are given in Table 2 and <0.05 was considered significant.

DISCUSSION

Depression has been on the rise steeply in all parts of the globe leading to significant morbidity, decreased the quality of life and mortality. In our present study, the antidepressant effect of ketamine when coadministered with conventional antidepressants such as imipramine and escitalopram was the main objective of this study. The study was conducted with the Forced Swim Test of mice, a standard animal model predictive of antidepressant activity.

Berman *et al.* conducted the first placebo-controlled, double-blinded trial to assess the treatment effects of a single NMDA receptor antagonist in patients with depression. It was found that patients with depression showed significant improvement in depressive symptoms when given intravenous ketamine (5 mg/kg) which was assessed by the Hamilton depression rating scale.[11-13] Ketamine was also evaluated for treatment-resistant depression with repeated corticosterone (CORT)-treated rats as an animal model and found to be effective.[14] Zarate *et al*. results also concluded that targeting the NMDA receptor complex may bring about rapid and relatively sustained antidepressant effects. This line of research is favorable for developing new treatments for depression with the potential to decrease much of the morbidity and mortality associated with the delayed onset of action of conventional antidepressants.[15,16] A number of studies have been published on the mechanism of antidepressant effect of ketamine. The summary of pharmacodynamics is (1) blockade of interneuronal NMDA receptors, (2) disinhibition of pyramidal cells leading to a glutamate surge, (3) activation of the AMPA receptors, (4) blockade of the excitotoxic extrasynaptic NMDA receptors, (5) activation of synaptogenic intracellular signaling and brain-derived neurotropic factor pathways, and (6) stimulation of the mammalian target of rapamycin.[17–21] In another study, Salat *et al*. studied the antidepressant effect of ketamine, norketamine and dehydro ketamine using the forced swim test. They concluded that ketamine (10 mg/kg) and norketamine (50 mg/kg) reduced immobility time whereas dehydro norketamine did not. Interestingly

Table 1: ANOVA test for antidepressant effect denoted by decrease in immobility time

ANOVA					
Time in seconds					
Comparison	**Sum of squares**	**df**	**Mean square**	**F**	**Significant**
Between groups	20068.472	5	4013.694	3.290	0.017
Within groups	36599.833	30	1219.994		
Total	56668.306	35			

Table 2: ***Post-hoc*** analysis

Post-hoc	**(I) Group**	**(J) Group *n*=6**	**Mean difference (I-J)**	**SE**	**Significant**
LSD	Control	Imipramine	44.83333*	20.16593	0.034
		Ketamine	48.00000*	20.16593	0.024
		Escitalopram	60.50000*	20.16593	0.005
		Ketamine+imipramine	68.16667*	20.16593	0.002
		Ketamine+escitalopram	69.66667*	20.16593	0.002

**P* value < 0.05. LSD: Least significant difference

oral administration of ketamine did not affect motility. In our present study also ketamine dose has been kept at 10 mg and a significant reduction in immobility time was seen.[22] A study was conducted by Réus *et al.,* indicates that coadministration of imipramine and NMDA receptor antagonist, ketamine, may have an increased antidepressive activity than treatment with imipramine alone.[23] In our study also coadministration of ketamine with imipramine and also with escitalopram has shown an increased antidepressant effect as evidenced by the reduction in immobility time in forced swim test.

This study has some limitations as the sample size is smaller as the principles of 3 Rs. were followed, needs research on a larger scale, clinical testing is necessary and different dose ranges have to be tried. The strength of the study is that robust statistical analysis has been done.

CONCLUSION

Hence, ketamine may be considered as a good candidate for adjuvant therapy, dose reduction of coadministered antidepressants and also for rapid onset of action which is lacked by the conventional antidepressants. Ketamine along with conventional antidepressants can be evaluated in humans to provide a rapid relief from depression in treatment-resistant cases. Further research would pave the way for a newer group of antidepressant that would act on NMDA receptors.

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