Original Article

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Efficacy of Ketamine as an Adjuvant to Antidepressants in the Treatment of Depression

Psychiatry/Mental Health Section

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ABSTRACT

Introduction: Depression is the second leading cause of morbidity worldwide. Currently, available antidepressants mostly target the monoamine system. The onset of action and response rates for these antidepressants are varied. Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist has shown rapid onset of action in the treatment of depression. The available literature about intravenous (i.v.) ketamine as an adjuvant to oral antidepressants is limited.

Aim: To study if ketamine is beneficial as an adjuvant to antidepressants in the treatment of depression.

Materials and Methods: This study was a prospective interventional study conducted at JSS Medical College and Hospital, Mysuru, Karnataka, India, between January 2019 to January 2021. Total 60 patients diagnosed with depression and receiving 20 mg per day of the Selective Serotonin Reuptake Inhibitor (SSRI) escitalopram were recruited. The patients were divided into two groups of 30. Group I was continued only on the oral antidepressant antidepressant and the group II in addition to the oral antidepressant received 3 doses of i.v. infusion of ketamine hydrochloride, on alternate days. All the patients were assessed using the Montgomery-Asberg Depression Rating Scale (MADRS) and the Beck Scale for Suicidal Ideation (BSSI) at baseline and after 14 days. Statistical measures like Cramer's V, Independent samples t-test (to match both groups for age) and repeated measure Analysis of Variance (ANOVA) was employed and data collected were analysed through the IBM Statistical Package for the Social Sciences (SPSS) statistics for windows, version 20.0.

Results: The mean age of the sample population was 37.883±8.128 years. There was statistically significant improvement in depressive symptoms in group II when compared to group I. There was a decrease in mean MADRS scores by 6.07 in Group I and by 8.10 in Group II (p-value=0.011). The improvement was statistically significant in four items on the MADRS scale, namely, reported sadness (p-value=0.015), inner tension (p-value=0.021), pessimistic thoughts (p-value=0.00034) and suicidal thoughts (p-value=0.001), as well as the total MADRS score (p-value=0.011). The mean change in BSSI scores from baseline to final reading improved in both the groups (p-value=0.740).

Conclusion: Intravenous ketamine as an adjuvant to oral antidepressant medications, showed greater and more rapid improvement than that seen with oral antidepressants alone. It can be considered as an effective adjuvant to other antidepressants and future studies are required to establish this.

Keywords: Major depressive disorder, Mood disorder, Suicide

INTRODUCTION

Depression is a global burden that causes significant morbidity and mortality. It contributes greatly to deterioration of interpersonal relationships, risk of substance abuse, suicides, and an increase in disability adjusted life years [1]. According to the World Health Organisation, close to 800,000 people die due to suicide every year [2]. Out of these, about 135,000 (17%) suicides happen in India [3].

The mainstay of treatment for depressive disorders remain medications acting via the monoamine pathways [4,5]. However, their efficacy is often unsatisfactory as evidenced in the large, randomised, multi-step National Institute of Mental Health (NIMH)-funded Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. In this study, only 47% of subjects showed response to standard antidepressant treatment and only a third achieved remission [4]. In another large scale study, more than half of the depressed patients, who were treated with two antidepressants, had remission only after six months of treatment [6]. An open label study assessing the cost efficacy of and compliance to antidepressant medications in a rural setting in India reports that only 33.4% of the subjects tolerated, responded to and remained compliant to the prescribed 24 weeks of antidepressant treatment [7].

A significant proportion of patients remain refractory despite adequate dosage, duration of treatment and compliance to multiple mono-therapy medications, or augmentation strategies and combinations, which include mood stabilisers and electroconvulsive therapy [8]. Most antidepressants show clinically noticeable efficacy after a lag time ranging from one to four weeks [9]. Furthermore, the efficacy of antidepressants in bipolar depression has been brought into question [10]. Treatment modalities that exert rapid antidepressant effects are an unmet need and to achieve meaningful advances in the treatment of depression, engaging novel molecular targets is necessary [11].

In the quest to find alternative models for pathophysiology of depression apart from the monoamine hypothesis, various gene expression studies, postmortem investigations as well as brain imaging studies have been conducted. These studies postulate glutamatergic transmission abnormalities in the aetiology of depression. Ketamine, a dissociative anaesthetic, antagonises N-Methyl-D-Aspartate (NMDA) receptors [12-16]. The mechanisms of antidepressant effect of ketamine are thought to be through its disinhibitory action on the glutamatergic system, its enhancing effect on α-Amino-3-hydroxy-5-Methyl-4-isoxazolepropionic Acid (AMPA) receptor receptors, and also its partial agonism at D2 Dopaminergic receptors [17]. The antagonistic action of ketamine on NMDA receptors is due to slow open channel blocking/unblocking kinetics. It specifically affects a type of channel closure, called "trapping block" [18]. Animal models have also demonstrated rapid antidepressant effects of ketamine at subanaesthetic doses [19].

Preclinical data indicate that within hours of its administration, ketamine increases the number and functioning of the synaptic connections in the hippocampus and cortical regions. Ketamine rapidly reverses neuronal and behavioural changes associated with chronic stress through its activation of the mammalian target

of rapamycin signaling pathway. Ketamine also stimulates brain derived neurotrophic factor signaling [20,21]. Recent studies have found that the antidepressant effect of ketamine was lesser in depressed patients who were carriers of Val66Met (rs6265) single nucleotide polymorphism; representing an attenuation of brain derived neurotropic factor functioning [22-24].

A previously conducted study reported rapid antidepressant effects of ketamine in patients with treatment resistant depression. It also demonstrated that the initial rapid antidepressant effect of ketamine postinfusion gradually waned with each passing day [25]. Similar effects were also seen with bipolar depression [26]. Most of these previously conducted studies have utilised ketamine as monotherapy. The clinically relevant question of the possible use of ketamine as an adjuvant to currently available modalities has not been widely addressed. Thus, this study aimed to assess the effectiveness of ketamine in multiple successive doses as an adjuvant to oral antidepressant medication. The novelty of this study is that it looks at the effect of repeated dosing of ketamine, something not explored into enough by previous studies. Also, it looks into ketamine being used as an adjuvant, which is also something that has not been explored enough previously.

MATERIALS AND METHODS

The study was a prospective interventional study conducted in Psychiatry Outpatient Department (OPD) at JSS Medical College, Mysuru, Karnataka, India, between January 2019 to January 2021. It included patients in the age group of 20 to 59 years. The study was approved by the Institutional Ethical Committee (Approval number: JSS/MC/PG/4623/2018-19, dated 2/11/2018).

Inclusion criteria:

- Subjects diagnosed with moderate or severe depression by a qualified Psychiatrist according to the International Classification of Diseases,Tenth Revision (ICD-10) Classification of mental and behavioural disorders [27].
- Patients with both unipolar as well as bipolar depression, with or without obsessive compulsive symptoms.
- Subjects who gave written informed consent, in a language best understood by them.

Exclusion criteria:

- Subjects with psychotic symptoms.
- Subjects with a history of any other major co-morbid psychiatric disorder, organic disorders, or substance use disorders except (nicotine or caffeine).
- Patients with cardiac ailments, hypertension, urinary tract infections or abnormalities on fundoscopy were also excluded from the study.

Sample size calculation: A total of 60 subjects were enrolled by purposive sampling, with the formula

$n=Z^2pq/d^2$

Considering 4% of global prevalence of depression [28] and Z value of 1.96 and d value of 0.05. The 60 adult subjects were divided into two groups of 30. Both the groups were matched for age using Independent samples t-test.

Procedure

Both the groups of patients were kept on a dose of 20 mg of the orally administered Selective Serotonin Reuptake Inhibitor (SSRI), escitalopram throughout the course of the entire study. The patients in the first group were continued only on the oral antidepressant, tablet escitalopram (20 mg) per day [29], without being administered ketamine infusions. The second group was additionally administered three intravenous (i.v.) ketamine infusions, on three alternate days [30]. The subjects were assessed according to the Montgomery-Asberg Depression Rating Scale (MADRS) [31] and the Beck Scale for Suicidal Ideation (BSSI) [32].

For Group I:

Confirmation of diagnosis and informed consent
↓
Application of the MADRS and the BSSI at the time of enrolment
↓
Antidepressant medication- Tablet escitalopram 20 mg per day, continued over two weeks
↓
Reassessment by applying the MADRS and the BSSI two weeks after enrolment

For Group II:

Confirmation of diagnosis and informed consent
↓
Application of the MADRS and the BSSI at the time of enrolment and continuation of tablet escitalopram 20 mg per day over two weeks
↓
Detailed preanaesthetic evaluation conducted by a qualified anaesthesiologist
↓
Administration of injection midazolam 1 mg i.v. followed by injection glycopyrrolate 0.2 mg i.v. by a qualified anaesthesiologist to attenuate the potential ketamine induced emergence phenomena [33] and hypersalivation [34] respectively
↓
Administration of i.v. infusion of ketamine hydrochloride 0.5 mg/kg, diluted in 100 mL normal saline, over 40 minutes, under supervision of a qualified anaesthesiologist [30]
↓
Ongoing monitoring of patient's physiological status and vital signs during the infusion
↓
Three such does on alternate days following due procedure as described
↓
Reassessment by applying the MADRS and the BSSI two weeks after first dose of i.v. ketamine

STATISTICAL ANALYSIS

The level of significance was set to 0.05. Data collected were analysed through the IBM Statistical Package for the Social Sciences (SPSS) statistics for windows, version 20.0 (IBM Corp., Armonk, NY, USA). Descriptive statistical measures like mean, standard deviation, frequency and percentage were used. Inferential statistical measures like Cramer's V, Independent samples t-test (to match both groups for age) and repeated measure Analysis of Variance (ANOVA) were employed.

RESULTS

Socio-demographic characteristics: [Table/Fig-1] showed the socio-demographic details of the participants in the study. The mean age of the sample population was 37.883±8.128 years. Amongst the study subjects, 33 were females (16 in group I and 17 in group II) and 27 were males (14 in group I and 13 in group II). The gender ratio of male:female was 1:1.22. Maximum number of study subjects fell in the age groups of 31-40 and 41-50 years. The majority of the patients were Hindu (93.33%), married (78.30%), illiterate (58.33) and from a rural background (76.67%).

Clinical characteristics: The mean ages for subjects in group I and group II were 37.40±8.365 years and 38.367±7.998 years, respectively. Both the groups were matched for age using Independent samples t-test and there was no difference between them with regards to age. [Table/Fig-1] also shows the age distribution of the patients in both the groups. A majority of the study participants were diagnosed with recurrent depressive disorder (61.67%). Other diagnoses included bipolar depression (23.3%),

Variables	Group I	Group II	Total	Cramer's V test	p-value
Age (years)					
21-30	7 (23.3%)	4 (13.3%)	11 (18.3%)	0.238	0.334
31-40	13 (43.3%)	9 (30%)	22 (36.7%)		
41-50	8 (26.7%)	13 (43.3%)	21 (35%)		
51-59	2 (6.7%)	4 (13.3%)	6 (10%)		
Gender					
Male	14 (46.7%)	13 (43.3%)	27 (45%)	0.034	0.795
Female	16 (53.3%)	17 (56.7%)	33 (55%)		
Marital status					
Married	24 (80%)	23 (76.7%)	47 (78.3%)	0.04	0.754
Unmarried	6 (20%)	7 (23.3%)	13 (21.7%)		
Religion					
Hindu	28 (93.33%)	28 (93.33%)	56 (93.33%)	0	1.00
Others	2 (6.67%)	2 (6.67%)	4 (6.67%)		
Education status					
Illiterate	17 (56.66%)	18 (60%)	35 (58.33%)	0.086	0.803
Below secondary	6 (20%)	7 (23.34%)	13 (21.66%)		
Secondary and above	7 (23.33%)	5 (16.66%)	12 (20%)		
Region					
Urban	8 (26.66%)	6 (20%)	14 (23.33%)	0.079	0.542
Rural	22 (73.34%)	24 (80%)	46 (76.67%)		

[Table/Fig-1]: Socio-demographic characteristics.
Test of significance-Cramer's V test, The level of significance was set to 0.05

Unipolar depression (11.7%) and depression with obsessive compulsive symptoms (3.3%), as shown in [Table/Fig-2].

A 66.7% of the subjects had been diagnosed with severe depression while the rest (33.3%) had been diagnosed with moderate depression, as depicted in [Table/Fig-3].

Diagnosis	Group I	Group II	Total
Bipolar depression	8 (26.7%)	6 (20%)	14 (23.3%)
Unipolar depression	5 (16.7%)	2 (6.7%)	7 (11.7%)
Depression with obsessive compulsive symptoms	2 (6.7%)	0 (0)	2 (3.3%)
Recurrent depressive disorder	15 (50%)	22 (73.343%)	37 (61.67%)

[Table/Fig-2]: Diagnosis of the study participants.
Cramer's V test=0.305; p-value=0.234

Severity	Group I	Group II	Total
Moderate depression	11 (36.7%)	9 (30%)	20 (33.3%)
Severe depression	19 (63.3%)	21 (70%)	40 (66.7%)

[Table/Fig-3]: Severity of Depression.
Cramer's V test=0.071; p-value=0.584

Overall, baseline demographic and clinical characteristics did not differ significantly across both the treatment groups. All the study subjects were on the oral antidepressant escitalopram 20 mg per day, which was continued throughout the course of the study.

Changes in the MADRS scores: The changes in MADRS scores from baseline to final reading improved in both the groups as illustrated in [Table/Fig-4]. For group I (subjects receiving only oral antidepressant escitalopram 20 mg per day) the decrease in the mean total scores observed was 6.07 and for group II (subjects who received three i.v. infusions of ketamine hydrochloride on alternate days along with antidepressant escitalopram 20 mg per day) the decrease in the mean total scores observed was 8.10. Statistically significant difference was observed in mean changes in the total MADRS scores between group I and group II (p=0.011).

MADRS item	Group	Mean scores		Change (Reduction)	F	p-value
		Baseline	Final			
Apparent sadness	I	3.37	2.90	0.47	0.350	0.556
	II	2.97	2.40	0.57		
Reported sadness	I	3.53	2.87	0.66	6.288	0.015
	II	3.33	2.20	1.13		
Inner tension	I	3.23	2.77	0.46	5.659	0.021
	II	3.53	2.57	0.96		
Reduced sleep	I	3.47	2.70	0.77	0.546	0.463
	II	3.60	2.97	0.63		
Reduced appetite	I	3.23	2.70	0.53	0.418	0.521
	II	3.13	2.70	0.43		
Concentration difficulties	I	3.30	2.73	0.57	0.395	0.532
	II	3.40	2.73	0.67		
Lassitude	I	3.40	2.77	0.63	0.159	0.692
	II	3.53	2.97	0.56		
Inability to feel	I	3.37	3.03	0.34	1.000	0.321
	II	2.97	2.77	0.20		
Pessimistic thoughts	I	4.13	3.37	0.76	15.575	0.0003
	II	5.00	3.47	1.53		
Suicidal thoughts	I	3.63	2.80	0.83	11.956	0.001
	II	4.50	3.10	1.40		
Total MADRS score	I	34.70	28.63	6.07	6.851	0.011
	II	35.97	27.87	8.10		

[Table/Fig-4]: Changes in the Montgomery-Asberg Depression Rating Scale (MADRS) Scores.
Test of significance-Repeated Measure ANOVA, The level of significance was set to 0.05

Out of the 10 items in the MADRS, statistically significant difference was observed for changes in the scores for 4 of the items, among subjects in group II as compared to subjects in group I. The items for which significant difference in the changes were observed were item 2: Reported sadness (p-value=0.015), item 3: Inner tension (p-value=0.021), item 9: pessimistic thoughts (p-value=0.0003) and item 10: suicidal thoughts (p-value=0.001), as depicted in [Table/Fig-4].

No statistically significant differences were seen in mean changes for the other six items in the MADRS, when comparing both the groups.

Changes in the Beck Scale for Suicidal Ideation (BSSI) scores: The mean change in BSSI scores from baseline to final reading improved in both the groups as illustrated in [Table/Fig-5]. For group I (subjects receiving only the oral antidepressant escitalopram 20 mg per day) the decrease in the mean scores observed was 4.83 and for group II (subjects who received three i.v. infusions of ketamine hydrochloride on alternate days along with the antidepressant escitalopram 20 mg per day) the decrease in the mean scores observed was 6.14. However, no statistically significant difference was observed in mean changes in BSSI scores between group I and group II (p-value=0.740).

Groups	Scores (Mean±SD)		Decrease
	Baseline	Final	
I	23.20±5.598	18.37±5.702	4.83
II	26.27±5.239	20.13±4.208	6.14
F=0.112			
p-value=0.740			

[Table/Fig-5]: Changes in the Becks's Scale for Suicidal Ideation Scores.
Test of significance-Repeated Measure ANOVA

In the present study, with the dosing pattern employed, eight patients out of 30 who were administered ketamine, experienced mild, transient adverse reactions which resolved within 2 hours after the infusions. These included a transient rise in blood pressure, dizziness, headache and nausea. Two of the patients also experienced mild

dissociative symptoms which resolved spontaneously within an hour, without requiring intervention. The patients were monitored throughout by a qualified anaesthesiologist.

DISCUSSION

This study tries to test the efficacy of ketamine as an adjuvant treatment in a "real world" setting. There are studies which demonstrated the rapid antidepressant action after single i.v. infusion of ketamine in a subanaesthetic dose [12-16]. Single i.v. infusion of ketamine has also been shown to bring about a quick reduction in suicidal ideation [35]. In a study the antidepressant effects of ketamine were not found to be statistically significant when measured after a period of seven days post single infusion [25]. Studies on repeated dosing remain limited. As discussed earlier, the lag time as well as the response rates to antidepressants is variable. The present study makes an attempt to establish the complimentary role of ketamine to antidepressants in increasing recovery rates as well as the rapidity of recovery, after three successive doses.

This study demonstrates that ketamine administered in repeated doses, along with antidepressants, significantly reduces depressive symptoms when compared to subjects receiving only antidepressants, assessed seven days post infusion. A double blind, randomised, placebo controlled study administered ketamine twice and thrice within a week to patients with treatment resistant depression and found statistically significant decrease on the MADRS that persisted on day 15 after administration [36]. The present study found that the improvement as seen on the MADRS scale, sustained after two weeks of the first dose of infusion. There was statistically significant improvement in four items of the MADRS, namely reported sadness, inner tension, pessimistic thoughts and suicidal thoughts among patients who received ketamine as an adjuvant to escitalopram. One study which administered ketamine as an i.v. bolus in six doses over two weeks, found significant decrease in anxiety within 1 hour of the first dose, with the effects lasting for up to two weeks [37]. Similarly, the current study found a statistically significant decrease in inner tension, which in the MADRS is represented as feelings of ill-defined discomfort, edginess, inner turmoil and mental tension mounting to either panic, dread or anguish.

An earlier study reported a reduction in clinician rated explicit as well as implicit suicidal cognition with ketamine. It showed that suicidal cognition got continuously eradicated after thrice weekly repeated ketamine infusion [38]. The findings in the current study of a significant reduction in reported sadness, pessimistic thoughts and suicidal thoughts in the group of patients administered ketamine as an adjuvant to escitalopram, is in keeping with the findings of these above mentioned studies. The current study also employed the BSSI. Though there was a decrease in the scores in both the groups, there was no statistically significant difference between them.

Other drugs have been tried as adjuvants to antidepressants, which include gingko biloba [39], L-Thyroxine [40], omega-3 fatty acids [41,42] and N-acetyl cysteine [43]. The study which used gingko biloba as an adjuvant to the antidepressant citalopram, found improvement in depressive symptoms at the end of two weeks but the effect was more pronounced after four weeks [39]. The study that augmented serotonergic antidepressants with L-thyroxine in females with refractory depression, found significant improvement in 64.7% of the patients after a four week period [40]. Studies using omega-3 fatty acids found improvement after six weeks [41,42]. The study which used N-acetyl cysteine reported improvement only after 20 weeks [43]. However, the literature regarding the use of ketamine as an adjuvant to antidepressants, is limited.

Antidepressant drugs might rarely cause an increase in agitation and suicidal ideation as an adverse effect and is more likely at the time of antidepressant initiation and antidepressant dose up-titration [44]. The finding in the present study of a rapid decrease in inner tension along with the marked decrease in suicidal ideation brought about by ketamine may, in theory, be able to counteract this antidepressant induced agitation and ketamine may thus be used as an adjuvant to antidepressants as risk mitigation strategy for suicide. This however is subject to future research.

According to a meta-analysis, down regulation of glutamate and glutamine in the anterior cingulate cortex could be one of the contributing factors for depressive symptoms. The findings in the current study support NMDA receptor antagonism as a possible new direction and option in the treatment of depression [45].

As elaborated in the results section, the adverse effects experienced by a few patients in the present study were transient and the patients recovered fully within two hours. These findings are consistent with a study which reported that ketamine is well tolerated at sub-anaesthetic doses [46].

Limitation(s)

An open-label design and concomitant administration of SSRI could possibly have influenced the results. Specifically, it would not be possible to assess the extent of observed decrease in depressive symptoms and suicidal ideation occurring exclusively due to the use of ketamine. The study did not include an assessment of subjects immediately after ketamine infusions, which prevents it from commenting upon the early response to ketamine (within hours) as observed in other studies. The study also did not include a comparison of effects of ketamine between unipolar and bipolar depression. The lack of long term follow-up and assessment of subjects administered ketamine can also be considered a limitation.

CONCLUSION(S)

There was statistically significant improvement in the group of subjects that received ketamine. Ketamine was found to have a good, rapid response with a significant decrease in suicidal ideation, when used along with the SSRI escitalopram. This suggests that it can be used as an effective adjunct to antidepressant medications, especially at the beginning of starting oral antidepressant medications and in cases where patients are at high risk of self-harm or suicide.

Considering that SSRIs are likely to remain at the forefront of the treatment of depression in the foreseeable future, more studies that involve SSRIs and the adjuvant use of ketamine should be conducted. Further studies comparing benefits of ketamine in unipolar depression with bipolar depression would also help in determining the profile of patients who may benefit from this potentially game changing treatment option. Another pertinent issue with administration of ketamine could be its potential for abuse. Further research is also needed to gain more clarity regarding the use of ketamine in a clinical setting it's dosing and frequency, safety and long term effects, maintenance treatments and precautions which could potentially lead to it gaining approval as part of the guidelines for the treatment of depression.

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