

# Efficacy and Safety of Single Intravenous Ketamine Infusion as an Add-on to Escitalopram in Major Depression: A Randomized, Double-blind, Placebo-controlled Study

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## ABSTRACT

**Background:** There is a paucity of studies exploring the role of ketamine as augmenting agent to conventional antidepressants.

**Materials and methods:** Sixty patients with major depressive disorder (MDD) were randomized to 4 weeks' double-blind treatment with escitalopram 10 mg/day + single-dose intravenous (IV) ketamine (0.5 mg/kg over 40 minutes) or escitalopram 10 mg/day + placebo (0.9% IV saline). Depressive symptoms were measured using the Montgomery–Asberg depression rating scale (MADRS), adverse effects were measured with the brief psychiatric rating scale (BPRS), young mania rating scale (YMRS), and clinician administered dissociative states scale (CADSS). Patients were assessed at baseline, 4, 24, and 48 hours and 7 days and 28 days. Response (50% MADRS score reduction) was the primary outcome.

**Results:** The MADRS scores showed significant reduction in the group receiving ketamine as compared to group receiving placebo at 4, 24, and 48 hours, 1 week, and 28 days ( $p < 0.001$ ). By 4 weeks, compared to escitalopram + placebo-treated patients, more of escitalopram + ketamine-treated patients responded (80% vs 20%) and remitted (21.67% vs 0%). Rapid response was evident at 4 hours in ketamine group as compared to placebo (36.67% vs 0%). Both CADSS and YMRS scores were significantly higher ( $p < 0.001$ ) in the ketamine group as compared to the placebo group at 4 hours but not at 24 and 48 hours and 7 and 28 days.

**Conclusion:** Single-dose IV ketamine as an add-on to 10 mg/day escitalopram is efficacious, resulting in more rapid and robust response over 4 weeks. Dissociative and mania-like symptoms emerging post-infusion are mild and transient, not warranting treatment discontinuation. Further research into the role of ketamine augmentation in MDD is required for its clinical applicability.

**Keywords:** Depression, Ketamine, Randomized controlled trial.

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## INTRODUCTION

Major depressive disorder (MDD) is a common psychiatric disorder affecting people of all ages, genders, and different socioeconomic groups in India and all over the world. In 2015, MDD is ranked by the World Health Organization (WHO) as the single largest contributor to global disability, accounting for 7.5% of all years lived with disability.<sup>1</sup>

Although effective pharmacological and psychosocial interventions exist, it may take weeks or months before clinically relevant efficacy is apparent.<sup>2</sup> This further increases suicide risk and illness burden, particularly during the initial days after starting antidepressants.<sup>2</sup> With the possible exception that drugs with dual serotonin and norepinephrine mechanisms may be marginally more effective than the selective serotonin reuptake inhibitors, currently available drugs for treating depression have marginal differences in efficacy.<sup>3</sup> Research over the last decade has focused on the role of glutamatergic system in the pathophysiology of MDD and to expedite antidepressant action.<sup>4,5</sup>

Data from published placebo-controlled, double-blind, randomized clinical studies on IV ketamine infusion in the treatment of depression present “compelling evidence that the antidepressant effects of ketamine infusion are both rapid and robust, albeit transient.”<sup>6</sup> Ketamine in subanesthetic doses is safe in healthy individuals and has rapid-onset efficacy in patients with severe and even treatment-refractory depression.<sup>7</sup> The intermittent use of low, subanesthetic doses of ketamine has not been reported to be associated with cystitis and other medical concerns.<sup>7</sup>

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Most trials examining the role of ketamine in the treatment of MDD are crossover studies, limited by small sample sizes, methodological variations, and have targeted treatment-resistant depression, thereby limiting the generalization of the findings. The effects of add-on ketamine on the currently available antidepressants have not been examined, and it is unknown whether concurrent initiation or oral antidepressant treatment with a single IV dose of ketamine could expedite antidepressant efficacy and reduce the lag of the first few weeks until clinically relevant antidepressant effects are seen with oral antidepressants. Hu et al. carried out a 4-week double-blind randomized placebo-controlled trial of single IV dose of ketamine as augmentation to escitalopram in MDD patients and found that ketamine augmentation significantly reduced time to response and remission as compared to placebo.<sup>8</sup> Additional research is required

to elucidate the role of ketamine as an adjunct to existing treatments. In some studies, patient were off medication;<sup>5,9</sup> ongoing medications were continued unchanged in others.<sup>10,11</sup> In this context, consideration to continue necessary antidepressant and other medications during a ketamine trial has been suggested, especially because maintenance of antidepressant treatment will be required, should the patient respond or remit.<sup>12</sup> Therefore, the present study is designed to determine the efficacy, safety, and tolerability of a single IV ketamine infusion as an add-on to escitalopram in patients with MDD; and its methodology is a replication of Hu et al., with few variations.

The primary hypotheses for the present study are the following: (1) rapid response (same or next day) can be achieved in patients with major (unipolar) depression; (2) rapid response (same or next day) can be sustained in patients with unipolar depression; (3) compared to placebo (0.9% IV saline), ketamine augmentation of escitalopram would be associated with significantly shorter time to antidepressant response and remission, faster and clinically significant improvements in depressive symptoms and suicidal thoughts, and acceptable tolerability.

The present study aims to determine the antidepressant effects and safety of low-dose single IV ketamine infusion (0.5 mg/kg over 40 minutes) combined with escitalopram initiation in MDD.

## MATERIALS AND METHODS

### Study Type

Interventional.

### Study Design

- Allocation: randomized
- Intervention: parallel
- Blinding: double (investigator, participant)

Enrollment of participants was commenced after approval from the Institute Research Review Committee and Institute Ethics Committee. Application for registration was made with clinical trials registry, India.

## GENERAL ELIGIBILITY

### Inclusion Criteria

- Patient seeking treatment at the Department of Psychiatry, Geetanjali Medical College and Hospital (GMCH), Udaipur.
- Male or female patients, 18–65 years of age.
- Each subject must have a level of understanding sufficient to agree to all required tests and examinations and sign an informed consent document.
- Subjects must fulfill diagnostic and statistical manual of mental disorders-IVth edition- text revision (DSM-IV-TR)<sup>13</sup> criteria for nonpsychotic MDD established by treating psychiatrists and confirmed by a structured clinical interview Mini International Neuropsychiatric Interview Plus.<sup>14</sup>
- Current depressive episode of at least 4 weeks duration.
- Subjects must have an initial score of  $\geq 21$  on the Hamilton depression rating scale at screen and at baseline.
- In women of childbearing age, a negative pregnancy test within 24 hours.

### Exclusion Criteria

- History of drug/alcohol use disorder in the past 6 months (other than nicotine and/or caffeine).

- History of psychiatric disorder other than MDD which are judged to be the primary presenting problem.
- History of inefficacy, hypersensitivity, and/or intolerance to escitalopram and/or ketamine.
- History of suicide attempt in the current episode.
- Pregnant or breastfeeding women.
- Major/serious, unstable illnesses including hepatic, renal, gastroenterological, respiratory, cardiovascular (including ischemic heart disease), endocrinological, oncologic, neurologic, immunologic, or hematologic disease.
- Subjects with terminal illness and/or admitted in intensive care unit.
- Subjects with one or more seizures without a clear and resolved etiology.
- Treatment with a reversible monoamine oxidase inhibitor (MAOI) within 4 weeks prior to study.
- Subjects on psychotropic medications in the preceding 2 weeks.
- Subjects on corticosteroids and anticancer therapy in the preceding 4 weeks.
- Subjects with abnormal complete blood counts, erythrocyte sedimentation rate, serum creatinine, blood urea, random blood sugar, liver and thyroid function tests, electrocardiogram (ECG), and chest radiograph (posteroanterior view).
- Subjects receiving structured psychotherapy.
- Current employee/staff of Geetanjali University or their immediate family member.
- Subjects with a history of presence of metallic (ferromagnetic) implants (e.g., heart pacemaker, aneurysm clip, joint prosthesis).

### Setting and Location where the Data was Collected

Outpatient and inpatient units of the Department of Psychiatry, Geetanjali Medical College and Hospital (GMCH), Udaipur, Rajasthan.

### Intervention

Subjects who satisfied the above eligibility criteria were randomized in blocks of 30 each to 4 weeks of fixed-dose escitalopram 10 mg/day (5 mg for first three days) plus a single saline solution infusion (placebo) or fixed dose escitalopram 10 mg/day plus a single subanesthetic dose of IV ketamine hydrochloride (total dose of 0.5 mg/kg) administered over 40 minutes. The solutions were provided in identical 50-mL syringes. Ketamine forms a clear solution when dissolved in 0.9% saline. Infusions were administered by an anesthesiologist in the Department of Anesthesiology over 40 minutes via an infusion pump. The anesthesiologist and outcome assessor were blind to the group membership of patients. Concurrently, both groups were initiated on 10 mg/day fixed-dose escitalopram, a dose within the therapeutic range recommended by the National Institute for Clinical Excellence (NICE, UK). Besides escitalopram, benzodiazepines were avoided and only zolpidem was used sparingly as needed for insomnia. Other medications not affecting the central nervous system were allowed.

### Primary Outcome Measures

- Comparison of response rates, defined as a  $\geq 50\%$  reduction from the baseline Montgomery–Asberg depression rating scale (MADRS) and remission rates, defined as MADRS total score  $\leq 10$ <sup>15</sup> between two study groups.
- Comparison of change in symptom severity assessed using MADRS periodically between ketamine + escitalopram and placebo + escitalopram groups till 4 weeks.

## Secondary Outcome Measures

- Psychotic and manic side effects were measured by the 4 items (suspiciousness, unusual thought content, hallucinations, and conceptual disorganization) of the brief psychiatric rating scale (BPRS),<sup>16</sup> and the 11-item young mania rating scale (YMRS),<sup>17</sup> respectively.
- Dissociative symptoms were measured by clinician administered dissociative states scale (CADSS).<sup>18</sup>

## Assessment Schedule

Patients underwent assessment with the MADRS, BPRS, YMRS, and CADSS at baseline, and 4, 24, and 48 hours, 7 and 28 days after the end of ketamine or placebo infusion.

Digital pulse oximetry, heart and respiratory rate, blood pressure, and ECG were recorded every 5 minutes for 1 hour beginning 5 minutes prior to the infusion. Two raters with >5 years of clinical experience and blind to the study protocol and treatment assignment independently assessed the patients using the above measurements. Prior to the study, the two raters conducted a reliability exercise of the use of the MADRS, BPRS, YMRS, and CADSS. Patients were excluded from the study if they developed a manic or hypomanic episode, attempted suicide,

had severe medical condition or suffered from newly emerging side effects that they reported to be intolerable. Those excluded from the study received antidepressant treatment as part of their ongoing clinical care.

## Data Analysis

Data were collected using predesigned proforma. Statistical analyses were done using the Statistical Package for Social Sciences for Windows, version 16 (SPSS Inc., Chicago, Ill, USA). Continuous covariates were expressed as mean with standard deviation. All statistical analyses were done at 95% confidence interval, and  $p < 0.05$  was considered statistically significant.

## RESULTS

Sixty patients were randomized to a ketamine group in which patients received escitalopram 10 mg/day + IV ketamine ( $n = 30$ ) and a placebo group in which patients received escitalopram 10 mg/day + 50 mL saline solution ( $n = 30$ ).

## Sociodemographic Variables

Two groups did not differ significantly in sociodemographic characteristics (Table 1).

**Table 1:** Sociodemographic variables of the case and control groups

	Variable	Case	Control	$\chi^2$	<i>p</i> value
Age (years)	18–24	5 (16.7%)	2 (6.7%)	3.57	0.312
	25–34	12 (40.0%)	14 (46.6%)		
	35–44	10 (33.3%)	7 (23.3%)		
	45–60	3 (10%)	7 (23.3%)		
Sex	Male	17 (56.7%)	13 (43.3%)	1.06	0.302
	Female	13 (43.3%)	17 (56.7%)		
Education	Illiterate	7 (23.3%)	8 (26.7%)	5.40	0.493
	Primary	9 (30.0%)	5 (16.7%)		
	Middle school	8 (26.7%)	5 (16.7%)		
	High school	2 (6.7%)	2 (6.7%)		
	Pre-degree/diploma	1 (3.3%)	3 (10.0%)		
	Degree/graduate	3 (10.0%)	5 (16.7%)		
	Postgraduate	0 (0.0%)	2 (6.7%)		
Marital status	Married	18 (60%)	16 (53.3%)	0.27	0.871
	Single	7 (23.3%)	8 (26.7%)		
	Divorced/widowed	5 (16.7%)	6 (20.0%)		
Average monthly income	<10 K	6 (20.0%)	9 (30.0%)	8.16	0.14
	10–20 K	4 (13.3%)	5 (16.7%)		
	20–30 K	7 (23.3%)	3 (10.0%)		
	30–40 K	8 (26.7%)	2 (6.7%)		
	40–50 K	4 (13.3%)	9 (30.0%)		
	>50 K	1 (3.3%)	2 (6.7%)		
Occupation	Unskilled	8 (26.7%)	5 (16.7%)	13.23	0.040
	Skilled	6 (20.0%)	7 (23.3%)		
	Govt.	3 (10.0%)	0 (0.0%)		
	Private	3 (10.0%)	10 (33.3%)		
	Self	8 (26.7%)	5 (16.7%)		
	Business	0 (0.0%)	3 (10.0%)		
	Professional	2 (6.7%)	0 (0.0%)		
Religion	Hindu	28 (93.3%)	27 (90.0%)	0.21	0.640
	Muslim	2 (6.7%)	3 (10.0%)		

**Table 2:** Assessment of Montgomery–Asberg depression rating scale (MADRS), brief psychiatric rating scale (BPRS), young mania rating scale (YMRS), and CADSS scores of two groups

Time point	Variable	Escitalopram + IV ketamine			Escitalopram + placebo			t	p value
		n	Mean	SD	n	Mean	SD		
Baseline	MADRS total	30	40.73	10.498	30	38.40	5.210	1.091	0.280
	YMRS total	30	1.60	0.894	30	1.87	0.900	-1.151	0.254
	BPRS	30	31.80	6.895	30	34.03	4.635	-1.472	0.146
	CADSS total	30	2.80	2.219	30	2.07	1.660	4.272	0.153
4 hours	MADRS total	30	21.87	8.435	30	37.33	4.678	-8.783	<0.001
	YMRS total	30	3.07	1.639	30	1.53	0.819	4.584	<0.001
	BPRS	30	26.30	5.736	30	34.70	3.239	-6.984	<0.001
	CADSS total	30	4.27	3.493	30	1.37	1.273	-0.501	<0.001
24 hours	MADRS total	30	21.47	8.050	30	37.07	4.690	-9.171	<0.001
	YMRS total	30	1.10	0.885	30	0.87	0.860	1.036	0.305
	BPRS	30	25.28	5.182	30	32.07	4.068	-5.610	<0.001
	CADSS total	30	0.87	1.196	30	1.03	1.377	-3.273	0.619
48 hours	MADRS total	30	21.40	7.740	30	35.53	4.569	-8.613	<0.001
	YMRS total	30	0.03	0.183	30	0.67	0.922	-3.690	0.080
	BPRS	30	24.37	4.664	30	31.63	3.926	-6.528	<0.001
	CADSS total	30	0.10	0.305	30	0.73	1.015	-3.266	0.002
1 week	MADRS total	30	18.80	6.488	30	29.40	4.760	-7.215	<0.001
	YMRS total	30	0.00	0.000	30	0.30	0.702	-2.340	0.063
	BPRS	30	21.47	4.175	30	25.97	3.605	-4.468	<0.001
	CADSS total	30	0.00	0.000	30	0.37	0.615	-1.000	0.002
1 month	MADRS total	30	16.27	6.982	30	23.33	4.619	-4.623	<0.001
	YMRS total	30	0.00	0.000	30	0.00	0.000	1.450	NA
	BPRS	30	19.80	2.441	30	22.33	2.845	-3.702	<0.001
	CADSS total	30	0.00	0.000	30	0.03	0.183	-1.000	0.321

### Clinical Profile

In group receiving ketamine, 8 patients (26.67%) were treatment refractory and 11 (36.67%) patients had recurrent depressive disorder. Of the 11 patients, 5 had had more than three episodes. Three patients had history of suicidal attempt though not in current episode.

In the group receiving placebo, 5 patients were treatment refractory (16.67%) and 12 (40%) patients had recurrent depressive disorder. Of the 11 patients, 5 had more than three episodes. Two patients had history of suicidal attempt in the past.

### Symptom Ratings and Treatment Response

Baseline MADRS scores for cases and controls showed no significant difference ( $p = 0.280$ ). The MADRS scores dropped significantly in the group receiving ketamine as compared to the group receiving placebo at 4, 24, and 48 hours and 1 week and 28 days ( $p < 0.001$ ).

Among the patients in the ketamine group, 36.67% showed 50% reduction in MADRS scores at 4 hours compared to none in the placebo group. At 28 days, 80% patients in the ketamine group showed 50% reduction in MADRS scores as compared to 20% in the placebo group. At end of 28 days, 23.33% from the ketamine group had MADRS score  $< 10$  as compared to none from the placebo group.

The baseline BPRS scores for cases and controls showed no significant difference ( $p = 0.280$ ). The BPRS scores dropped significantly in the ketamine group as compared to the placebo group at 4, 24, and 48 hours and 1 week and 28 days ( $p < 0.001$ ).

### Adverse Events and Study Discontinuation

Dissociative symptom score assessed using CADSS at baseline showed no significant difference between the two groups. The score was significantly higher in the ketamine group as compared to the placebo group at 4 hours (maximum score—12,  $p < 0.001$ ) after which a reversal was observed with scores being significantly higher at 48 hours and 7 days interval in the placebo group as compared to the ketamine group ( $p < 0.001$ ). The YMRS scores increased significantly with the ketamine group but only at the 4 hours interval. Patients in the ketamine group experienced mild side effects which were not observed after 4 hours of the infusion; and these included nausea ( $n = 4$ ), dizziness ( $n = 10$ ), and headache ( $n = 5$ ). In the placebo group, the only side effects observed within 4 hours of the infusion were dizziness ( $n = 3$ ). None of the patients in either group dropped out of the study within the 4-week time period (Table 2).

### DISCUSSION

The acute antidepressant efficacy of ketamine has been proven by the number of randomized controlled trials (RCTs) mainly in patients with treatment-resistant depression. But there have been only a few studies on the use of ketamine in routine clinical settings where patients are likely to be on other medications especially antidepressants. To the best of our knowledge, so far there has been one published RCT by Hu et al.<sup>8</sup> to test the efficacy of ketamine as an augmentation agent to oral antidepressant medication.

The present investigation is a methodological replication of the RCT by Hu et al.<sup>8</sup> with certain differences. In our study, the sample size was doubled. Hu et al. had 55.6% patients with treatment-resistant depression in their study, making it difficult to generalize their results.<sup>12</sup> In our study, 20% of the patients were diagnosed with treatment-resistant depression.

Our study aimed to test whether single-dose IV ketamine when given with conventional oral antidepressant can speed up and augment the response of the latter. Our study differed from Hu et al. in some ways. In present investigation, IV ketamine augmentation of escitalopram showed greater response and remission as compared to placebo. Patients treated with ketamine augmentation demonstrated rapid symptom reduction as evidenced by decline in MADRS scores within 4 hours of infusion and this benefit was sustained till 4 weeks. Majority of the patients achieved response and approximately one fourth of patients achieved remission with ketamine augmentation at 28 days. Patients receiving ketamine did experience dissociative symptoms and mania-like symptoms initially, but it was transient and did not last beyond 24 hours. This finding is consistent with the observations by Zarate et al.<sup>9</sup> and Murrrough et al.<sup>19</sup> but contrary to the finding of Hu et al. No clinically significant adverse effects or tolerability issues were observed in both the study groups warranting treatment discontinuation.

Standard antidepressants have proven efficacy in treating depression but the lag between initiation of drug and clinical response remains a glaring limitation. Ketamine has rapid albeit transient antidepressant effect that wears off by 10 to 12 days.<sup>20</sup> At present, there is no satisfactory strategy to prolong its efficacy except for repeated infusions.<sup>21</sup> However, repeated infusions may run the risk of neurotoxicity as well potential drug abuse.<sup>22</sup> The findings of the present investigation show that combining ketamine with escitalopram can give quicker initial response and also potentiate the response to escitalopram over 1 month while avoiding the potential pitfalls of repeated ketamine infusions. Therefore, ketamine augmentation is a potentially beneficial strategy to alleviate initial symptom distress and hasten the recovery in patients with depression.

Despite the novelty of the present RCT, the authors acknowledge certain limitations. It would be desirable to include a third comparison group of patients treated with ketamine alone. However, ethical concerns preclude this endeavor. Time to response analysis using Kaplan–Meier statistic would provide a more comprehensive understanding of the time-based clinical effects of ketamine. Further multicentric studies including groups of antidepressants may provide insight into the clinical efficacy of ketamine in conjunction with antidepressants other than escitalopram.

## CONCLUSION

Single-dose IV ketamine augmentation of 10 mg/day escitalopram was efficacious, resulting in more rapid and robust response over 4 weeks. It was safe and tolerable, with dissociative and mania-like symptoms emerging post-infusion being mild and transient which do not warrant treatment discontinuation. Further research into the role of ketamine augmentation in MDD is required for its clinical applicability.

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