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Major Depressive Disorder

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EFFECT OF SINGLE DOSE OF KETAMINE IN PATIENTS OF MAJOR DEPRESSIVE DISORDER-A PAKISTANI PERSPECTIVE

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ABSTRACT

Objective: To evaluate the effect of a single dose of Ketamine in treatment of severe Major Depressive Disorder MDD in Pakistani patients.

Study Design: Quasi-experimental study.

Place and Duration of Study: The study was conducted at Combined Military Hospital, Gilgit, from Apr 2017 to Mar 2018.

Methodology: Twenty nine subjects for this study had a primary diagnosis of severe Major Depressive disorder with a score of more than 19 on the HAM-D (Hamilton rating scale for depression) scale. These patients were divided into two groups. Group A received injection ketamine IV whereas group B received placebo 0.9% normal saline. Both were reassessed after 24 hours and there HAM-D scores were measured again.

Results: Out of the total 29 patients, response was present in 14 (48.2%) and 15 (51.8%) did not respond to the treatment. Out of 19 patients that were treated with ketamine, 12 (63.1%) showed response to treatment while 7 (36.9%) did not respond. Out of 10 patients that were treated with placebo, 2 (20%) showed response to treatment while 8 (80%) did not respond. The *p*-value with a confidence interval of 95% was 0.033 showing that the difference in the two treatments was statistically significant.

Conclusion: Ketamine demonstrated rapid antidepressant effects in this study, further supporting N-methyl-D-aspartate (NMDA) receptor modulation as a novel mechanism for accelerated improvement in severe forms of depression. However further trials are needed to establish long term effects of the drug.

Keywords: Ketamine, Major depressive disorder MDD, NMDA receptor.

INTRODUCTION

Depressive disorders have been identified as second leading cause of disability by the Global Burden of Disease 2010[1]. It also showed that Major Depressive Disorder (MDD) accounts for 8.2% of global burden of disease[1]. It is estimated that 14.3% of deaths worldwide, or approximately 8 million deaths each year, maybe attributable to mental disorders out of which 2.74 million are due to mood disorders the highest among all[2]. Although there have been advances in the understanding of the psychopharmacology and many new classes of anti depressants have been introduced, the response of patients to antidepressant therapy alone still remains just 60-70%[3]. A substantial number of patients do not achieve a clinically meaningful response despite multiple antidepressant trials and augmentation strategies[3]. A major hindrance in all treatments has been the delayed response of patients to these antidepressants. Treatments that exert rapid antidepressant effects are a major necessity, as the usual lag time to therapeutic effect is 4-12 weeks if patients show a response[3]. Over the last decade a novel attempt to overcome this issue has been the use of ketamine some labeling it as the "clozapine of depression"[4]. Recent studies with ketamine have shown a rapid onset of antidepressant effect usually within 2 hours of an infusion[5,6]. However this effect is relatively short lived, and a strategy to sustain ketamine's efficacy for a longer duration through optimal dosing has not yet been determined. Much of the research that has assessed the efficacy of ketamine in patients with treatment-resistant depression were randomized

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controlled trials using a single dose; the duration of response in these studies ranged from 3 to 17 days only[5,6,7,8].

Ketamine works as a noncompetitive, N-methyl-D-aspartate glutamate receptor antagonist[9]. At sub anesthetic doses, ketamine-induced N-methyl-D-aspartate (NMDA) receptor antagonism on GABA ergic interneurons blocks outflow (glutamatergic) neuronal inhibition. This leads to an acute glutamate 'surge' that then goes on to activate AMPA receptors which cause an increase in intracellular sodium (Na+) and fast excitatory currents. This triggers multiple downstream second messenger/signal transduction pathways which lead to an increase in the level of BDNF and postsynaptic density protein expression[10-14]. The composite interplay of glutamate receptors on the surface of neurons and astrocytes maintains synaptic and extrasynaptic glutamate levels in order to facilitate recycling back to the presynaptic neuron, prevent excitotoxic cell damage/death and promote synaptogenesis particularly within the prefrontal cortex[15]. This can help diminish the effects of chronic stress and depression.

We designed the present study to test the rapid antidepressant efficacy of ketamine in Pakistani subjects with severe MDD, using an active placebo control condition. We hypothesized that ketamine would be superior to placebo in improving depressive symptoms 24 hours following a single infusion. The primary outcome at 24 hours was chosen to reflect a potential rapid antidepressant effect.

METHODOLOGY

This quasi-expeimental study was conducted at Combined Military Hospital (CMH) Gilgit, from April 2017 to March 2018. The sample size was calculated by WHO sample size calculator with a level of significance 5% and was found to be 29. A total of 29 subjects having a primary diagnosis of severe MDD (single or recurrent) with a score of >19 on the HAM-D scale were selected in the study. They were enrolled into the study after informed consent of the patient and ethics approval from the ethics committee of CMH Gilgit. These patients were 18-60 years of age and received their respective therapies from the initiation of treatment at CMH, Gilgit. The criteria that excluded patients from the study was non-consenting patients, presence of psychotic features in the current episode or a history of psychotic features; any bipolar disorder (current or past) or any psychotic disorder (current or past), any substance abuse (past or present), any comorbidity including diabetes mellitus and hypertension, pregnancy, breastfeeding mothers, children and adolescents, patients with serious suicidal risk and patients taking Lithium, anti depressants, anti convulsants, psychostimulants, anti psychotics or oral contraceptives.

Sampling technique used was consecutive sampling. Patients were divided into two groups by random number tables in a ratio of 2:1. Patients who fulfilled the ICD-10 criteria were diagnosed with depression after detailed history. Hamilton rating scale for depression (HAM-D) in Urdu was administered to these patients[16]. All patients having a score of 19 or more were enrolled into the study. These patients were then divided into intervention group A which were given injection ketamine and control group B which was given a placebo that was 0.9% normal saline. Patients were allocated to any ofthe two groups by lottery method in a ratio of 2:1. Patients were asked for ECG to be done prior to the infusion and to come with an overnight fast. They were detained for four hours after injections to monitor for any side effects. The injections were given in the intensive care unit in the presence of both psychiatrist and anesthetist. Ketamine was given in a dose of 0.5 mg/kg over 40 minutes. Pulse, blood pressure, digital pulse oximetry and ECG were being monitored during the infusion. These groups were reviewed after 24 hours. HAM-D was used to determine the improvement in depressive symptoms. An uplifting in the mood was determined by a change in the HAM-D (Hamilton rating scale for depression) score from severe to mild score i.e. 8 to 13 or normal i.e. <8. Confounding variables were identified and excluded

by exclusion criteria. Data was analyzed using SPSS 20.0. Mean and standard deviation were calculated for quantitative variables. Frequency and percentages were calculated for qualitative variables. Independent sample t-test was used to compare the scores between the 2 groups. Post stratification Fisher exact test was applied and *p*-value ≤0.05 was considered significant.

RESULTS

There were 29 patients (mean age 33.1 ± 8.75 years) in which female subjects were 13 (44.8%) and male subjects were 16 (55.2%) table-I. A total of 21 (72.4%) of the patients were married whereas 7 (24.1%) were single and 1 (3.4%) were divorced/widowed. Occupationally 15 (51.7%) patients were employed, 7 (24.1%) were house wives, 6 (20.7%) were unemployed and 1 (3.4%) was retired. Eighteen (62.1%) of the patients were educated and 11 (37.9%) were uneducated out of the total 29 patients, response i.e. an uplifting in the mood determined by change in the HAM-D (Hamilton rating scale for depression) score from severe to mild score i.e. 8 to 13 or normal i.e. <8, was present in 14 (48.3%) patients. While 15 (51.7%) patients did not respond to the treatment. Out of 19 patients that were treated with ketamine, 12 (63.2%) showed response to treatment while 7 (36.8%) did not respond. Out of 10 patients that were treated with placebo, 2 (20%) showed response to treatment while 8 (80%) did not respond. Chi square test was used to determine the difference in the response of the two treatments. After the application of the test, the *p*-value was found to be 0.033 (table-II). This showed that the difference in the two treatments was statistically significant. Hence it showed that ketamine can help improve severe depression within a short period of 24 hours.

Table-I: Baseline patient characteristics.

Patient Characteristics	Ketamine n=19	Placebo n=10	*p*-value
Gender			
Male	10 (52.7%)	06 (60%)	0.51
Female	09 (47.3%)	04 (40%)	
Age			
20-40 years	15 (78.9%)	08 (80%)	0.67
41-60 years	04 (21.1%)	02 (20%)	
Mean ± SD	6.9 ± 33.3	11.9 ± 33.7	
Marital Status			
Single	10 (52.7%)	07 (70%)	0.69
Married	03 (15.7%)	03 (30%)	
Divorced/ widow	06 (31.6%)	-	
Occupational Status			
Employed	10 (5.7%)	05 (50%)	0.28
Unemployed	09 (47.3%)	03 (30%)	
House wife	-	01 (10%)	
Retired	-	01 (10%)	
Educational status			
Educated	1.70 ± 21.36	08 (80%)	0.149
Uneducated		02 (20%)	
HAM-D Score 1st Interview			
Mean ± SD	3.06 ± 12.47	2.27 ± 20.50	0.259
HAM-D Score Post Treatment			
Mean ± SD		1.71 ± 15.40	0.010

Table-II: Chi square test result showing response to treatment groups.

Treatment Group	Efficacy		*p*-value
	Yesn (%)	Non (%)	
Ketamine (Group A)	12 (63.1%)	07 (36.9%)	0.033
Placebo (0.9% normal saline) (Group B)	02 (20%)	08 (80%)	

DISCUSSION

The goal of treatment in major depression is remission. Many a times in depression the response is suboptimal which is associated with continued disabling symptoms, higher rates of relapse and recurrence, poorer work productivity, more impaired psychosocial functioning, and potentially higher risk for suicide. Despite recent developments in the understanding of the psychopharmacology and the discovery of several classes of anti-depressants, merely 60%-70% of patients with depression respond to antidepressant therapy alone[3]. A major drawback of current anti depressants is the delayed onset of action which is usually 3-4 weeks[3]. This study has determined ketamine is an effective source of treatment whose major advantage is an early onset of action.

In a net analysis data were collected from seven RCTs employing ketamine and it was found to be associated with higher rates of clinical remission relative to other drugs used as

placebo (saline or midazolam) at 24 h [OR 7.06, number needed to treat (NNT)=5], 3 days (OR 3.86, NNT=6), and 7 days (OR 4.00, NNT=6), as well as higher rates of clinical response at 24 h (OR 9.10, NNT=3), 3 days (OR 6.77, NNT=3), and 7 days (OR 4.87, NNT=4). The standardized mean difference at 24 h based on depression rating scale scores was 0.90 which was in favor of ketamine[17]. In a study assessing the effect of six doses of ketamine in 2 weeks it was seen that after completion of three ketamine infusions in 1st week, 7.1% responded; after all six ketamine infusions in 2nd week, 41.7% responded and 16.7% remitted. However, all but one responder relapsed within 2 weeks after the final infusion. Repeated doses of intravenous ketamine were initially found to be feasible, efficacious and well tolerated[18]. Murrough *et al*, used a series of up to six IV infusions of ketamine (0.5 mg/kg) which were administered three times weekly over a 12-day period. Participants who met the response criteria were monitored for relapse for up to 83 days from the last infusion. The overall response rate was found to be 70.8%. There was a significant mean decrease in Montgomery–Asberg Depression Rating Scale score at 2 hours after the first ketamine infusion (18.9 ± 6.6, $p<0.001$). The median time to relapse after the last ketamine infusion among responders was 18 days[19]. Singh *et al* concluded that repeating the dose of ketamine 2-7 days after the first dose can help in the extension of its benefits for upto months[20]. A study by Zarate *et al*, showed that subjects receiving ketamine showed significant improvement in depression compared with subjects receiving placebo within 2 hours of injection, which remained effective throughout the following week. Of the 17 subjects treated with ketamine, 71% met response and 29% met remission criteria a day following ketamine infusion. 35% percent of subjects were able to maintain their response for at least 1 week[21]. A quantitative meta-analysis of 5 RCTs concluded that ketamine significantly reduced depressive symptoms with the overall effect size at day 1 being statistically significant, and this effect was sustained at 7 days postinfusion[22]. Another meta analysis of 6 randomized, double-blind and placebo-controlled trials of ketamine in major depression revealed ketamine to have an overall antidepressant efficacy from 1-723 days.

In a study of intranasal ketamine, response criteria were met by 8 of 18 patients (44%) 24 hours after ketamine administration compared with 1 of 18 (6%) after placebo (p=0.033). Intranasal ketamine was well tolerated with minimal dissociative effects and was not associated with clinically relevant changes in hemodynamic parameters[24]. Hu *et al*, showed that a single-dose i.v. ketamine augmentation of Escitalopram was safe and effective in severe MDD, leading to a hope that ketamine may help increase and speed up the response of patients to oral antidepressants[25].

This study looked into the effect of ketamine in depression. It supported the contention that ketamine can have an early effect in severe depressive cases which can be a source of great relief for certain acute patients. Previous studies have shown that the subanesthetic dose of 0.5 mg is usually well tolerated in patients. Even during this study no major adverse event was noticed. However the study as a whole did not look into the possible side effects. A major point of concern is the duration of effect of treatment which previous studies have shown is quite short. Future studies will need to look into methods of prolonging the effect of ketamine. Research has shown that augmenting current antidepressants with ketamine from start of treatment in severe cases can have miraculous effects[26]. However this aspect needs further studies to confirm the benefits of using augmentative strategy from the start and following it through in long term maintenance treatment.

CONCLUSION

Ketamine demonstrated rapid antidepressant effects in this study, further supporting N-methyl-D-aspartate (NMDA) receptor modulation as a novel mechanism for accelerated improvement in severe forms of depression. However further trials are needed to establish long term effects of the drug.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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