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Efficacy of Electroconvulsive Therapy and Ketamine Therapy in Major Depressive Disorder; A Comparative Study

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ABSTRACT

Objective: To evaluate and compare the efficacy of Electroconvulsive therapy (ECT) and Ketamine infusions in hospitalized patients suffering from major depressive disorder (MDD).

Study Design: Comparative cross-sectional study.

Place and duration of study: Armed Forces Institute of Mental Health, Rawalpindi Pakistan, from Feb to Apr 2021.

Methodology: Forty in-patients diagnosed as having MDD were randomly allocated ECT/Ketamine intervention as per international standards. Either group of patients acted as a control for the other. Their Beck Depressive Inventory (BDI) scores before and after the completion of treatment cycles were assessed to determine their response to treatment.

Results: The Ketamine-Group showed fewer depressive symptoms than the ECT Group. The depressive symptoms were reduced in 16(80.78%) patients after Ketamine infusions, while 15(77.78%) patients showed improvement after ECT sessions. In addition, the response to Ketamine was quicker.

Conclusion: This study has reported that low dose Ketamine has a more rapid impact than Electroconvulsive therapy in improving symptoms of depression in major depressive disorder patients.

Keywords: Electroconvulsive therapy, ECT versus ketamine, Ketamine, Major depressive disorder.

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INTRODUCTION

Major Depressive Disorder (MDD) annually affects around 350 million people across the globe and is an extremely severe and chronic psychiatric disease linked with significant morbidity and increased medical costs.[1] It is associated with physical and emotional impairment and a higher risk of suicide.[2] According to the World Health Organization, by 2021, depression will turn into the second major reason for disability in the whole world with higher frequency rates in teenagers.[3] Major Depressive Disorder is widely treated by psychopharmacological and psychotherapy, and electroconvulsive therapy (ECT).[4] Since its introduction, Electro Convulsive therapy (ECT) has been applied to various psychiatric illnesses with special emphasis on depressive disorders. In a recent randomized controlled trial, ECT was more effective in treatment-resistant Bipolar Depression.[5] Electroconvulsive therapy (ECT) is a successful MDD therapy with a 79 percent response rate and a 75 percent remission rate. However, sufficient seizure duration and higher electricity doses are needed to maximize this treatment's antidepressant impact.[6,7] In the diagnosis of MDD, electroconvulsive therapy continues to be the gold standard; its response latency is shortened compared to conventional drug therapy.[8]

Ketamine, a glutamatergic n-methyl-D-aspartate (NMDA) antagonist, has been one of the most significant breakthroughs in depression over the last 20 years and has been due to the exploration of the rapid antidepressant impacts of anaesthetic injections of intravenous (IV) Ketamine.[9] A high dose of Ketamine and prolonged use can cause delirium and other psychiatric disorders. In contrast, the low dose of Ketamine is better and can improve ECT effectiveness in patients with MDD.

Moreover, there have only been a couple randomized controlled trials that compared Ketamine with other antidepressant therapies.[10] This study was therefore designed to compare the efficacy of ECT versus Ketamine anaesthesia in patients with major depressive disorder. The findings will enable two therapies to be directly compared and will have significant consequences for the patient's choice, healthcare policy, and clinical practice.

METHODOLOGY

The comparative cross-sectional study was carried out at Armed Forces Institute of Mental Health, Rawalpindi Pakistan, from February to April. After

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The Ethics and Scientific Committee of Hospital gave approval of the study. A total sample size was estimated via the EPi Tools Epidemiological calculator based on the results by Sharma *et al*. which has shown that in 82.3%, of participants depressive symptoms reduced after Ketamine infusion.[11]

Inclusion Criteria: Patients of either gender, aged 18-50 years, having major depressive disorder according to the Diagnostic and Statistical Mental Disorder Manual (DSM-V) and according to the Antidepressants History Form (ATHF), two or more appropriate trials of antidepressant strategies must have been performed on them throughout their lifespan, to which they did not completely, responded were included in the study.

Exclusion Criteria: Patients having bipolar disorder, concomitant presence of psychiatric illness other than the major depressive disorder, patients with any surgical comorbid condition, dependency other than nicotine-containing drugs, patients with a history of significant adverse effects linked to anaesthetics, patients with body implant such as pacemakers, intracranial electrodes, and clips, pregnant Ladies, patients with primary psychotic disorder, patients with manic and hypomanic episode were excluded from the study.

Consecutively 40 hospitalized subjects suffering from a major depressive disorder were enrolled. The sample was randomized as 1:1 manner into two groups of twenty. Group-A was given an ECT infusion, while Group-B received Ketamine. After all the participants signed the consent, detailed physical examinations and testing were to exclude physical comorbidities. A detailed examination and evaluation to know the anaesthesia fitness of patients was also conducted. A structured clinical interview of all patients with a psychiatrist was carried out to include the participants that fulfilled the diagnostic requirements of MDD and are currently in the most serious depressive episode. Before the study, all participants underwent the first baseline Beck Depression Inventories scale survey. A BDI survey was used to rate the severity of MDD in patients. In the scoring method, 24–36 scoring indicates severe depression, and 37-plus scoring indicates more extreme depression, generally necessary to enter a clinical trial.

Because of the complexity, nature, and design of these treatments, the treatment groups at a patient level cannot be blinded. Therefore, the participants were given the choice of treatment approach to receive either six intravenous injections of Ketamine that were 0.5mg/kg-45min or six ECT sessions every 48-hours. Those participants who refused ECT out of fear and stigma were offered Ketamine therapy. The BDI and Hamilton Depression Rating Scale (HDRS) were followed every 24-hours after each therapy and post one week after the last ECT session or intravenous infusion of Ketamine.

According to clinical guidelines, patients in Group-A underwent ECT at the tertiary care hospital site. ECT session was given to the patients six times every 48-hours at different frequencies ranging from 50 to 400mv for different durations ranging from 4 to 5seconds by using the Thymatron DGX apparatus. It was accompanied by an Atropine injection (0.5mg) followed by a general anaesthetic injection of Propofol (2 to 3mg/kg) supported by 0.5mg of succinylcholine, induced by a Bitemporal stimulation application and therapeutic seizure induction. EEG recording was used to monitor the duration of seizures during ECT. Brief-pulse stimulation's pulse width, frequency, and amplitude were all held steady at 1.0-milli-second, 70hertz, and 800milli-amperes, respectively. Changes in the duration of stimulation were used for titration of the ECT dose.

Patients of Group-B received intravenous Ketamine injections. An IV pump delivered 0.5 mg/kg of Ketamine hydrochloride dilute in 0.9% saline over a 40-minute cycle. Infusions were provided by anesthesiologist assistants at the tertiary care hospital, with the guidance of a physician with continuous monitoring of heart and respiration rate.

Clinical evaluation of remission was evaluated by Beck Depression Inventory (BDI) and Hamilton Depression Rating Scale (HDRS) to rate the depressive symptoms.[12,13] The evaluation of these tools was conducted by the researcher weekly before the ECT and Ketamine were terminated. Patients were again evaluated based on all tools in the first and sixth weeks after ECT and Ketamine were discontinued. The adverse effects of Ketamine and ECT therapies in all patients were well tolerated. The parameters in both groups have not changed significantly, including stroke volume, cardiac output, blood pressure, heart rate, cardiac velocity, and total peripheral resistance, only on taking the 2nd and the third dose of Ketamine systolic blood pressure and heart rate increase in two patients out of twenty patients. The hemodynamic parameters have not been substantially changed in the ECT-Group.

Data were analyzed using Statistical Package for the social sciences (SPSS) version 23.00 and MS Excel

2016 software. Mean±SD was calculated for continuous variables. Frequency and percentage were calculated for categorical variables chi-square was used. The *p*-value ≤ 0.05 was considered significant.

RESULTS

A total of 40 patients have been evaluated in this study, 20(100%) patients of Group-A received only ECT sessions and 20(100%) patients of Group-B received only intravenous Ketamine infusion. Mean BDI score after the first treatment with ECT was 36.51±11.84 that became 15.66±7.51 one week after the treatment with ECT on the other hand in Group-B treated with Ketamine mean BDI score after the first treatment was 20.22±9.23 that became 10.88±7.49 one week after the first treatment with Ketamine. When HDRS scores were assessed after the first treatment with ECT, it was 31.44±7.26, which became 14.00±4.90 one week after treatment with ECT; on the other hand, in Group-B, HDRS scores after the first treatment were 16.88±6.58 that reduced to 9.55±9.80 one week after the first treatment as shown in Table-I.

Table-I: Clinical Scale Rating of BDI and HDRS score of all Patients receiving ECT or Ketamine (n=40)

Parameters	ECT-Group (n=20) Mean±SD	Ketamine-Group (n=20) Mean±SD
Age	34.97± 8.17	35.37±8.97
Baseline BDI Score	42.44±9.53	34.66±10.70
First treatment	36.51±11.84	20.22±9.23
1-week post-treatment	15.66±7.51	10.88±7.49
Baseline HDRS score	35.88±6.47	30.22±5.78
First treatment	31.44±7.26	16.88±6.58
1-week post-treatment	14.00±4.90	9.55±4.98

After the first treatment with ECT, there was a reduction in depressive symptoms among 2(11.11%) patients compared to 9(44.44%) patients treated with Ketamine. After the first week of treatment with ECT, 16(77.78%) patients showed improvement in depressive symptoms. In comparison, 18(80.78%) patients had a reduction in depressive symptoms after Ketamine treatment (p<0.001), as shown in Table-II.

Table II: The Depressive Symptoms Reduction evaluated through HDRS and BDI of ECT treatment and Ketamine Infusion (n=40)

Variables	ECT-Group (n=20) n (%)	Ketamine-Group (n=20) n (%)	*p*-value
First treatment	2 (11.11)	9 (44.44)	<0.001
1-week post-treatment	16 (77.78)	18 (80.78)	<0.001

After ECT, 15(75.80%) patients reported improvement in sleep disturbance, worthlessness, indecisiveness, PTS, neuro-cognitive func-tions and loss of interest. 13(65.67%) patients felt improvement in depressed mood and behaviour. In comparison, 16(78.98%) patients reported improve-ment in anxiety and 9(44.44%) patients' suicidal thoughts were reduced. On the other hand, after treat-ment with Ketamine, 16(79.25%) patients reported improvement in suicidal thoughts, feeling of worth-lessness, neuro-cognitive functions and loss of interest, 15(73.48%) patients showed improvement in depressed mood, PTS, and indecisiveness. In comparison, 14(73.54%) felt improvement in anxiety, sleep disturbance and behaviour (p<0.001), as shown in Table-III.

Table-III: The comparison of Depressive Symptoms Reduction in ECT and Ketamine Groups (n=40)

Depressive Symptoms	ECT-Group (n=20) n (%)	Ketamine-Group (n=20) n (%)	*p*-value
Depressed mood	13(65.67)	15(73.48)	<0.001
Loss of interest	15(74.45)	16(78.12)	
Neurocognitive dysfunction	15(75.80)	16(79.25)	
Suicidal thoughts	9(44.44)	16(77.81)	
Anxiety	16(78.98)	14(71.45)	
PTS	15(74.98)	15(73.28)	
Indecisiveness	15(74.76)	15(76.77)	
Feelings of worthlessness	15(75.64)	16(79.87)	
Sleep disturbances	15(77.12)	14(73.54)	
Behavioral changes	13(73.08)	14(73.89)	

DISCUSSION

This study highlighted that repeated and ongoing treatment with Ketamine's low doses (0.5mg/kg) and ECT in patients suffering from MDD have rapid antidepressant effects. Ketamine had 72-hours and 1-week onset of antidepressant effects after the last Ketamine injection when evaluated with BDI and HDRS. Interestingly, additional analysis showed substantially fewer signs of depression in the first, second, and one-week post-treatments Ketamine-administered patients than those who received ECT.[14] After administration of Ketamine infusion, 15(77.8%) individuals exhibited a marked reduction in suicidal thoughts, 14(73.4%) had improvement in depressed mood, 16(79.2%) individuals noticed an improvement in neurocognitive functions, loss of interest and feeling of worthlessness. It is interesting to note that sleep and anxiety-related symptoms responded well to ECT compared to Ketamine infusion. However, there was no significant difference between ECT and Ketamine infusion when the effects on behavioural changes were compared.[15] Individuals with MDD that have failed to respond to different treatments must need new and

alternative options with improved outcomes. Although ECT is still one of the most efficient treatments for MDD individuals who are resistant to other treatments, it is underutilized. Ketamine is a highly promising, successful new antidepressant therapy with rapid and speedy antidepressant effects, high response rates, and few side effects.[16] ECT and Ketamine have never been compared directly in a well-powered randomized trial; this study has overcome this gap by directly comparing the efficacy of ECT and Ketamine in treating MDD individuals in a cross-sectional and well-powered randomized trial in a tertiary care hospital in Pakistan. Ketamine is an appropriate alternative to ECT for immediate relief in patients with severe symptoms of depression needing urgent psychiatric treatment. Ketamine's antidepressant effects through the glutamate pathway have been confirmed to have anti-suicidal effects.[15,16] Ketamine has an unknown effect on the participant's brains by decreasing serotonin production while increasing dopamine output, which is also essential for mood control.[17,18]

This study introduces a unique intravenous Ketamine maintenance strategy. Our study found that this approach effectively maintained antidepressant response & reduced suicidal ideation over a short period.

CONCLUSION

Ketamine is an appropriate alternative to ECT to rapidly relieve serious symptoms of depression in patients that need immediate medical treatment. While both ECT and Ketamine have reduced depressive symptoms in both groups, the findings have revealed that Ketamine began its action more quickly. However, ECT has higher remission for a longer period than Ketamine.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

AAB: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

SA & SAK: Data acquisition, data analysis, data interpre-tation, critical review, approval of the final version to be published.

NS & TBN: Concept, critical review, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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