"RAPID ANTIDEPRESSANT EFFECTS OF KETAMINE COMPARED WITH ELECTROCONVULSIVE THERAPY IN PATIENTS WITH SEVERE DEPRESSION: A RANDOMIZED CONTROL TRIAL."

BY

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ABSTRACT

Background

Severe depression has high morbidity and mortality. Treatment modalities like antidepressants take weeks to act, hence are useless in emergencies. Electroconvulsive therapy (ECT) although has a rapid antidepressant effect, comes with hindrances in the form of availability of set-up, oxygen support and an anaesthetist, associated cognitive side effects, contraindications and stigma. It requires 3-5 sessions to show response. Ketamine, an N-Methyl-D-Aspartate (NMDA) receptor antagonist is stipulated to show rapid antidepressant response. However, its comparison with ECT has been inadequately studied, especially in the Indian population.

Aim

To study the rapid antidepressant effect of ketamine as compared with ECT in patients with severe depression

Method

Forty inpatients diagnosed with severe depression, were randomly allocated to either ECT or Ketamine group. Following due consent, each patient received modified ECT or Ketamine hydrochloride infusion every alternate day for upto 3 times under a qualified anaesthetist's supervision. Depressive symptoms were measured using the 17-item Hamilton Depression Rating Scale (HAM-D17) at baseline and 24 hours after each intervention. Data was analysed using appropriate statistical methods.

Results

Patients receiving Ketamine showed a faster reduction in HAM-D17 score over the course of 3 infusions. This was found to be significant and steeper when compared with that of patients who received 3 sessions of ECT.

Conclusion

This study suggests that Ketamine produces rapid antidepressant effects. The response rate being significantly higher than that of ECT indicates that Ketamine is a superior alternative when administered in patients with severe depression.

Keywords: Severe depression, Electroconvulsive therapy, Ketamine

ABBREVIATIONS

ECT	Electroconvulsive Therapy
NMDA	N-Methyl-D-Aspartate
BDNF	Brain Derived Neurotrophic Factor
IKK	Inhibitor of kB Kinase
NF-kB	Nuclear Factor - kB
TCA	Tricyclic Antidepressants
MAOI	Monoamine Oxidase Inhibitor
STAR-D	Sequenced Treatment Alternatives to Relieve-Depression
SSRI	Selective Serotonin Reuptake Inhibitor
SNRI	Serotonin and Noradrenaline Reuptake Inhibitor
GABA	Gamma-aminobutyric acid
ECS	Electroconvulsive Shock
MMSE	Mini Mental State Examination
HMSE	Hindi Mental State Examination
B4ECT-ReCoDe	Battery for ECT Related Cognitive Deficit
MDD	Major Depressive Disorder
AMPA	amino-3-hydroxy-5- methylisoxazole-4-propionate
mTOR	mammalian Target of Rapamycin
CSP	Chronic stress pathology
PFC	prefrontal cortex
NAc	Nucleus Accumbens
IV	Intravenous
Mg/kg	milligrams/kilograms
RCT	Randomised Control Trial
ICD	International Classification of Diseases

DCR	Diagnostic Criteria for Research
KLES	Karnataka Lingayat Education Society
B.P.	Blood Pressure
HAM-D17	Hamilton Depression Rating Scale
BPRS	Brief Psychiatric Rating Scale
NPO	Nil per oral
ANOVA	Analysis of Variance
COVID-19	Corona Virus Disease-19
SD	Standard Deviation
SDE	Severe Depressive Episode
RDD	Recurrent Depressive Disorder
BPAD	Bipolar Affective Disorder
BDI	Beck's Depression Inventory
TRD	Treatment Resistant Depression
MADRS	Montgomery-Asberg Depression Rating Scale

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INTRODUCTION

Severe depressive disorder is a common psychiatric illness worldwide, associated with high morbidity and mortality. Most common treatment options for the same currently include antidepressant medications, Electroconvulsive therapy among others. Antidepressant medications are efficacious, however take weeks to show adequate response, therefore cannot be made useful in emergency cases for example, extreme suicidal ideations. They also come with an array of side effects. Electroconvulsive therapy (ECT) is a well-established, beneficial treatment for severe depressive disorder and has a rapid onset of action as well. But significant symptom reduction with ECT takes 2 weeks or administration of 5-7 ECTs in severely depressed(1,2) Various other factors for example cognitive side effects, associated stigma, and contraindications such as raised intracranial tension also make it difficult to administer ECTs.

Another emerging treatment option for depression is Ketamine, an anaesthetic agent, which is an "N-methyl-d-aspartate (NMDA) receptor antagonist"(3,4). Ketamine's first preclinical rapid antidepressant effect was reported by Trullas and Skolnick in 1990(5). Following this discovery, multiple studies have demonstrated the antidepressant effect of Ketamine and have observed it to occur within few hours after a single infusion of Ketamine(6). Consequently, multiple studies, as we will discuss later, have been done to establish the rapid antidepressant effects of Ketamine. However, limited studies have compared this with ECT, which is currently the widely used treatment option for rapid reduction of depressive symptoms in severely depressed individuals. Even lesser number of studies have been done on the Indian population to evaluate the same.

The present treatment modalities for depression would take a long time for their action. There is an absolute requirement of a pharmacological agent with a rapid antidepressant action. Therefore, the aim of the present study is to investigate the antidepressant effects of Ketamine in comparison with ECT in severe depression patients. If Ketamine's efficacy is proved to be superior, it can be considered over ECTs especially in patients where rapid antidepressant action is required, and ECT is contraindicated or not useful, and in patients who don't want to receive ECT.

OBJECTIVES

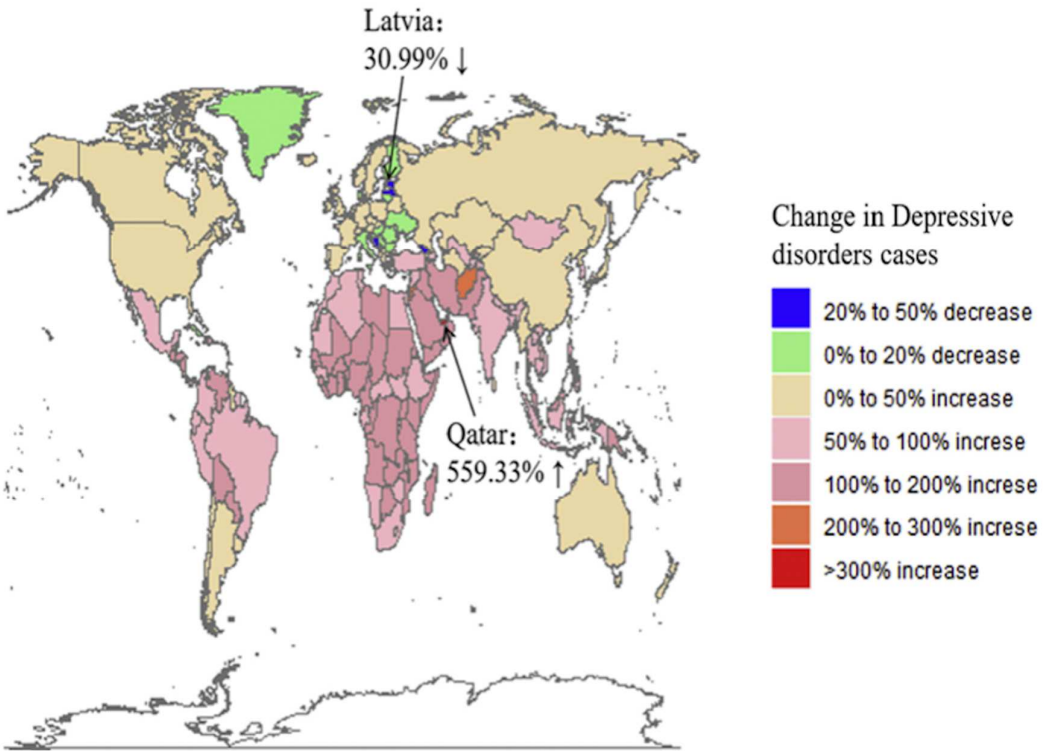
Primary Objective: To compare rapid antidepressant effects of Ketamine with Modified Electroconvulsive Therapy.

Secondary Objective: To identify the demographic and clinical factors that would predict the rapid antidepressant actions of Ketamine

REVIEW OF LITERATURE

DEPRESSION

Depression has become one of the most common illnesses worldwide. According to the World Health Organisation, it is affecting approximately 3.8% of the population, with 5.0% being adults and around 5.7% adults being more than 60 years. Around 280 million people in the world have been estimated to be suffering from depression. A study aimed to determine the global burden of depression and how it has changed between 1990 and 2017, found an increase of 49.86% in the number of incident cases of depression worldwide from 1990 to 2017. [7]



Picture 1: The relative change in incident cases of depression between 1990 and 2017[7]

Most patients recover from major depressive episodes, however the possibility of recurrence of these episodes is common.[8] A large number of the patients, 12% and 7%, respectively, after 5 and 10 years of prospective follow-up, are still depressed i.e., they have prolonged periods of illness, and the course can be established as chronic for such patients.[9] Moreover, the rate of recurrence has been found to be high in those patients who eventually recover and in less than 10 years, almost 75% of the patients go through more than one episode of major depression [10,11]. Mortality in depressive episodes is also a serious concern with suicidal ideations being a common risk factor, especially between the age group of 15 and 24 years.[12]

The etiopathogenesis of depression has been widely studied. It is established that it mainly involves neurotransmitters serotonin and norepinephrine.[13] However, the various symptom domains seen in depression, which include emotional, physiological, social and cognitive symptoms suggest a more complex etiopathogenesis. Various depressed human and rodent depression models show evidence towards neuroplasticity, altered synaptic remodelling in various brain structures, certain neurotrophic factors e.g., BDNF, IKK, NF-kB, transcription factors and epigenetics, increase in pro-inflammatory cytokines, microglial and astrocyte function being involved. Thus, suggesting that factors beyond monoamines contribute to depression, which could be a reason for the limited efficacy of antidepressants.[14]

This knowledge can pave way for research on further treatment options for depression. Treatment of depression primarily modifies the brain pathways which involve monoamines (serotonin, norepinephrine, or dopamine).[15] First-generation antidepressants include the class of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). They are effective antidepressant medications, however, frequently lead to unwanted side-effects. They are also contraindicated in a number of

physiological and pathological conditions, and overdose can lead to toxicities, thus limiting their wider use.

A landmark study, "Sequenced Treatment Alternatives to Relieve-Depression (STAR-D)" reported that remission of depressive symptoms was noted following adequate trial of Selective Serotonin Reuptake inhibitor (SSRI) for a duration of 12 weeks[16]. In line with the results of this study, commonly prescribed antidepressant medications, i.e., newer generation antidepressants are the ones belonging to selective serotonin reuptake inhibitors (SSRI) or serotonin and noradrenaline reuptake inhibitors (SNRI).

Approximately 70% of depressed patients are estimated to respond effectively to the prescribed antidepressants, while an estimated 30% of depressed patients do not respond to the same.[16,17] According to the National Institute of Mental Health, remission from depressive symptoms is achieved by approximately only 27% of the patients within 12 weeks of starting antidepressant treatment while adjunctive medications have a very little role to play in achieving this[18]. Moreover, stable remission was estimated to be achieved roughly by 7 weeks in the patients who showed an adequate response to the prescribed antidepressants.

However, it is widely argued that there exists a rising prevalence of cases of depression despite an established use of antidepressants.[19] This could be as a result of poor compliance, adverse effects, treatment-resistance or comorbidities. Also, it is argued that their efficacy is limited due to intolerance, delayed therapeutic onset, limited effectiveness and relapse issues.[20] Having said that, urgency for another treatment option is evident. [21]

ELECTROCONVULSIVE THERAPY

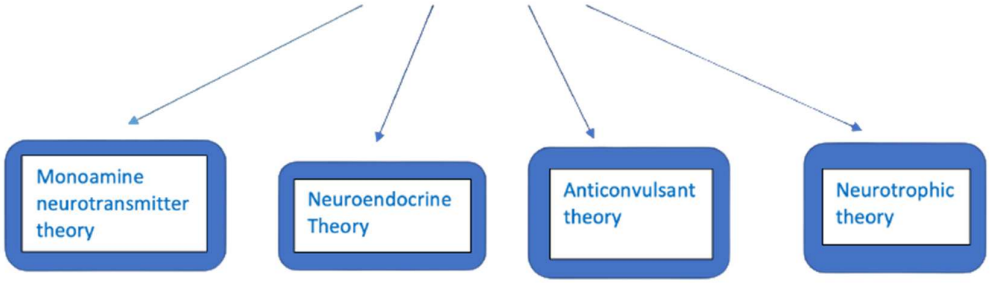
Electroconvulsive therapy (ECT) was introduced by Italian Neuropsychiatrists, Ugo Cerletti and Lucio Bini.

It is another standard treatment widely used in cases of severe and treatment resistant depression. It is also used when antidepressant medications do not provide adequate improvement in symptoms.[22,23] It is an efficacious treatment option in both unipolar and bipolar depression.[23] ECT has been studied to have a faster onset of action than the established antidepressants, but it needs a minimum of 5-7 treatments for an approximate duration of 2 weeks to achieve considerable reduction in symptoms.[1,2]

Mechanism of action of ECTs:

The mechanism of action of ECT is not well understood. Various hypotheses ranging from the neurotransmitter and neuroendocrine dysregulation being corrected by ECTs, GABAergic anticonvulsant effects being brought about by ECTs, or that ECTs are also involved on the molecular level, are postulated. Since ECTs trigger a generalized seizure, it leads to biological changes which cannot be explained by a single mechanism of action[24]

The four fundamental theories of ECT's mechanism of action are (24,25)



Picture 2: Theories of mechanism of action of ECT

(1) **Monoamine Neurotransmitter Theory**: According to the classical monoamine neurotransmitter theory, ECT increases availability of various neurotransmitters, or it changes receptor susceptibility. ECTs cause enhancement of neurotransmission in the dopaminergic, serotonergic and adrenergic system [26], and effect on GABA and glutamate neurotransmission has been studied as well.[27,28] GABA and Glutamate have also been studied to have a role in producing antidepressant effect seen with Ketamine[29], as we will discuss later.

(2) **Neuroendocrine Theory**: The neuroendocrine theory implies that ECT causes a release of hormones, like prolactin, thyroid-stimulating hormone, adrenocorticotropic hormone, and endorphins from the hypothalamic or pituitary system.[30] It is argued that it is the release of these hormones that leads to the antidepressant effect produced by ECTs. This theory is further strengthened by the evidence that in melancholic depression, there is dysregulation of the hypothalamic-pituitary-adrenal axis. It is also suggested that this dysregulation is ameliorated with successful ECTs.[31]

(3) **Anticonvulsant Theory**: The anticonvulsant theory states that ECT's efficacy is due to the anticonvulsant nature of the entire treatment. Various studies observed that there is a rise in seizure threshold (and a decrease in seizure duration) after a course of ECTs. These findings are in favour of this hypothesis.[32,33] These effects could be due to enhanced gamma-aminobutyric acid (GABA) transmission and that localized suppression of neural metabolic activity is associated with therapeutic response to ECT[33]

(4) **Neurotrophic Theory:** According to the neurotrophic theory, ECT might be responsible for bringing about neurogenesis and elevating neurotrophic signalling in the brain, which lowers their antidepressant effect. Electroconvulsive shock

(ECS), which is an animal model of ECT, has been used in various animal studies. One such study has used ECS on the rat hippocampus. They have demonstrated increased neurogenesis and synaptogenesis.[34,35] Certain neurotrophic factors, for example, brain-derived neurotrophic factor (BDNF), have been demonstrated to be raised after ECS in animals and ECT in humans.[36] Functional neuroimaging studies that have been done conclude that ECT paradoxically reduces the "hypo frontality" further as demonstrated in depressed patients. [37]

MODIFIED BRIEF PULSE ECT: -

In the modern practice, ECTs most commonly administered are the Modified brief pulse ECT.

Picture 3: Modified Electroconvulsive therapy set-up

Historically, ECTs have been at the receiving end of a damaging stigma, which was primarily due to the initial days of ECT administration wherein it was given without administering muscle relaxants and anaesthetic agents. This was known as unmodified ECTs. Unmodified ECT would also constitute the administration of ECT under anaesthesia but without a muscle relaxant. Modified ECTs are those which are given under anaesthesia, followed by a muscle relaxant which is then followed by a seizure-inducing electrical stimulus. [38]

ECT machines that were used earlier (before mid-1980s) functioned on a sinusoidal pulse wave which reportedly caused considerable cognitive deficits. Such side effects were less in the ultra-brief (UB) and brief (B) pulse waves which are used in the modern ECT machines.[39] In brief pulse ECTs, brief pulses of a duration of

0.5ms are given and no stimulus is given in between. Tissue recovery from post-depolarization refractory period made intermittent stimulation in the form of pulses more efficient. This is unlike when stimulus is given in sine wave form as was the case in earlier ECT machines.

Brief pulse ECT is beneficial as it is able to cause seizures with lesser charge and energy compared to sine wave, hence reducing the cognitive side effects[40]

Types of electrode placements for ECTs: Cognitive deficits, for e.g.: loss of memory has been a notable primary concern with patients who have received ECT; however, with recent advancements in the administration of ECTs, it is possible now to modify the ECT electrode placement to decrease the risk for the aforementioned adverse effect. In the present day ECT practice, three types of electrode placements are utilised, namely.[41]:

1) Unilateral,
2) Bifrontal and
3) Bitemporal

Current ECT research is aimed at assessment and evaluation of other electrode placements to decrease the cognitive adverse effects induced by ECT. For example, the bifrontal electrode placement permits electrical current to be centred in the frontal lobes, where the most clinical efficacy is required. The mesial temporal lobes, whose damage could lead to memory impairment, are bypassed[42]

Frequency of treatment: ECTs can be given twice-weekly or thrice-weekly. Spacing days between subsequent ECT procedures ensures reduced cognitive side effects. The twice-weekly regime is associated with considerably lower current being administered, a relatively shorter overall hospital stays and fewer ECTs being given as compared to the thrice-weekly regime[43]

Clinical monitoring:

1) **During the procedure** – Monitoring includes monitoring of vital signs (pulse rate, blood pressure, temperature), blood oxygen saturation, electrocardiogram, electroencephalogram and electromyogram (to record the duration of the motor seizure). These parameters should be monitored continuously throughout the ECT administration procedure until the patient is out of the effect of general anaesthesia and the equipment for their measurement should remain available in the treatment and recovery area following ECT administration.

2) **Along the course of ECTs** – Resolution of depressive symptoms can be best evaluated using a structured rating scale such as the Hamilton Depression Rating Scale or the Montgomery-Åsberg Depression Rating Scale. These scales should be administered at baseline followed by at least a weekly administration to assess response to treatment. Similarly, a test to assess the cognitive function such as the Mini-Mental State Examination (MMSE) or Hindi Mental State Examination (HMSE) or Battery for ECT Related Cognitive Deficits(B4ECT-ReCoDe) should be administered at baseline and at the end of treatment course or more frequently if cognitive side effects are a concern.

Looking at the currently available treatment options for depression, as discussed above, certain key factors are concerning. These include:

(a) the crucial time lost while antidepressants achieve response and remission,

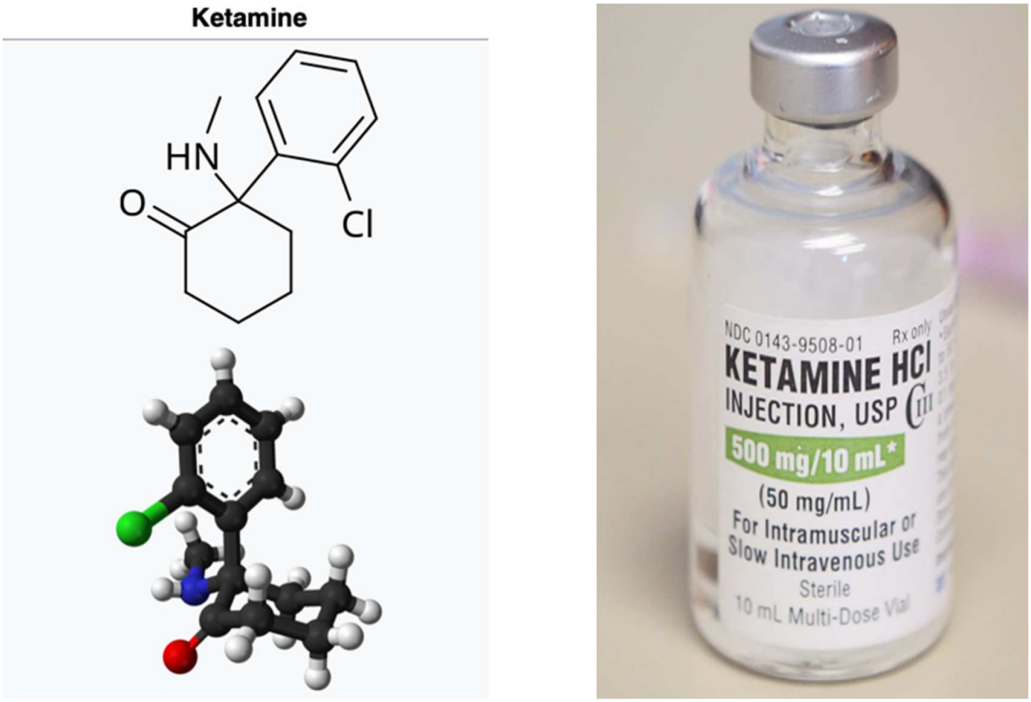
(b) the cognitive side effects with regards to ECT,

(c) recent advances in research pointing at the current neurobiological mechanism of depression being more than just the monoaminergic phenomenon.

This warrants the need for a new treatment option for depression, preferably having a rapid action with fewer side effects. Studies across the globe have shown that glutamatergic / NMDA receptor might also have a vital role in pathophysiology of severe depression[44], although further studies in this direction are required.

KETAMINE

Ketamine is an accepted anesthetic drug used for diagnostic and surgical procedures in adults, obstetric patients and children.[45]



Picture 4: Ketamine, (a) molecular structure[46], (b) a vial of Ketamine Hydrochloride

MECHANISM OF ACTION:

Studies have confirmed that Ketamine, a non-competitive antagonist of NMDA receptor produces significantly rapid antidepressant response in both animal and human models.[47,48] This led to shifting in focus of research to role of glutaminergic pathways in treatment of depression.

Glutamate is a crucial excitatory neurotransmitter in the central nervous system. It takes part in the pathophysiology of MDD via its cognate receptors. Ketamine acts by blocking the NMDA receptor, probably on GABA interneurons,

therefore leading to disinhibition of activity of pyramidal neurons in the cortex, followed by an increase in the release of glutamate. This triggers a "cascade of signalling pathways, including – activation of amino-3-hydroxy-5- methylisoxazole-4-propionate (AMPA) receptor, secretion of brain-derived neurotrophic factor (BDNF) secretion and activation of mammalian target of rapamycin (mTOR) signalling."[29]

Another hypothesis is related to the "synaptic chronic stress pathology (CSP) model" in the prefrontal cortex (PFC), hippocampus and dopaminergic nucleus accumbens (NAc). It suggests that synaptic disruption might be a possible underlying pathology in multiple psychiatric illnesses associated with chronic distress.[49] The synaptic CSP model suggests that "chronic stress can lead to glial cell reduction, reduced capacity of glutamate reuptake, elevated extra synaptic glutamate levels leading to excitotoxicity, resulting in neuronal atrophy, loss of dendritic spine density and decreased glutamate neurotransmission."[50] CSP animal model points towards reduced strength of neurotransmission during prolong exposure to stress, in sustained synapses of PFC due to decreased number of postsynaptic NMDA and AMPA receptors.[51]

It is proposed that, within 24 hours of being administered, ketamine could reverse CSP in prefrontal cortex, hippocampus and NAc by postsynaptic glutamate activation along with subsequent upregulation of neurotrophic signalling and increased protein synthesis, thus restoring synaptic connectivity which supposedly lasts for days or even weeks[50]. Furthermore, the model of synaptic CSP proposes that

chronic stress causes dysregulation of monoaminergic synapses and hyperconnectivity in dopaminergic NAc.[50,52] These synaptic modifications in the PFC and NAc have been both related to depressive symptoms in earlier preclinical studies.[53] These findings conclude that synaptic hypoconnectivity in PFC and hippocampus as well as hyperconnectivity of dopaminergic NAc, suggesting two individual pathways playing a role in clinical depression.[54,55]

This Dual Pathology model reflects majorly on the fact that patients with underlying glutamatergic impairment would be treatment-resistant with the monoaminergic antidepressants that are being widely used, which otherwise would be effective in reducing symptoms of depression in the patients with an underlying monoaminergic pathology.[54]

Several studies in the past have been done to study the rapid antidepressant effects of Ketamine. One such study done by DiazGranados et al[56] in 2010 studied rapid antidepressant effect of single infusion of Ketamine and found reduction in depressive symptoms significantly within 40 min of the infusion, which remained significant at 80, 120, and 230 min post-infusion.

The antidepressant action of ketamine has also been supported by "Price et al[57] demonstrated rapid reduction in depressive symptoms in patients with severe depression following repeated infusions of sub anaesthetic doses of Ketamine." "Murrough et al[58] also support antidepressant effect of ketamine. Participants showed improvement at 2 h after the first infusion of ketamine. The effect was largely maintained for the entire duration of the infusion period."

Few Indian studies have been done as well to study Ketamine's rapid antidepressant effects. A study done by "Thakurta et al[59] on Indian subjects also demonstrated rapid effect of ketamine on depressive symptoms in depressed patients with single IV infusion of sub anaesthetic doses of Ketamine after being medication free for a period of 2 weeks. Significant reduction in depressive symptoms was found at minute 40 following infusion which remained significant up to day 2 post-infusion at each time point."

Randomised control studies done previously have compared Ketamine to placebo in reducing depressive symptoms rapidly. In one such study, it was demonstrated that "a sub anesthetic dose of intravenous Ketamine (0.5 mg/kg) infusion rapidly reduced depressive symptoms. The study proved Ketamine to be superior to placebo. Four patients out of eight showed improvement which was more than 50 % in Hamilton rating scale for depression within 72 hours of infusion." This was the first randomized placebo study to demonstrate the antidepressant effects of Ketamine.[48]

Similarly, "a single-blinded, randomised controlled prospective study on Indian Population by Pathak et al[60] in 2021 compared rapid effects of Ketamine with placebo on depressive symptoms. Significant decline in the depressive symptoms within the 6 hours of the first infusion was demonstrated as compared to those who received placebo." A "double blind RCT study was conducted by Zarate et al[61] on 18 patients with treatment-resistant depression which confirmed Ketamine's rapid antidepressant effects. In this study, subjects were medication free at least 2 weeks

prior to the infusion. Notably, the response rate obtained with Ketamine after 24 hours was 71%, which was similar to that described after 6–8 weeks of treatment with traditional monoaminergic-based antidepressants."

Ketamine's rapid antidepressant action, being within few days or even few hours of administration is a revelational discovery which paves way for researchers and clinicians to develop a potentially life-saving antidepressant agent, particularly by reducing the risk of suicide in depressed patients which is high with the currently used antidepressant medications due to their delayed onset of action.[62] A randomized study comparing Ketamine and Propofol for ECT anaesthesia also demonstrated that Ketamine is associated with an earlier antidepressant response during first 2 weeks of ECT.[63]

So far, 3 Randomised control trials (RCT) have been documented to have directly compared rapid antidepressant effects of Ketamine with ECTs. "Ghasemi et al[64] in 2013 conducted one such study wherein patients diagnosed with severe depression where randomized into 2 groups. One group received ECT, and the other group received Ketamine. Ketamine group showed to be as effective as ECT in improving depressive symptoms in patients and also has significantly rapid antidepressant effects compared with ECT."

"Kheirabadi et al[65] in 2019, conducted a randomised study and compared the effect of intravenous Ketamine with ECT. Improvement in depressive symptoms was observed in both the groups with no statistical difference between the same." One RCT done by "Sharma et al[66] in 2020 in which 25 patients diagnosed with severe

depression were randomized into two groups and administered ECT and intravenous Ketamine (0.5mg/kg) for six alternate day sessions over a period of two weeks. The findings of this study suggested ECT to be superior to Ketamine in producing rapid antidepressant effects." However, this was the only study we could find in our literature search with results favoring ECT over Ketamine.

In conclusion, ECT though effective in reducing depressive symptoms, comes with its limitations. Such as:

1) It being a more invasive procedure
2) Need for the equipment and an anaesthesia team (Picture 3)
3) Requirement for oxygen support
4) Response taking at least 3-5 sessions
5) Associated stigma
6) Cognitive side effects
7) Contraindications such as raised intracranial tension

Ketamine with its rapid antidepressant properties, can overcome these limitations.

The available literature proves that Ketamine has rapid antidepressant effects when administered in severely depressed patients and can potentiate anti-depressant effects of ECT in severe depression. Having said that, is Ketamine as effective or even superior, upon direct comparison with ECT in severe depression still requires further investigation.

MATERIALS AND METHODS

The study was designed as a Randomized control study, aimed at comparing the rapid antidepressant effect of Ketamine to that of Modified Electroconvulsive Therapy in patients diagnosed with severe depression. The study was conducted on patients with ICD -10 DCR diagnosis of Severe Depressive Episode (1stEpisode/Recurrent Depressive Disorder / Bipolar Depression) admitted in the Psychiatric In-patient Department of KLES Dr. Prabhakar Kore Hospital, Belagavi. Data collection took place between 1st January 2021 and 31st December 2021. Patients were recruited using purposive sampling.

The source of the sample were the admitted patients in the Psychiatric In-patient Department.

Sample Size:

ECT arm: 30 patients

Ketamine arm: 30 patients

Sampling Procedure:

n = 2(Z alpha + Z beta)^2 (S^2)/ ($n_{1+}n_2$)^2

Alpha = 0.5; Z alpha = 1.96

Beta = 0.2; Z beta = 0.84

$n_{1=}$ 6; n_2 = 12

n = 2(1.96 + 0.84) * 64/6^2

n = 27.8 (approx. = 30 patients) in each arm

Inclusion Criteria:

- Patients aged between 18-65 years of age
- Patients with ICD-10 DCR diagnosis of
    - Severe Depressive Episode without psychotic symptoms.
    - Bipolar affective disorder, current episode severe depression without psychotic symptoms.
    - Recurrent Depressive disorder, current episode severe depression without psychotic symptoms.

Exclusion criteria:

- Age < 18 years and > 65 years
- Severe depression with psychotic symptoms.
- Primary psychotic disorder.
- Bipolar Affective Disorder, current episode mixed
- Intellectual Disability Disorder
- Dementia
- Mood disorder due to general medical conditions.
- Hypertension (with B.P. > 140/90 mmHg)
- Glaucoma
- History of seizures, raised intracranial tension
- Pregnant and lactating females
- Serious medical condition
- Substance dependence

Ethical Clearance

Prior to commencement, the ethical clearance was obtained from Institutional Ethics Committee, Jawaharlal Nehru Medical College, Belagavi. Ethical clearance number- MDC/DOME/46, dated 25/01/2021.

TOOLS

1) **HAM-D17**[67] – HAMILTON DEPRESSION RATING SCALE. It is a scale used for assessment and quantification of depressive symptoms in patients diagnosed to be suffering from an affective disorder of the depressive type. The scale is supposed to be applied by a qualified and trained medical/psychiatric professional. It is compatible with ICD-10 DCR criteria for depressive disorders, although is not a diagnostic scale. It contains 17 variables. These variables are measured either on a 5-point or a 3-point scale, depending on whether the variables are quantified or not.
2) **BPRS**[68] – BRIEF PSYCHIATRIC RATING SCALE. It was developed by "Overall and Gorham (1962)", to evaluate the array of psychiatric symptoms in a patient. A total of 18–24 symptoms are described in the scale. Each of these symptom has to be rated on a scale from one to seven points depending on their severity.
3) **HMSE**[69] – HINDI MENTAL STATE EXAMINATION. It is based on the Mini Mental State Examination and evaluated similar cognitive domains as the MMSE. HMSE is designed considering the overall literacy level and socio-cultural factors

of the Indian population. It is used for assessment of cognitive functions and for the assessment of neurodegenerative disorders such as dementia.

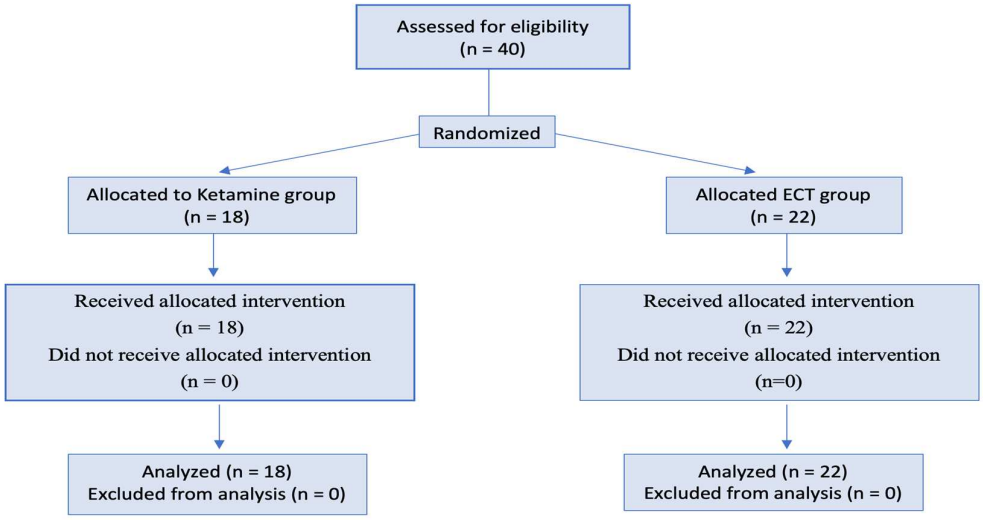
Procedure:

All patients were recruited as per the inclusion and exclusion criteria. Patient's socio-demographic details was collected using a predesigned proforma. Severity of depression was measured using Hamilton Rating Scale for Depression (HAM-D17). The samples were randomized into two groups 30 for Ketamine and 30 for ECT using a computerized randomization tool on the Microsoft Excel version 16.661.

Ketamine group: Patients were kept NPO for at least 6 hours before the intervention. They were premedicated with injection Glycopyrrolate(0.004mg/kg) IV following which they received infusion of "Ketamine hydrochloride (0.5mg/kg) IV over 45 minutes every 48 hours for 3 times i.e., on days 1, 3 & 5." Heart rate, blood pressure and blood oxygen monitoring for all patients was done during infusion and 10 minutes after infusion to watch for muscle spasms and apnea that could occur in rare cases. Patients were monitored during the procedure for any Ketamine-induced emergence phenomena and if present, were to be managed appropriately with anti-psychotic. Ketamine intervention was decided to be discontinued for that patient. During the study procedure, a close watch was kept on patients receiving Ketamine to look for any signs of dependence. Appropriate measures were decided to be taken if found so.

ECT group: Patients were kept NPO for at least 6 hours before the intervention. They were premedicated with injection Glycopyrrolate(0.004mg/kg) IV. Following which, patients were given short general anaesthesia using injection Thiopentone followed by muscle relaxant injection Succinylcholine. Once patients were under anaesthesia, they received "bipolar brief pulse modified ECT every 48 hours for 3 times i.e., on days 1,3 & 5." ECT's were given according to the standard guidelines. HMSE scoring were repeated for the patients after on days 2, 4, 6 and if significant cognitive decline was found, ECT were decided to be discontinued for the patient.

Both the procedures were done under a qualified anesthetist's presence. For both the groups HAM-D17 scoring was repeated after 24 hours following the procedure for 3 times i.e., on days 2,4 & 6 to look for differences in the scores as compared with baseline scoring. Assessment for study purposes was stopped after 3 procedures. However, the treatment continued further as required.



Picture 5 – Diagram showing flow of participants through each stage of a randomized trial

Data Analysis

Data obtained was tabulated in Microsoft excel version 16.661 and subjected to appropriate statistical analyses. Descriptive statistics were presented as percentages for categorical variables, mean and standard deviation for continuous variables. The strength of association (p value) was calculated using unpaired t test (non-parametric) for continuous variables and Fisher's exact test, Chi-square test was applied for categorical variables. Changes in HAM-D17 scores over the course of study period from baseline were analysed using repeated measures ANOVA with Greenhouse–Geiser corrections. Statistical significance was set at p value less than 0.05.

RESULTS

A total of 40 cases were randomised through computer generated random numbers into two groups, one group receiving ECT and the other receiving Ketamine. Due to constraints related to the COVID-19 pandemic, the initially calculated target sample size fulfilling the inclusion criteria during the study period i.e. January 2021 to December 2021, could not be enrolled in the study. Total cases in each Ketamine and ECT group were 18 and 22 cases, respectively. The data obtained was analysed and the final results were tabulated.

Table 1: Comparison of Demographic variables between Ketamine and ECT group

S. No.	Variables		Ketamine (n = 18) n (%)	ECT (n = 22) n (%)	$\chi 2$	p-value
1.	Age (In years)	<=30	4(22.22%)	4(18.18%)	3.8820	0.1440
		31-40	3(16.67%)	10(45.45%)		
		>41	11(61.11%)	8(36.36%)		
		Mean (SD)	38.4 (7.7)	38.8 (9.05)		
2.	Gender	Male	14(77.8%)	6(27.3%)	10.10	0.001*
		Female	4(22.2%)	16(72.7%)		
3.	Education	Not received	2(11.1%)	6(27.3%)	-	0.258#
		Received	16(88.9%)	16(72.7%)		
4.	Occupation	Unemployed	7(38.9%)	15(68.2%)	4.468	0.183#
		Semi-skilled	5(27.8%)	4(18.2%)		
		Skilled	2(11.1%)	0(0.0%)		
		Professional	4(22.2%)	3(13.6%)		
5.	Marital status	Unmarried	2(11.1%)	4(18.2%)	-	0.672#
		Married	16(88.9%)	18(81.8%)		

*($p<0.05$)
#Fischer exact test

Upon comparing the demographic variables between the two intervention groups using Chi-square test (Refer Table 1), in the present study, majority of the patients are above the age of 31 years, 81.8% in ECT group and 77.8% in Ketamine group. Mean age in ECT group being 38.4 ± 7.7(in years) and that in Ketamine group being 38.8 ± 9(in years). Out of the 40 cases enrolled, majority of the females (72.7%) received ECT while majority of the males (77.78%) received Ketamine. Upon comparing the educational status amongst cases in both the groups, majority cases in both ECT group (72.7%) and Ketamine group (88.9%) were found to be educated. Majority of the patients in both the groups were found to be unemployed (ECT group = 68.18%, Ketamine group = 38.9%), followed by semi-skilled (ECT group = 18.18%, Ketamine group = 27.78%), professionals (ECT group = 13.64%, Ketamine group = 22.2%) and skilled (ECT group = 0.0%, Ketamine group = 11.1%). Out of the total cases enrolled in the study, majority of the cases in each intervention group were found to be married (ECT group = 81.8%, Ketamine group = 88.9%). Both the groups were found to be comparable in terms of demographic variables as no significant difference was found in between them except for gender ($p < 0.05$)

Figure 1: Comparison of gender distribution of cases in Ketamine and ECT group

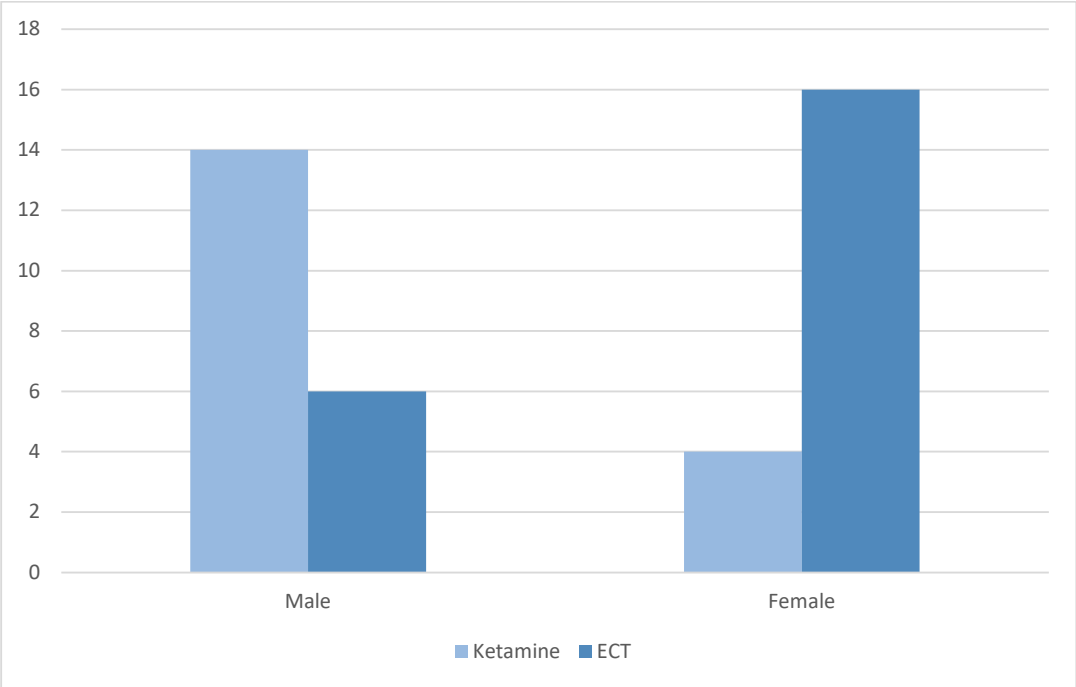


Table 2: Comparison of the clinical profile between Ketamine and ECT group

S. No.	Variables		Ketamine (n = 18) n (%)	ECT (n = 22) n (%)	$\chi 2$	p-value
1.	Diagnosis	SDE	10(55.6%)	13(59%)	2.65	0.448
		RDD with SDE	6(33.3%)	9(41%)		
		BPAD with SDE	2(11.1%)	0(0.0%)		
2.	Number of episodes	Single	11(61%)	11(50.0%)	0.494	0.482
		Multiple	7(39%)	11(50.0%)		
3.	ECT received in past	No	14(77.8%)	20(91%)	-	0.381
		Yes	4(22.2%)	2(9%)		
4.	Family history of psychiatric illness	No	12(66.7%)	12(54.5%)	0.606	0.436
		Yes	6(33.3%)	10(45.5%)		
5.	Duration of total illness(months)	Mean (SD)	56.4(67.15)	57.2(61.15)	-	0.683
6.	Duration of current episode (months)	Mean (SD)	6.3 (2.57)	6.7 (4.12)	-	0.756

Table 2 compares the clinical factors between the two intervention groups. Upon comparing the diagnosis of cases (Figure 2) included in the present study, majority patients in both the groups were diagnosed with Severe Depressive Episode (SDE), (ECT group = 59%, Ketamine group = 55.6%) with Recurrent Depressive Disorder (RDD), current episode SDE being the 2nd most common diagnosis in both the groups (ECT group = 41%, Ketamine group = 33.3%). Bipolar Affective Disorder

(BPAD), current episode SDE included 0% cases in ECT group and 11% cases in Ketamine group. Equal number of cases in ECT group had history of single and multiple episodes as compared to Ketamine group with had majority patients with current episode being the first (61%). Majority patients in both the groups did not receive ECT in the past (ECT group = 91%, Ketamine group = 77.78%) nor have a family history of psychiatric illness (ECT group = 54.5%, Ketamine group = 66.6%). In the present study sample, duration of illness (in months) was compared (ECT group, mean = 57.2, SD = 61.15, Ketamine group, mean = 56.4, SD = 67.15). The mean duration of current episode (in months), for ECT group = 6.7, SD = 4.12 and for Ketamine group = 6.3, SD = 2.57. Both the groups did not have any statistical difference in any of the clinical factors studied.

Figure 2: Comparison of distribution of samples in the Ketamine and ECT group on the basis of their diagnosis

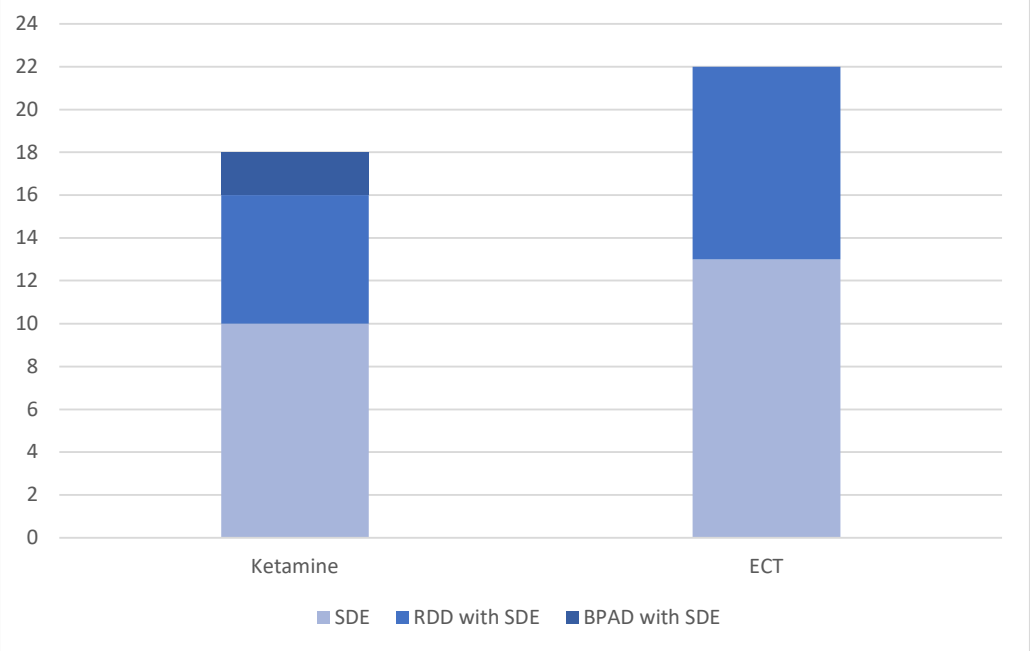


Table 3: Medication use during current depressive episode in patients receiving Ketamine and ECT

Medication		Ketamine Group (n = 18) n (%)	ECT group (n = 22) n (%)	$\chi 2$	p-value
Single antidepressant	SSRI	01(5.5%)	05(22.8%)	0.3402	0.5597
	SNRI	17(94.5%)	15(68.1%)		
	TCA	00(0.0%)	02(9.1%)		
>1 antidepressants		00(0.0%)	00(0.0%)	-	-
Antipsychotics		01(5.5%)	01(4.5%)	-	1.0[#]
Mood stabilisers		04(22.2%)	04(18.1%)	-	1.0[#]
Benzodiazepines		15(83.3%)	18(81.8%)	-	1.0[#]

[#]Fischer Exact Test

The current medication history of patients in both group were compared. Majority of patients in both groups were found to be on SNRIs (Ketamine group = 94.5%; ECT group = 68.1%) followed by SSRIs (Ketamine group = 5.5%; ECT group = 22.8%). No patients in Ketamine group were on TCAs as compared to 9.1% patients in ECT group. None of the patients in both groups were on more than one antidepressants. Antipsychotics were being given to 5.5% patients in Ketamine group and 4.5% patients in ECT group. 22.2% patients in Ketamine group were on mood stabilisers as compared to 18.1% in ECT group and Benzodiazepines were prescribed to 83.3% patients in Ketamine group and 81.8% in ECT group.

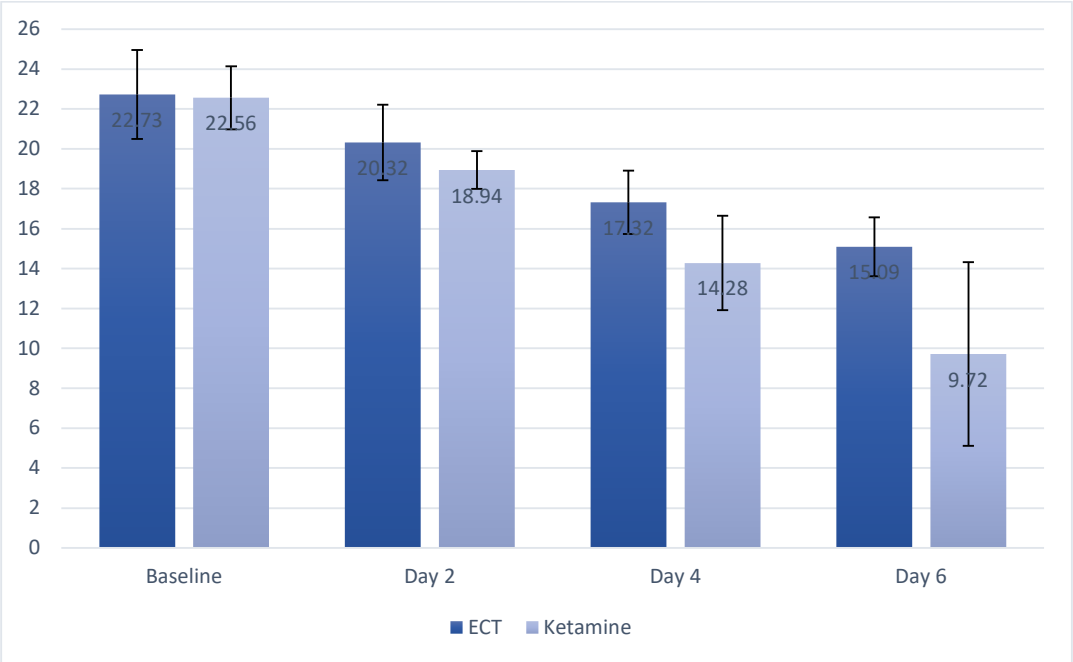
Table 4: Comparison of mean HAM-D17 scores at different treatment time points between ECT and Ketamine group

VARIABLE	GROUP	MEAN (SD)				TIME	GROUP *TIME INTERAC-TION	GROUP *GROUP INTERAC-TION
		Baseline	Day 2	Day 4	Day 6	F	F	F
HAM-D SCORE	ECT (n = 22)	22.73 (2.23)	20.32 (1.89)	17.32 (1.59)	15.09 (1.48)	209.69	25.78	13.34
	Ketamine (n = 18)	22.56 (1.58)	18.94 (0.94)	14.28 (2.37)	9.72 (4.6)			
p-VALUE		0.7849	0.0077*	0.0001*	0.0001*	<0.001	<0.001	<0.001

*p<0.05

Upon comparing the mean Ham-D17 scores for ECT and Ketamine groups over different treatment time points (Refer Table 4 and Figure 3), baseline scores of both groups were comparable (ECT = 22.73 ± 2.23; Ketamine = 22.56 ± 1.58) with no significant difference between the two (p = 0.7849). Difference between mean Ham-D17 scores on day 2, day 4, day 6 for both the groups (ECT = 20.32 ± 1.89, Ketamine = 18.94 ± 0.94, p = 0.0077; ECT = 17.32 ± 1.59, Ketamine = 14.28 ± 2.37, p = 0.0001; ECT = 15.09 ± 1.48, Ketamine = 9.72 ± 4.6, p = 0.0001, respectively) was found to be significant. Following Greenhouse-Geisser correction, the time effect was found to be significant (F = 209.69, p<0.001). The analysis showed that group*time interaction effect as well as the group*group interaction effect for both the intervention groups was significant (group*time interaction effect; F = 25.78, p<0.001; group*group interaction effect; F=13.34, p<0.001).

Figure 3: Comparison of ECT group and Ketamine group with HAM-D17 scores at different treatment time points



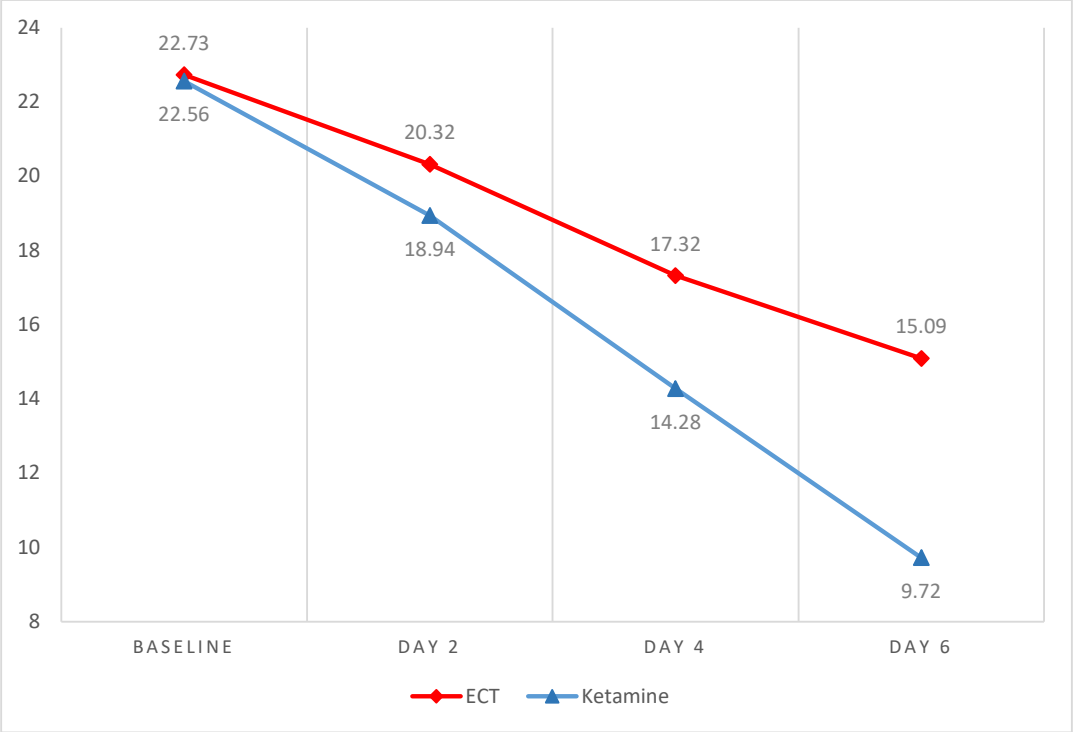


Table 5: Comparison of ECT and Ketamine with percentage changes in HAM-D17 from baseline to Day 6

Groups	Mean (%)	SD (%)	P-value
ECT	32.98	9.11	0.0002*
Ketamine	55.81	23.55	

*p<0.05

Upon comparing the percentage change in Ham-D17 score from baseline to day 6 between the two groups (Refer to Table 5, Figure 7), mean % change for ECT group was 32.98 ± 9.11 whereas for Ketamine group, it was 55.81 ± 23.55. This difference was found to be significant (p = 0.0002). The same is represented on a bar graph in figure 7.

Figure 4: Comparison of ECT and Ketamine with percentage changes in HAM-D17 from baseline to Day 6

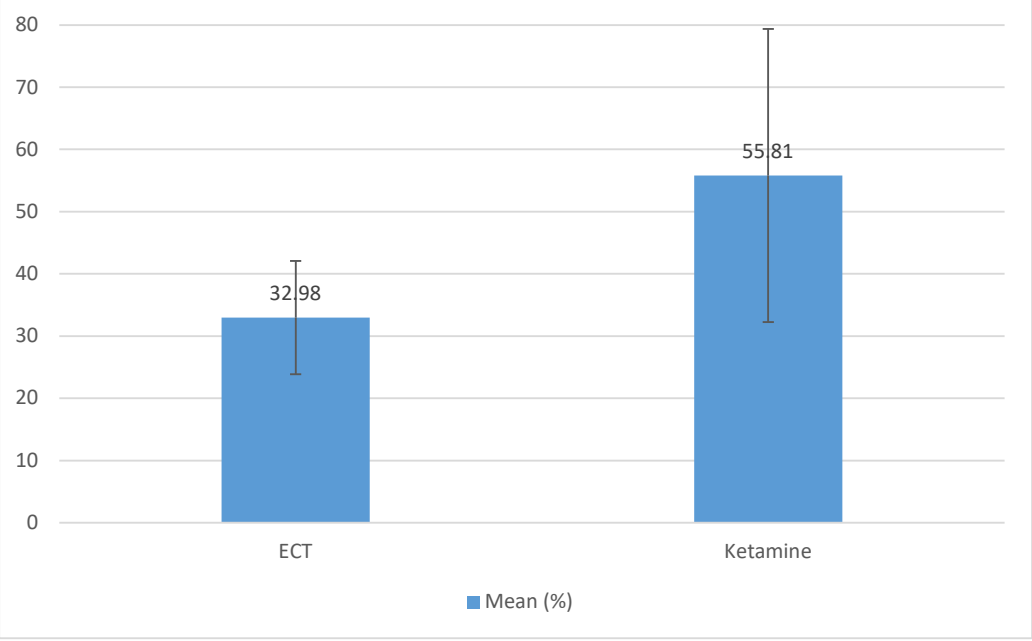


Table 6-10 studies the correlation between Ketamine response and various demographic and clinical factors. Ketamine response was measured using change score (HAM-D17 score at baseline minus HAM-D17 score at day 6).

Table 6: Correlation between Ketamine response (Change score) with Age

VARIABLE	Change score (R)	p-VALUE
Age(in years)	0.4005	0.0996

Upon correlating age of samples in Ketamine group with their response to the intervention, it was found that they have a mildly positive correlation (R = 0.4005). However, this correlation was not found to be statistically significant (p = 0.0996).

Table 7: Correlation between Ketamine response (Change score) with gender

VARIABLE		Change score (Mean ± SD)	p-value
Gender	**Male**	14.5 ± 4.620	0.015*
	Female	7 ± 5.774	

Ketamine response was correlated with gender of the patients, mean change score of males (14.5 ± 4.620) was found to be higher than that of females (7 ± 5.774). This difference was found to be statistically significant (p = 0.015). The same has been depicted in Figure 5 as follows.

Figure 5: Correlation between Ketamine response (Change score) with gender

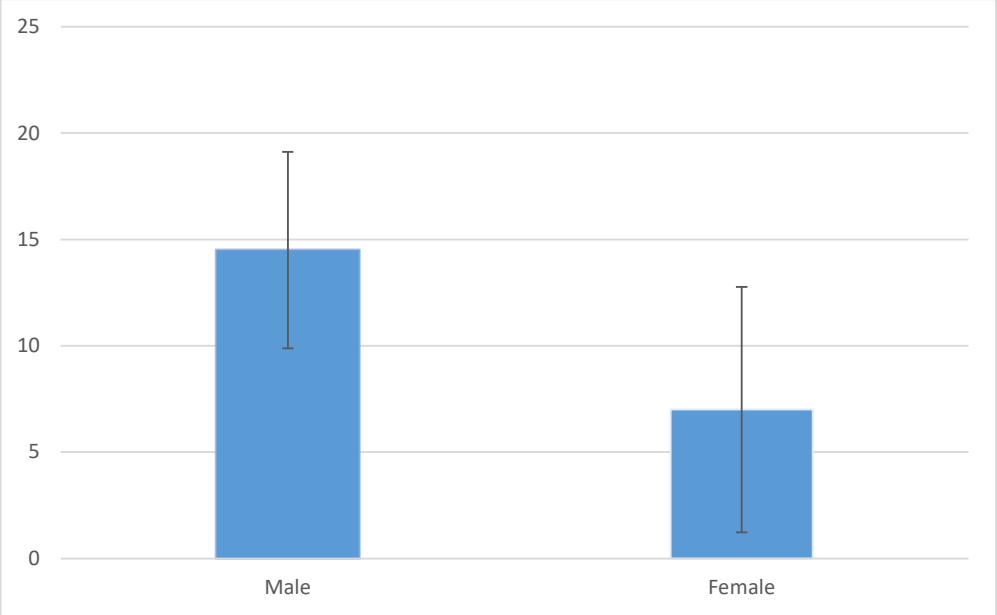


Table 8: Correlation between Ketamine response (Change score) with Diagnosis

VARIABLE		Change score (Mean ± SD)	p-value
Diagnosis	**SDE**	11.9 ± 6.657	0.6010
	RDD with SDE	13.16 ± 4.834	
	BPAD with SDE	16.5 ± 0.7071	

When Ketamine response was correlated with diagnosis of the patients, those diagnosed with BPAD, current episode SDE were found to have the maximum mean change score (16.5 ± 0.7071) followed by those diagnosed with RDD, current episode SDE (13.16 ± 4.834). Patients diagnosed with a single episode of SDE were found to have the least mean change score (11.9 ± 6.657). However, this difference was not found to be statistically significant (p = 0.6010).

Table 9: Correlation between Ketamine response (Change score) with duration of illness

VARIABLE	Change score (R)	p-value
Duration of illness	0.01742	0.9453

Upon correlating Ketamine response with duration of illness of the patients, they were found to have almost no correlation (R = 0.01742). However, this was not found to be statistically significant (p = 0.9453).

Table 10: Correlation between Ketamine response (Change score) with treatment received in the past

VARIABLE		Change score (Mean ± SD)	p-value
Treatment received in past	**No**	10.33 ± 7.633	0.4258
	Yes	14.08 ± 4.316	

When Ketamine response was correlated with treatment received in the past, patients who had received treatment in the past showed a higher change score (14.08 ± 4.316) than those who had not received any treatment in the past (10.33 ± 7.633). However, this was not found to be statistically significant (p = 0.4258).

DISCUSSION

Severe depression, owing to its morbidity and mortality due to suicide, warrants early treatment which along with being efficacious, can also show a rapid onset of action. Electroconvulsive therapy is a rapidly acting treatment modality, most commonly used for severe depression presently. However, associated stigma, cognitive side effects and anesthesia related complications limit its use. Ketamine is another treatment option showing promise in having rapid action in reduction of depressive symptoms but there is little data available on the Indian population. Considering depression being a rising concern and limited evidence available over a pharmacological treatment that can be used in case of an emergency, the present study aims to evaluate the rapid antidepressant action of Ketamine and compare it to that of modified electroconvulsive therapy.

Our study was conducted in a tertiary care hospital, on 40 inpatients diagnosed with Severe depression who were randomly allocated into 2 intervention groups namely ECT and Ketamine.

(1) Comparison of demographic variables between the patients in both intervention groups (Refer to Table 1)

The mean ages of the patients in Ketamine and ECT groups were 38.8 years and 38.4 years, respectively. Identical mean age of 35.22 years in Ketamine group and 40 years in ECT group was found in a similar RCT done in the past[64]. Another study done by Kheirabadi et al[65] comparing Ketamine and ECT had the mean age of the participants in the ketamine group as 41.7 ± 12.9 and that of the ECT group as 36.4 ± 14.1 years. The mean age group was much the same (Ketamine group = 34.42 years and ECT group = 41.38 years) in a recent Indian pilot study done to compare

antidepressant effects of Ketamine and ECT.[66] Our study sample has a comparable age group with other likewise studies done in the past.

Majority of the females (72.7%) received ECT while majority of the males (77.78%) received Ketamine as depicted in table 1 and figure 1. The study population in the RCT done by Ghasemi et al constituted 56% females in each Ketamine and ECT group.[64] Whereas in the study done by Kheirabadi et al[65], females constituted 36% of all the participants, and there was no significant difference in terms of gender composition of the groups. Majority patients who received Ketamine were females (66.7%) in the RCT done by Sharma et al.[66] This finding could be a chance factor due to the randomization process.

Educational status of the patients in both the intervention groups was compared (Refer to Table 1). Majority of the patients were formally educated in both Ketamine and ECT groups (88.9% in Ketamine and 72.7% in ECT group). This finding is likely due to the strata of patients presenting to the hospital being formally educated and does not hold any clinical significance. We could not find a similar comparison in the other RCTs that compared the antidepressant action of Ketamine and ECT.

Most of the people were found to be unemployed in both groups (38.9% in Ketamine group and 68.2% in ECT group) when compared for occupation as seen in Table 1. This can be explained by the fact that a lot of the patients presenting to the hospital are farmers which was included as an unemployed status during collection of data. This does not hold any clinical significance. As far as our literature search goes, the other RCTs comparing antidepressant action of Ketamine and ECT did not compare occupation of their samples.

When participants in the 2 groups were compared for marital status (Refer Table 1), majority patients were found to be married (88.9% in Ketamine group and 81.8% in ECT group). This finding could be due to the mean age group studied which mostly contains the married population too. The population studied by Ghasemi et al[64] also constituted of married patients mostly (55.6% in Ketamine group and 66.7% in ECT group). This could be due to chance factor and holds no clinical significance.

(2) Comparison of clinical variables between the patients in both intervention groups (Refer to Table 2)

Upon comparing diagnosis (Refer to Table 2 and Figure 2), majority patients in both groups were diagnosed with single episode of severe depression (55.6% in Ketamine group and 59% in ECT group) followed by recurrent depressive episodes and bipolar depression. The study population of Sharma et al(66) was similar as most of them were also diagnosed with unipolar depression (75% in Ketamine arm and 53.8% in ECT arm).

The duration of illness of samples was compared between Ketamine and ECT group (refer to Table 2). Mean duration of illness of patients in Ketamine group was 56.4 (± 67.15) months while that in ECT group was 57.2 (± 61.15) months. The same was compared by Sharma et al in their study. Mean duration of illness of patients in Ketamine group was 87.17 (± 87.64) months while that in ECT group was 85.23 (± 120.39) months. These time durations were greater than that of our study and could be a chance factor. We could not find these comparisons in other similar studies done in the past.

We compared the duration of current episode of patients recruited in each group (Refer to table 2). Patients in Ketamine group had mean duration of current episode of 6.3 (± 2.57) months while the same in ECT group was 6.7 (± 4.12) months. Ghasemi et al in their study compared the length of current episode. The mean duration of current episode of patients in Ketamine group was 8.77 (± 8.91) months while that in ECT group was 9.22 (± 10.97) months. These time durations were greater than that of our study and could be a chance factor. We could not find these comparisons in other similar studies done in the past.

Majority of the patients in Ketamine group had a single episode of depression (61%) whereas equal number of patients in ECT group had single and multiple episodes of depression (Refer to Table 2). This difference was found to be non-significant and does not hold any clinical significance. We could not find other similar RCTs comparing number of episodes between the two intervention groups.

Only few patients in both the groups had received ECTs in the past (22.2% in Ketamine group and 9% in ECT group). The study sample of Sharma et al had 25% patients in Ketamine group and 38.5% in ECT group with past history of having received ECT. This was similar to the Ketamine group of our study population.

Most of the patients in our study did not have a family history of psychiatric illness (66.7% in Ketamine group and 54.5% in ECT group). This criterion was not found to have been studied in other RCTs which compared antidepressant effects of Ketamine with ECT.

(3) Comparison of medication use during current depressive episode between the patients in both intervention groups (Refer to Table 3)

When the medication use of patients during current episode in both intervention groups were compared, all the patients were at least on one antidepressant medication. Out of those, a greater number of patients in ECT group were found to be on SSRIs (22.8% in ECT group; 5.5% in Ketamine group). However, more people in Ketamine group were on SNRIs (94.5% in Ketamine group; 68.1% in ECT group). However, this difference was not found to be statistically significant and hence could be due to chance. 5.5% patients in Ketamine group and 4.5% in ECT group were on antipsychotics, 22.2% patients in Ketamine group were on mood stabilisers as compared to 18.1% in ECT group and Benzodiazepines were prescribed to 83.3% patients in Ketamine group and 81.8% in ECT group. These differences however were not significant. In the study done by Sharma et al,[66] 58.3% patients in Ketamine group and 62.5% patients in ECT group were on SSRIs. 74.9% patients in Ketamine group and 69.3% in ECT group were on antipsychotics. 46.2% patients in ECT group were on mood stabilisers while none of the patients in Ketamine group were prescribed the same. Benzodiazepines were prescribed to 8.3% patients in Ketamine group and to 30.8% in ECT group. This difference was found to be non-significant and does not hold any clinical importance.

(4) Rapid antidepressant effect of Ketamine as compared to Modified ECT (Refer to Table 4 and Figure 4)

Out of 40, 22 patients received modified electroconvulsive therapy and 18 patients received subanesthetic doses of intravenous Ketamine. Each intervention was given 3 times, on day 1, day 3 and day 5 of the study period.

The mean score on 17-item HAM-D17 scale for 40 depressed patients were analysed at baseline and at 24 hours after the first, second and third infusions (Refer to Table 4 and Figure 3). Out of the 40 patients, the 22 patients receiving ECT, showed a reduction in the mean HAM-D17 score from 22.73 ± 2.23 at baseline to 20.32 ± 1.89 on day 2 of the study period (i.e., 24 hours after the 1st infusion), 17.32 ± 1.59 on day 4(i.e., 24 hours after 2nd infusion) and 15.09 ± 1.48 on day 6(i.e., 24 hours after 3rd infusion) showing ~33% reduction from baseline (Refer to Table 5 and Figure 4). Whereas the 18 patients who received repeated Ketamine infusions showed a fall in the mean HAM-D17 score from 22.56 ± 1.58 at baseline to 18.94 ± 0.94 on day 2, 14.28 ± 2.37 on day 4 and 9.72 ± 4.6 on day 6 of the study period showing ~56% reduction from baseline, which was found to be significant (Refer to Table 5 and Figure 4). The findings suggest that ketamine initiates a rapid response (i.e., >50% reduction in HAM-D17 scores from baseline) in patients with severe depressive disorder following 3 infusions.

After three treatment sessions, Repeated Measures ANOVA analysis of the scores was done (Refer to Table 4). Both the intervention groups achieved significant improvement (compared to the baseline) in the depressive symptoms over time during the study period (time effect; $F = 209.69$; $p<0.001$). The analysis also showed that patients who received Ketamine showed a significantly greater and faster reduction in HAM-D17 scores (group *time interaction effect; $F = 25.78$, $p<0.001$).

The comparison of two treatment groups shows a significant difference for HAM-D17 score throughout all three sessions (group* group interaction effect; F = 13.34, $p<0.001$).

The decrease in scores (mean HAM-D17) was greater in the ketamine group when compared to the ECT group at all the evaluated time points over the study period, with significant differences observed with three repeated infusions along with ongoing conventional antidepressant medications.

Patients in the Ketamine arm showed mild adverse effects to the intervention in the form of drowsiness, transient rise in heart rate and blood pressure during the infusion which normalised 15-20 minutes following the end of infusion. No patient receiving Ketamine showed symptoms suggestive of dissociative anaesthesia or emergence phenomenon during the course of the study. None of the patients were found to have developed any signs of dependence to Ketamine. Mild and transient rise in heart rate and blood pressure was also seen in patients who received ECT which subsided following the procedure. However, they did not show any cognitive deficits during the study period i.e., following receiving 3 ECTs.

The rapid action of Ketamine in reducing depressive symptoms could be a result of multiple pathways postulated to give it it's antidepressant effect, as discussed earlier.

In a randomized study conducted by Ghasemi et al[64] in 2013, 18 patients with DSM-IV MDD diagnosis were divided into two groups. Nine patients each received either three intravenous infusions of ketamine hydrochloride (0.5 mg/kg over 45 min) or bilateral ECT on 3 days (every 48 hours). Depressive symptoms were measured at baseline, 24 hours after each treatment, 72 hours and one week after the last (third) ketamine or ECT using Beck Depression Inventory (BDI) and 25-item HAM-D17

scores. BDI scores reduced from 42.44 ± 9.53 at baseline to 23 ± 9.39 at day 6 in ECT group. Maximum reduction in scores (26.58%) was seen after 3rd ECT. In the Ketamine group, scores reduced from 34.66 ± 10.7 at baseline to 16 ± 11.79 at day 6 with maximum reduction (42.69%) seen after the 1st Ketamine infusion. 25-item HAM-D scores in ECT group reduced from 35.88 ± 6.47 at baseline to 19.44 ± 5.25 at day 6 with maximum reduction (20.76%) seen after 3rd ECT. Ketamine group showed reduction in HAM-D scores from 30.22 ± 5.78 at baseline to 13.77 ± 6.98 on day 6 with 41.97% reduction after the 1st infusion. These values were found to be significant. The results of this study are in line with our study and suggest that Ketamine has a rapid antidepressant action as compared to ECT. Moreover, this study points out that rapid antidepressant effect of Ketamine is seen following the 1st infusion itself.

Zarate et al[61] in 2006 conducted a double-blind, randomized, crossover, placebo-controlled study. Following a 2-week drug free period, 15 patients with major depression received a single IV infusion of either ketamine hydrochloride (0.5 mg/kg) or placebo on two test days 2 weeks apart. Patients were assessed at baseline and at 40, 80, 110, and 230 minutes and 1, 2, 3, and 7 days after infusion. Within 40 min, depressive symptoms significantly reduced in patients who received ketamine as compared to those who received placebo; this was found to be significant through day 3. In our study, first assessment was done at the interval of 24 hours after the first Ketamine infusion and significant improvement in HAM-D17 scores was seen. In this way, our study's findings are reflected in this study as well suggesting that Ketamine has a rapid antidepressant effect.

An earlier study done by Thakurta *et al*[59] on Indian subjects assessed resolution of depressive symptoms with single IV infusion of ketamine hydrochloride

(0.5 mg/kg) after a 2-week medication-free period in depressed patients. Significant decline in HAM-D17 scores was seen within 80 minutes of ketamine infusion, (22.96 ± 1.2 at baseline to 17.5 ± 5.34 at 80 minutes post infusion) which remained persistent up to day 2 (15.6 ± 4.64). However, it was a single-arm study with no comparator group. Single infusion of Ketamine was administered and follow-up period was of only 2 days. Our study sample did not undergo a medication-free period. In our study, assessment was done after 24 hours of infusion and a total if 3 infusions were given. Nevertheless, both the studies conclude that Ketamine indeed has a brisk effect on reducing depressive symptoms.

Pathak et al[60] compared rapid effects of Ketamine with placebo on depressive symptoms in a single-blinded, randomised controlled prospective study on Indian Population. The study analysed the mean HAM-D17 score of 60 depressed patients at baseline and at 6 hours after the first infusion, followed by evaluation at day 1 up to day 6. Patients who were infused ketamine, showed a significant decline in the mean HAM-D17 score within the 6 hours of the first infusion (HAM-D17 score from 29.30 ± 3.436 to 20.10 ± 3.133; 31% reduction). Mean HAM-D17 score reduced from 29.30 ± 3.436 at baseline to 10.10±1.125 at day 6. These changes were significantly higher than the decline in the mean scores of the patients who were infused normal saline as placebo. Findings of this study can be compared with our study and it can be concluded that Ketamine shows a quick response in reducing depressive symptoms.

The findings of a recent study by Price et al[57] support our study that subanesthetic dose of IV ketamine has rapid effects on depressive symptoms in TRD, and that acute improvements can be sustained through repeated ketamine infusions. Reductions of the scores in Montgomery–Asberg Depression Rating Scale (MADRS) were sustained for 12 days by repeated infusions.

The evidence on antidepressant effect of ketamine has also been contributed by DiazGranados et al.[56] Subjects with MDD received a single infusion of ketamine (0.5 mg/kg) and rated at baseline, 40, 80, 120, and 230 min post-infusion with MADRS and HAM-D17. Scores decreased significantly within 40 min; these decreases remained significant at all time points. However, this was an open-label study without any comparator group and effects of only single infusion of Ketamine were studied.

Murrough et al[58] supported rapid and sustained antidepressant effect of ketamine. Participants with TRD were administered a series of up to six IV ketamine infusions, three times weekly over a period of 12 days. There was a large mean decrease in MADRS score at 2 hours following the first ketamine infusion. Assessment was done over 12 days until the sixth infusion. Decrease in the MADRS scores was found to be sustained over this period suggesting a brisk and sustained response of ketamine on reducing depressive symptoms. The findings of this study support ours however, this study was done on patients with TRD. Our samples were not assessed for treatment resistance and we cannot comment on how the findings of our study would apply to patients with treatment resistant depression.

Kheirabadi et al[65] in 2019, conducted a randomised study to study the comparative effect of intravenous Ketamine with ECT. HAM-D17 scale was applied at baseline, before each treatment session, and four time points posttreatment (week 1 and months 1, 2, and 3). Improvement in depressive symptoms was observed in both the groups with no statistical difference between the same.

Sharma et al[66] in 2020 conducted an assessor-blinded randomized study to compare the antidepressant effects of intravenous ketamine infusion (0.5mg/kg over 45 minutes) and ECT (unilateral/bilateral) on 25 patients diagnosed with Severe

depression, administered for six alternate day sessions over a period of two weeks. Ketamine arm included 41.7% patients who were diagnosed with psychotic depression. Nine patients who received bifrontal ECTs got stimuli at 1.5–2 times their threshold while for remaining four patients who were on right unilateral ECTs, stimuli at 6 times their threshold were delivered. Out of the 12 patients receiving Ketamine, 3 patients dropped out before completing the trial duration (one due to adverse effect and two due to lack of efficacy). As a result, patients receiving ECT showed a higher response rate as compared to Ketamine. Our study was solely aimed at assessing whether Ketamine has a better antidepressant action over modified ECT. The ECT administration in our study was not controlled for electrode placements or seizure threshold as these are factors which could influence response as well as adverse effects. None of the samples in our study included psychotic depression as it was ruled out during the recruitment stage of the trial. No patients dropped out in our study or developed side effects to Ketamine. These factors can be a reason for findings observed in this study.

(5) Demographic and clinical factors that would predict the Ketamine response (Refer to Table 6 to Table 10)

Upon studying the demographic and clinical factors in patients who received Ketamine, correlation was drawn between Ketamine response and various demographic and clinical factors. Ketamine response was measured using change score (HAM-D17 score at baseline minus HAM-D17 score at day 6).

Upon correlating age of samples in Ketamine group with their response (Refer to Table 6), mildly positive correlation of response to Ketamine with increasing age was found (R = 0.4005). However, this correlation was not found to be statistically significant.

Ketamine response was correlated with gender of the patients (Refer to Table 7 and figure 5), males were observed to have a significantly higher response to Ketamine as compared to females (Mean change score; males = 14.5 ± 4.620, females = 7 ± 5.774; p = 0.015).

Correlation was drawn between Ketamine response and diagnosis of the samples (Refer to Table 8). Findings suggest that patients diagnosed with BPAD, current episode SDE have the maximum response to Ketamine (mean change score = 16.5 ± 0.7071) followed by those diagnosed with RDD, current episode SDE (mean change score = 13.16 ± 4.834). Patients diagnosed with single episode SDE show the least response to Ketamine (mean change score = 11.9 ± 6.657). Given the fact that the biology of these two conditions are putatively different, efficacy of ketamine might also vary for these two different varieties of depression. However, this difference was not found to be statistically significant (p = 0.6010).

When we correlated Ketamine response with duration of illness (Refer to Table 9), no significant correlation could be found between the two (R = 0.01742, p = 0.9453).

Ketamine response was found to be higher in patients who had received treatment in the past with a mean change score = 14.08 ± 4.316 (Refer to Table 10) than those who had not received any treatment in the past (mean change score = 10.33 ± 7.633). However, this observation was not found to be statistically significant (p = 0.4258).

To the best of our knowledge, no other RCT could be found which has correlated response to Ketamine with various demographic and clinical factors.

The aim of this study was a head to head comparison of rapid antidepressant effect of Ketamine with ECT. Our study randomised severely depressed patients into Ketamine and ECT groups and assessed rapid antidepressant response in those for the intervention received. On the basis of our findings, Ketamine emerged as being higher ranked than ECT in bringing down the depressive symptoms at a faster rate. The results are favourable for Ketamine, however need to be reconfirmed with a study done on a larger sample. The unequal gender distribution in both the intervention groups also poses as a drawback of the randomisation process and needs to be accounted for in upcoming studies. Having said that, Ketamine undoubtedly is coming forth as a promising rapid antidepressant and should be considered in emergency situations. ECTs owing to their limitations, for example, need for equipment, oxygen support, an anaesthetist and associated stigma and side effects, cannot be administered universally for all patients. Ketamine, if proven better can even become the treatment of choice in the future in severely depressed individuals; especially in

1) centres where ECTs are unavailable
2) emergency situations,
3) patients who do not wish to receive ECTs and
4) in whom ECTs are contraindicated.

Further research in this direction, hopefully will confirm as well as add to our existing knowledge on the same

CONCLUSION

Our current study suggests that Ketamine, commonly used as an anaesthetic agent, also has antidepressant action. Intravenous infusion of Ketamine can bring about rapid reduction of symptoms in patients with severe depression. Three such infusions can also bring about remission in the patients.

The improvement in scores of rating scales was steeper for patients who received Ketamine as compared to the patients who received Electroconvulsive therapy. This difference was found to be statistically significant. These findings show that Ketamine is a better and effective alternative to ECTs in patients diagnosed with severe depression and who require urgent treatment. However, the results need to be replicated with a larger study sample.

SCOPE AND LIMITATIONS

1) Limited studies have been found in our literature search which assess the rapid antidepressant effect of Ketamine. And even less studies are reported in literature which compare it with another established rapid antidepressant treatment i.e., ECTs.

2) Our study is a Randomised controlled trial including 40 patients which, to our knowledge, is the largest sample size so far in all the RCTs which have compared rapid antidepressant effect of Ketamine with ECT, thus increasing the overall reliability of the study.

3) As far as our literature search could go, we could not find any other study which correlated demographic and clinical factors of the samples with the rapid antidepressant action of Ketamine. The findings following having done this correlation add another dimension to our study and to its primary finding.

LIMITATIONS:

1) Initial sample size of 60 patients could not be achieved due to reduction in patient admissions and willingness for hospital stays due to the COVID-19 pandemic during the study period.

2) Majority of the patients in Ketamine arm were males while those in ECT arm were females pointing towards a limitation in the randomisation method used for allocating patients into either intervention groups.

SUMMARY

Our present study was designed as a Randomized control study, carried out in the Department of Psychiatry, KLES Dr. Prabhakar Kore Hospital and MRC from 1st January 2021 to 31st December 2021. The study was conducted on 40 patients with ICD -10 DCR diagnosis of Severe Depressive Episode (1stEpisode/Recurrent Depressive Disorder / Bipolar Depression) admitted in the Psychiatric In-patient Department of KLES Dr. Prabhakar Kore Hospital and MRC, Belagavi. Patients who matched the inclusion criteria were randomly assigned into Ketamine and ECT groups. Following randomization and taking due consent, severity of depression was measured using Hamilton Rating Scale for Depression (HAM-D17). Brief Psychiatric Rating Scale (BPRS) was also applied after admission to rule out presence of psychotic symptoms. Baseline cognitive assessment of the patients was done using HMSE before the procedure. Out of the 40 patients, 18 inpatients received 3 intravenous ketamine hydrochloride (0.5mg/kg) infusion over 45 minutes and 22 inpatients received 3 sessions of modified electroconvulsive therapy. HAM-D17 scores were measured 24 hours after each infusion to assess reduction in severity of depressive symptoms.

It was observed that both the groups were comparable in terms of demographic variables as no significant difference was found in between them except for gender (majority of the females i.e., 72.7% received ECT while majority of the males i.e., 77.78% received Ketamine). Both the groups did not have any statistical difference in any of the clinical factors studied. Mean HAM-D17 scores in Ketamine group fell from 22.56 at baseline to 9.72 at day 6 while those in ECT group showed a fall from 22.73 at baseline to 15.09 at day 6. The difference in HAM-D17 scores was found to be statistically significant at all time points studied. Moreover, mean %

change in Ham-D17 scores for ECT group was 32.98 ± 9.11 whereas for Ketamine group, it was 55.81 ± 23.55. This difference was also found to be significant.

Our findings suggest that Ketamine is superior to electroconvulsive therapy in reducing depressive symptoms at a faster pace with fewer side effects. Thus, this makes Ketamine a better alternative to ECT in severe depressive patients requiring immediate treatment. However, head to head comparison of larger samples of patients with severe depression will give a more definitive answer.

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ANNEXURE I

INFORMED CONSENT

Rapid Antidepressant Effects of Ketamine Compared with Electroconvulsive Therapy: A Randomized Control Trial

Principal Investigator (PI): REG NO: BQ0120001

Objective/Purpose of the study:

You/your relative are being requested to be a subject in this randomized control trial the purpose of which is to know the rapid antidepressant effects of Ketamine v/s Modified Electroconvulsive therapy in severe depressive patients conducted between 1st January 2021 and 31st December 2021, by **REG NO: BQ0120001**, a postgraduate student in the Department of Psychiatry and the study will be carried out under the direct supervision and guidance of Dr_____, Department of Psychiatry, Jawaharlal Nehru Medical College, Belagavi.

You/your relative have/has been requested to participate in this study as you/your relative are/is likely to have a Severe depression which needs intervention. Therefore, the above study not only helps in treating severe depression but also to prevent complication occurring out of the illness.

Signature of Patient/Legally Authorised Representative: _____

ASSENT

Rapid Antidepressant Effects of Ketamine Compared with Electroconvulsive Therapy: A Randomized Control Trial

Principal Investigator (PI): REG NO: BQ0120001

Objective/Purpose of the study:

Your relative is being requested to be a subject in this randomized control trial the purpose of which is to know the rapid antidepressant effects of Ketamine v/s Modified Electroconvulsive therapy in severe depressive patients conducted between 1st January 2021 and 31st December 2021, by **REG NO: BQ0120001**, a postgraduate student in the Department of Psychiatry and the study will be carried out under the direct supervision and guidance of Dr_____, Department of Psychiatry, Jawaharlal Nehru Medical College, Belagavi.

Your relative has been requested to participate in this study as your relative is likely to have a Severe depression which needs intervention. Therefore, the above study not only helps in treating severe depression but also to prevent complication occurring out of the illness.

Signature of Legally Authorised Representative: _____

Signature of Witness: _____

Procedure and Benefits:

Informed consent for Ketamine administration

I/we _____have been explained in detail about Ketamine administration. I/we understand that this treatment involves giving Ketamine hydrochloride 0.5mg/kg infusion over 45 minutes, which will be administered by a qualified anaesthetist. I/We have also been explained the need and course of this treatment. The benefits of the treatment are that there may be rapid improvement in the symptoms. We have also been explained the various side effects and complications of Ketamine administration which may be rarely fatal, the side effects may include rise in blood pressure, dizziness, blurred vision, headache, nausea, vomiting, and restlessness, rarely there may be hallucinations, euphoria, and delirium, which usually subsides after discontinuing treatment.

I/we also understand that this course of treatment numbering about 3 infusions which are given with a gap of 48 hours. I/we have been explained all this in our own vernacular language and we fully understand the need and all the possible problems associated with Ketamine. I/ we give full and informed consent for a course of Ketamine administration and will not hold doctors and hospital responsible for any complications that may arise.

Informed consent for Electroconvulsive therapy administration

I/we have been explained in detail about Electroconvulsive therapy. I/we understand that this treatment involves giving electric current to the head for a very short period and it will be done after giving very short acting general anaesthesia which will be administered by a qualified anaesthetist. General anaesthesia will be helpful in reducing pain or discomfort. We have also been explained in detail regarding the need and course of this treatment. We have also been explained in detail about various side effects and complications of this treatment which may rarely be fatal also. The complications may include injury, memory impairment for a short period, difficulty in respiration.

I/we also understand that this course of treatment numbering about 3 ECT's which are given with a gap of 48 hours. I/We have been explained all of this in our own vernacular language and we fully understand the need and all the possible problems associated with ECT's. I/ We give full and informed consent for a course of ECT administration and will not hold doctors and hospital responsible for any complications that may arise.

Alternatives:

Your/your relative's participation in this study is a completely voluntary decision. If you/your relative do/does not want to be a part of the study, you/your relative may refuse for the same or if you/your relative are/is already a part of the study and if you/your relative want/wants to withdraw from the study for any reason, you/your relative may do so without any hesitation. Discontinuation from the study for any reason will not affect your/your relative's current or future relationship with KLES Dr. Prabhakar Kore Hospital, Belagavi.

Privacy and confidentiality:

The information provided by you/your relative will be known to the PI and the members of the research team. This information will remain confidential and will be disclosed to others only with your/your relative's written permission or if required by the law.

Financial incentives for participation:

You/your relative will not be paid/offered any gifts for participation in the research. There will not be any remuneration for participating in the research and you/your relative will not be reimbursed for any expenses, such as bus/train/companion/assistant etc.

Authorization to publish results:

When the results of the research are to be published or discussed in conferences by the PI, no information will be disclosed that will reveal your/your relative's identity.

Signature of Patient/Legally Authorised Representative: _____

Signature of Investigator: _____

Date:

STATEMENT OF CONSENT

I/my relative have/has read and have/has completely understood the entire information given in the consent form, which explains all the details of the study, i.e, the purpose, procedure involved, risks & benefits, privacy & confidentiality, incentives and the authorization to publish the results of the study. My/my relative's signature in the space provided for signature below indicates that I/my relative have/has voluntarily agreed to participate in the study. I/my relative may withdraw my/my relative's participation for any reason or may be withdrawn by the investigator from the study for any reason at any time. I/my relative am/is not giving up any of my/my relative's legal rights by signing this consent form. I/my relative will be given a copy of this consent form.

Signature of the participant with date: _____

Name of the participant: _____

Signature of the authorized representative with date: _____

Name of the authorized representative: _____

Relationship of authorized person: _____

Signature of the witness with date: _____

Name of the witness: _____

Signature of the Investigator with date: _____

ಸಂಶೋಧನಾ ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ಸಲಹೆ

1. ನಾನು ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳುತ್ತಿದ್ದೇನೆ ಎಂದು ನಾನು ಅರ್ಥಮಾಡಿಕೊಂಡಿದ್ದೇನೆ.

2. ರೋಗಿಯ ಮಾಹಿತಿಹಾಳೆಯಲ್ಲಿ ನಮಾಹಿತಿಯನ್ನು ನಾನುಓದಿದ್ದೇನೆ ಮತ್ತು ಅರ್ಥಮಾಡಿಕೊಂಡಿದ್ದೇನೆ ಎಂದುನಾನು ದೃಢೀಕರಿಸುತ್ತೇನೆ. ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳುವ ಅನುಕೂಲಗಳು ಮತ್ತು ಅನಾನುಕೂಲತೆಗಳ ಬಗ್ಗೆ ಮಾಹಿತಿಯೊಂದಿಗೆಕಾರ್ಯವಿಧಾನವನ್ನು ನನಗೆ ವಿವರವಾಗಿವಿವರಿಸಲಾಗಿದೆ. ಪ್ರಯೋಗದಎಲ್ಲಾ ಅಂಶಗಳನ್ನು ಚರ್ಚಿಸಲು ನನಗೆ ಅವಕಾಶನೀಡಲಾಗಿದೆ, ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳು ಮತ್ತು ಅದರಮೇಲೆ ಈ ಕೆಳಗಿನವುಗಳನ್ನು ವಿವರಿಸಿರುವ ವಿಚಾರಣೆಯಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ಸಮ್ಮತಿನೀಡಲಾಗಿದೆ.

3.
ಈ ಅಧ್ಯಯನದ ಪಾಲ್ಗೊಳ್ಳುವ ನಿರ್ಧಾರ ಸಂಪೂರ್ಣವಾಗಿ ಸ್ವಯಂಪ್ರೇರಿತವಾಗಿದೆ ಮತ್ತು ನಾನು ಆಯ್ಕೆ ಮಾಡಬಹುದು ಎಂದು ನನಗೆ ತಿಳಿದಿದೆ. ಸಮಯದಹಂತದಲ್ಲಿ ಅಧ್ಯಯನದಿಂದ ಹೊರಬರಲು.

4. ವೈದ್ಯಕೀಯ, ವೈಜ್ಞಾನಿಕ ಅಥವಾಶೈಕ್ಷಣಿಕ ಉದ್ದೇಶಗಳಿಗಾಗಿ ನನ್ನ ದೇಹದಸೂಕ್ತವಾದಭಾಗಗಳನ್ನು ಒಳಗೊಂಡ ಕಾರ್ಯವಿಧಾನದ ಛಾಯಾಚಿತ್ರ ಅಥವಾ ರೆಕಾರ್ಡಿಂಗ್ಸನನ್ನ ಒಪ್ಪಿಗೆಯನ್ನು ಬಹಿರಂಗಪಡಿಸಲಾಗಿಲ್ಲ ಅಥವಾಚಿತ್ರಗಳನ್ನು ಒಳಗೊಂಡಿರುವ ವಿವರಣಾತ್ಮಕ ಪಠ್ಯಗಳ ಮೂಲಕ ಬಹಿರಂಗ ಪಡಿಸುವುದಿಲ್ಲ.

5. ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಮಾಡಿದಪರೀಕ್ಷೆಯಲ್ಲಿ ಯಾವುದೇ ಮಹತ್ವದ ಅಪಾಯವಿಲ್ಲ ಎಂದು ನಾನು ಅರ್ಥಮಾಡಿಕೊಂಡಿದ್ದೇನೆ.

6. ಪಡೆಯಬಹುದಾದ ಫಲಿತಾಂಶಗಳಿಗೆ ಯಾರಿಗೂ ಖಾತರಿ ಅಥವಾ ಭರವಸೆ ನೀಡಲಾಗಿಲ್ಲ.

7. ಮೇಲಿನ ರೂಪವನ್ನು ಅರ್ಥಮಾಡಿಕೊಂಡ ನಂತರ ನಾನುಭಾಗವಹಿಸಲು ಸ್ವಇಚ್ಛೆಯಿಂದ ನಿರ್ಧರಿಸಿದ್ದೇನೆ ಎಂದು ಈ ರೂಪದಲ್ಲಿ ನನ್ನ ಸಹಿಸೂಚಿಸುತ್ತದೆ.

ಭಾಗವಹಿಸುವವರಹೆಸರು / ಕಾನೂನುಬದ್ಧವಾಗಿ ಅಧಿಕೃತ ಪ್ರತಿನಿಧಿ

ಪ್ರತಿನಿಧಿಸಹಿ

ಸಂದರ್ಶಕರ ಹೆಸರು ಮತ್ತು ಸಂದರ್ಶಕರಸಹಿ

ದಿನಾಂಕ:

ಸ್ಥಳ:

अनुसंधान अध्ययन में भाग लेने के लिए सहमति

1. मैं समझता हूं कि मैंअध्ययन में भाग ले रहा हूं |

2. मैं पुष्टि करता हूं कि मैंने मरीज सूचना शीट में जानकारी पढ़ली है और समझली है।अध्ययन में समझाया गया है कि अध्ययन में भाग लेने के फायदे और नुकसान के बारे में जानकारी के साथ मुझे विस्तार से बताया गया है। मुझे परीक्षण के सभी पहलुओं पर चर्चा करने का अवसर दिया गया है, प्रश्न पूछें और इस तरह से ऊपर दिए गए मुकदमे में सहभागिता की सहमति है।

3. यह समझें कि इस अध्ययन में भागलेने का निर्णय पूरी तरह से स्वैच्छिक है और मुझे पता है कि मैं चुन सकता हूं एक समय परअध्ययन सेवा पस लेने के लिए

4. मेडिकल, वैज्ञानिक या शैक्षिक उद्देश्यों के लिए मेरे शरीर के उपयुक्तभाग सहित कार्य करने के लिए प्रक्रिया की तस्वीर या रिकॉर्डिंग के लिए सहमति दी गईहै, बशर्ते मेरी पहचान चित्रों में या उनके साथ आने वाली वर्णनात्मक ग्रंथों में प्रकट नहीं हुई है।

5. मैं समझता हूं कि इस अध्ययन में किए गए किसी भी महत्वपूर्ण जोखिम को शामिल नहीं किया गया है।

6. कोई गारंटी या आश्वासन किसी भी व्यक्ति द्वारा दिए गए परिणाम के रूप में नहीं दिया गया है।

7. इस फार्म पर मेरा हस्ताक्षर दर्शाता है कि मैंने ऊपर की जानकारी समझने के बाद खुशी-खुशी भाग लेने का फैसला किया है।

प्रतिभागी के नाम / कानूनी तौर पर अधिकृत प्रतिनिधि

हस्ताक्षर नाम

गवाह के हस्ताक्षर

साक्षात्कारकर्ता का नाम और हस्ताक्षर

दिनांक:

स्थान :

संशोधन अभ्यासक्रमात सहभागी होण्या साठी संमती

1. मला समजते की मी या अभ्यासात भाग घेत आहे.

2. मी पुष्टी करतो की मी रुग्णमाहिती पत्रकात माहितीवा चली आहे आणि समजून घेतली आहे. अभ्यासात भागघेण्याच्या फायदे आणि तोटेया विषयीमाहिती सहप्रक्रियात पशीलाने मला समजावून सांगितले गेले आहे. मला चाचणीच्या सर्व पैलूंवर चर्चा करण्याची, प्रश्न विचारण्याद्वारे आणि उपरोक्त दिलेल्याचाचणीत सहभागी होण्या ससंमती देण्याची संधी दिली गेली आहे.

3. समजूनघ्या कीया अभ्यासात भाग घेण्याचा निर्णय पूर्णपणे स्वयं सेवी आहे आणि मला याची जाणीव आहे की मीनि वडूशक तोए कावेळेस अभ्यासातून बाहेर पडण्यासाठी

4. वैद्यकीय, वैज्ञानिक किंवा शैक्षणिक हेतूं साठी माझ्या शरीराच्या योग्यभागां सहित कार्या साठी छायाचित्र काढणे किं वा रेकॉर्डिंग करण्या ससंमती देणे म्हणजेमाझी ओळखचित्रां मध्ये किंवा त्यांच्या सोबत असले ल्यावर्णनात्मक ग्रंथां मध्ये उघड झाली नाही.

5. मला हे समजते की या अभ्यासात केलेल्याचा चणी मध्ये कोणते ही लक्षणीय धोका समाविष्ट नाही.

6. कोणतीही हमी किंवा आश्वासन कोणी ही मिळ वूशकतील असे परिणाम म्हणून देत नाही.

7. या फॉर्म वर माझे स्वाक्षरी असे दर्शवते की मी उपरोक्त माहिती समजल्यानंतर सहभागी होण्या चानिर्णय घेतला आहे.

सहभागी चे नाव / कायदेशीर पणे अधिकृत प्रतिनिधी

स्वाक्षरी चे नाव

साक्षीदारांची सही नाव:

मुला खतकाराचे नाव वस्वाक्षरी

दिनांक:

ठिकाण:

ANNEXURE II

PROFORMA

I. SUBJECT'S DEMOGRAPHIC DETAILS:-

1. NAME : F _____ M_____L_____

2. AGE : _____ YRS.

3. GENDER : M [ ]

F [ ]

OTHER : _____

4. FORMAL EDUCATION : NOT RECEIVED [ ]

RECEIVED [ ]

5. OCCUPATION : UNEMPLOYED [ ]

SEMI-SKILLED WORKER [ ]

SKILLED WORKER [ ]

PROFESSIONAL [ ]

6. MARITAL STATUS : UNMARRIED [ ]

MARRIED [ ]

II. SUBJECT HISTORY :-

1. DIAGNOSIS : SEVERE DEPRESSIVE DISORDER WITHOUT PSYCHOTIC SYMPTOMS [ ]

BIPOLAR AFFECTIVE DISORDER, CURRENT EPISODE SEVERE DEPRESSION WITHOUT PSYCHOTIC SYMPTOMS [ ]

RECURRENT DEPRESSIVE DISORDER, CURRENT EPISODE SEVERE DEPRESSION WITHOUT PSYCHOTIC SYMPTOMS [ ]

SEVERE DEPRESSIVE DISORDER WITH PSYCHOTIC SYMPTOMS [ ]

BIPOLAR AFFECTIVE DISORDER, CURRENT EPISODE MIXED [ ]

2. DURATION OF ILLNESS : _____ MONTHS

3. DURATION OF CURRENT EPISODE: _____ MONTHS

4. NUMBER OF EPISODES : MANIC - _____

DEPRESSIVE - _____

5. TREATMENT RECEIVED IN THE PAST : YES [ ] NO [ ]

6. ECT RECEIVED IN THE PAST : YES [ ] NO [ ]

7. ASSOCIATED COMORBIDITIES: HYPERTENSION - YES [ ] NO[ ]

IF YES, B.P. - <140/90mmHg [ ]

>140/90mmHg [ ]

GLAUCOMA - YES [ ] NO [ ]

DIABETES MELLITUS - YES [ ] NO [ ]

SEIZURE DISORDER - YES [ ] NO [ ]

INTELLECTUAL DISABILITY - YES [ ] NO [ ]

DEMENTIA - YES [ ] NO [ ]

OTHERS, SPECIFY - _____

7. SUBSTANCE USE : (A) ALCOHOL USE - YES [ ] NO [ ]

IF YES, DEPENDANCE - PRESENT [ ] ABSENT [ ]

(B) SMOKING - YES [ ] NO [ ]

IF YES, DEPENDANCE - PRESENT [ ] ABSENT [ ]

(C) TOBACCO USE - YES [ ] NO [ ]

IF YES, DEPENDANCE - PRESENT [ ] ABSENT [ ]

(D) OTHERS, SPECIFY - _____

8. FAMILY HISTORY: AFFECTIVE DISORDERS - YES [ ]

NO [ ]

PSYCHOTIC DISORDERS - YES [ ] NO [ ]

III. PRE-INTERVENTIONAL WORK-UP :-

1. CONSENT TAKEN: YES [ ] NO [ ]

2. PHYSICAL EXAMINATION : HEIGHT - _____ CMS.

WEIGHT - _____ KGS.

BMI - _____ KG/M^2

B.P. - _____ mmHg

HEART RATE - _____ BEATS/MIN

FUNDOSCOPIC FINDINGS - RAISED INTRACRANIAL TENSION:

YES [ ] NO [ ]

3. HAM-D SCORE

DAY 1: _____

DAY 3: _____

DAY 5: _____

4. BPRS SCORE : _____

IV. INTERVENTION GIVEN:-

1. KETAMINE INFUSION GIVEN: YES [ ] NO [ ]

IF YES, SPECIFY (A) DOSE - _____

(B) HEART RATE - DURING INFUSION _____B/M

10 MINUTES AFTER INFUSION _____B/M

(C) BLOOD PRESSURE - DURING INFUSION _____mmHg

10 MINUTES AFTER INFUSION _____mmHg

(D) SpO_2 - DURING INFUSION _____ %

10 MINUTES AFTER INFUSION _____%

2. ECT RECEIVED : YES [ ] NO [ ]

IF YES, SPECIFY

(A) CHARGE OF ECT - _____mC

(B) SEIZURE DURATION - _____ SECONDS

(C) POST-ICTAL COMPLICATIONS - YES[ ] NO [ ]

IF YES, SPECIFY -_____

V. POST-INTERVENTIONAL FOLLOW-UP:-

1. HAM-D SCORE (24 HOURS FOLLOWING THE PROCEDURE)

DAY 2: _____

DAY 4: _____

DAY 6: _____

ANNEXURE IV

TOOLS

HAMILTON DEPRESSION RATING SCALE

HAMILTON DEPRESSION RATING SCALE (HAM-D)

(To be administered by a health care professional)

Patient Name _____ **Today's Date** _____

The HAM-D is designed to rate the severity of depression in patients. Although it contains 21 areas, calculate the patient's score on the first 17 answers.

☐ **1. DEPRESSED MOOD**
(Gloomy attitude, pessimism about the future, feeling of sadness, tendency to weep)
0 = Absent
1 = Sadness, etc.
2 = Occasional weeping
3 = Frequent weeping
4 = Extreme symptoms

☐ **2. FEELINGS OF GUILT**
0 = Absent
1 = Self-reproach, feels he/she has let people down
2 = Ideas of guilt
3 = Present illness is a punishment; delusions of guilt
4 = Hallucinations of guilt

☐ **3. SUICIDE**
0 = Absent
1 = Feels life is not worth living
2 = Wishes he/she were dead
3 = Suicidal ideas or gestures
4 = Attempts at suicide

☐ **4. INSOMNIA - Initial**
(Difficulty in falling asleep)
0 = Absent
1 = Occasional
2 = Frequent

☐ **5. INSOMNIA - Middle**
(Complains of being restless and disturbed during the night. Waking during the night.)
0 = Absent
1 = Occasional
2 = Frequent

☐ **6. INSOMNIA - Delayed**
(Waking in early hours of the morning and unable to fall asleep again)
0 = Absent
1 = Occasional
2 = Frequent

☐ **7. WORK AND INTERESTS**
0 = No difficulty
1 = Feelings of incapacity, listlessness, indecision and vacillation
2 = Loss of interest in hobbies, decreased social activities
3 = Productivity decreased
4 = Unable to work. Stopped working because of present illness only. (Absence from work after treatment or recovery may rate a lower score).

☐ **8. RETARDATION**
(Slowness of thought, speech, and activity; apathy; stupor.)
0 = Absent
1 = Slight retardation at interview
2 = Obvious retardation at interview
3 = Interview difficult
4 = Complete stupor

☐ **9. AGITATION**
(Restlessness associated with anxiety.)
0 = Absent
1 = Occasional
2 = Frequent

☐ **10. ANXIETY - PSYCHIC**
0 = No difficulty
1 = Tension and irritability
2 = Worrying about minor matters
3 = Apprehensive attitude
4 = Fears

HAMILTON DEPRESSION RATING SCALE (HAM-D)

(To be administered by a health care professional)

11. ANXIETY - SOMATIC
Gastrointestinal, indigestion
Cardiovascular, palpitation, Headaches
Respiratory, Genito-urinary, etc.
0 = Absent
1 = Mild
2 = Moderate
3 = Severe
4 = Incapacitating

12. SOMATIC SYMPTOMS - GASTROINTESTINAL
(Loss of appetite , heavy feeling in abdomen; constipation)
0 = Absent
1 = Mild
2 = Severe

13. SOMATIC SYMPTOMS - GENERAL
(Heaviness in limbs, back or head; diffuse backache; loss of energy and fatiguability)
0 = Absent
1 = Mild
2 = Severe

14. GENITAL SYMPTOMS
(Loss of libido, menstrual disturbances)
0 = Absent
1 = Mild
2 = Severe

15. HYPOCHONDRIASIS
0 = Not present
1 = Self-absorption (bodily)
2 = Preoccupation with health
3 = Querulous attitude
4 = Hypochondriacal delusions

16. WEIGHT LOSS
0 = No weight loss
1 = Slight
2 = Obvious or severe

17. INSIGHT
(Insight must be interpreted in terms of patient's understanding and background.)
0 = No loss
1 = Partial or doubtfull loss
2 = Loss of insight

TOTAL ITEMS 1 TO 17: _____
0 - 7 = Normal
8 - 13 = Mild Depression
14-18 = Moderate Depression
19 - 22 = Severe Depression
≥ 23 = Very Severe Depression

18. DIURNAL VARIATION
(Symptoms worse in morning or evening. Note which it is.)
0 = No variation
1 = Mild variation; AM ( ) PM ( )
2 = Severe variation; AM ( ) PM ( )

19. DEPERSONALIZATION AND DEREALIZATION
(feelings of unreality, nihilistic ideas)
0 = Absent
1 = Mild
2 = Moderate
3 = Severe
4 = Incapacitating

20. PARANOID SYMPTOMS
(Not with a depressive quality)
0 = None
1 = Suspicious
2 = Ideas of reference
3 = Delusions of reference and persecution
4 = Hallucinations, persecutory

21. OBSESSIONAL SYMPTOMS
(Obsessive thoughts and compulsions against which the patient struggles)
0 = Absent
1 = Mild
2 = Severe

* Adapted from Hamilton, M. *Journal of Neurology, Neurosurgery, and Psychiatry*. 23:56-62, 1960.

BRIEF PSYCHIATRIC RATING SCALE

CLIENT NAME: _____ DATE: _____
CLIENT ID#: _____ MD: _____

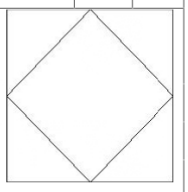
BRIEF PSYCHIATRIC RATING SCALE (BPRS)

Please enter the score for the term which best describes the patient's condition.

0 = not assessed, 1 = not present, 2 = very mild, 3 = mild, 4 = moderate, 5 = moderately severe, 6 = severe, 7 = extremely severe

1. **SOMATIC CONCERN** Degree of concern over present bodily health. Rate the degree to which physical health is perceived as a problem by the patient, whether complaints have a realistic basis or not. SCORE ☐	10. **HOSTILITY** Animosity, contempt, belligerence, disdain for other people outside the interview situation. Rate solely on the basis of the verbal report of feelings and actions of the patient toward others; do not infer hostility from neurotic defenses, anxiety, nor somatic complaints. (*Rate attitude toward interviewer under "uncooperativeness"*). SCORE ☐
2. **ANXIETY** Worry, fear, or over-concern for present or future. Rate solely on the basis of verbal report of patient's own subjective experiences. Do not infer anxiety from physical signs or from neurotic defense mechanisms. SCORE ☐	11. **SUSPICIOUSNESS** Brief *(delusional or otherwise)* that others have now, or have had in the past, malicious or discriminatory intent toward the patient. On the basis of verbal report, rate only those suspicions which are currently held whether they concern past or present circumstances. SCORE ☐
3. **EMOTIONAL WITHDRAWAL** Deficiency in relating to the interviewer and to the interviewer situation. Rate only the degree to which the patient gives the impression of failing to be in emotional contact with other people in the interview situation. SCORE ☐	12. **HALLUCINATORY BEHAVIOR** Perceptions without normal external stimulus correspondence. Rate only those experiences which are reported to have occurred within the last week and which are described as distinctly different from the thought and imagery processes of normal people. SCORE ☐
4. **CONCEPTUAL DISORGANIZATION** Degree to which the thought processes are confused, disconnected, or disorganized. Rate on the basis of integration of the verbal products of the patient; do not rate on the basis of patient's subjective impression of his own level of functioning. SCORE ☐	13. **MOTOR RETARDATION** Reduction in energy level evidenced in slowed movements. Rate on the basis of observed behavior of the patient only; do not rate on the basis of patient's subjective impression of own energy level. SCORE ☐
5. **GUILT FEELINGS** Over-concern or remorse for past behavior. Rate on the basis of the patient's subjective experiences of guilt as evidenced by verbal report with appropriate affect; do not infer guilt feelings from depression, anxiety or neurotic defenses. SCORE ☐	14. **UNCOOPERATIVENESS** Evidence of resistance, unfriendliness, resentment, and lack of readiness to cooperate with the interviewer. Rate only on the basis of the patient's attitude and responses to the interviewer and the interview situation; do not rate on basis of reported resentment or uncooperativeness outside the interview situation. SCORE ☐
6. **TENSION** Physical and motor manifestations of tension "nervousness", and heightened activation level. Tension should be rated solely on the basis of physical signs and motor behavior and not on the basis of subjective experiences of tension reported by the patient. SCORE ☐	15. **UNUSUAL THOUGHT CONTENT** Unusual, odd, strange or bizarre thought content. Rate here the degree of unusualness, not the degree of disorganization of thought processes. SCORE ☐
7. **MANNERISMS AND POSTURING** Unusual and unnatural motor benavior, the type of motor behavior which causes certain mental patients to stand out in a crowd of normal people. Rate only abnormality of movements; do not rate simple heightened motor activity here. SCORE ☐	16. **BLUNTED AFFECT** Reduced emotional tone, apparent lack of normal feeling or involvement. SCORE ☐
8. **GRANDIOSITY** Exaggerated self-opinion, conviction of unusual ability or powers. Rate only on the basis of patient's statements about himself or self-in-relation-to-others, not on the basis of his demeanor in the interview situation. SCORE ☐	17. **EXCITEMENT** Heightened emotional tone, agitation, increased reactivity. SCORE ☐
9. **DEPRESSIVE MOOD** Despondency in mood, sadness. Rate only degree of despondency; do not rate on the basis of inferences concerning depression based upon general retardation and somatic complaints. SCORE ☐	18. **DISORIENTATION** Confusion or lack of proper association for person, place or time. SCORE ☐

HINDI MENTAL STATE EXAMINATION

1	Is it morning or afternoon or evening?	1	0	
2	What day of the week is today?	1	0	
3	What date is it today?	1	0	
4	Which month is today?	1	0	
5	What season of the year is this?	1	0	
6	Under which post office does your village come?	1	0	
7	Which district does your village fall under?	1	0	
8	Which village are you from?	1	0	
9	Which block (If village has only blocks) OR Which numbered area is this?	1	0	
10	Which place is this?	1	0	
11	(I went to Delhi and brought three things - Mango, chair, and coin)	1	2	3
	Can you tell me what the three things I brought from Delhi Are?			
12a	Now can you tell me names of the days of the week starting from Sunday?			
12b	Now can you tell me names of the days backwards?	1-5		
13-15	What are the names of the three things Which I told you have brought from Delhi?	1	2	3
16	(Show the subject the wrist watch and pen) Can you tell me these objects?			
	(If yes, Items 17 & 18 apply) (If No, Item 17(a) apply)			
17; 18	Show him the wrist watch OR Show him the pen and say - What is this?	1	0	
	17; 18 (a). (If necessary) Identification by Touching what is this?			
19	Now I am going to say something, listen carefully and repeat it exactly as I say after I finish Phrase: "NEITHER THIS NOR THAT"	1	0	
20	Now look at my face and do exactly what I do. Close your eyes?	1	0	
21	First you take the paper in your right hand, then with your both hands, fold it into half once and then give the paper back to me.	1	2	3
22	Now say a line about your house? (something specifically about your houses) NOT INCLUDED IN HMSE TOTAL, If given -1, Not given - 0.			
23	Here is a drawing; you must copy this drawing exactly as shown in the space provided here. Score: Must draw two four sided figure =1; One figure should be mostly inside the other =2; Orientation of the figures should be obviously appropriate =3			
	Total score =			/31

S. No.	Patient	Age	Age/Sex	Education status	Occupation	Marital status	Diagnosis	Duration of illness	Duration of current episode (months)	No. Of Episodes	Treatment received in past	ECT received in the past	Family history of psychiatric illness	Medication details	ECT	Ketamine	HAM-D(baseline) (out of 50)	HAM-D(Day 2)	HAM-D(Day-4)	HAM-D(Day-6)	Change Score
1	Raj235	52	M	Educated	Ex-army	Married	RDD with SDE	16 years	7	3	Yes	No	Yes	SNRI, BZD	N	Y	22	20	18	17	5
2	Sak673	35	F	Educated	Ex-army	Married	SDE	9 months	9	1	Yes	No	No	TCA, LITHIUM, BZD	Y	N	25	20	12	8	3
3	Bha939	37	F	Educated	Student	Unmarried	SDE with Dissociation	6 months	6	1	No	No	No	SSRI, BZD	Y	N	19	18	18	17	8
4	Kal700	42	M	Educated	Farmer	Married	BPAD with SDE	6 years	7	2	Yes	No	No	SNRI, BZD	N	Y	24	20	14	8	17
5	Mal655	56	F	Uneducated	Housewife	Married	RDD with SDE	11 years	3	5	Yes	Yes	Yes	SNRI	Y	N	22	19	14	10	7
6	??R307	28	M	Educated	Businessman	Married	SDE	6 months	6	1	Yes	No	No	SNRI, BZD	Y	N	22	19	14	9	5
7	Div586	18	F	Educated	Farmer	Married	SDE	8 months	8	1	No	No	Yes	SNRI, BZD	N	Y	21	18	15	10	2
8	Aar959	41	F	Educated	Govt. service	Married	RDD with SDE	10 years	4	2	Yes	Yes	No	SNRI, BZD	Y	N	23	18	13	5	8
9	Man763	28	M	Educated	Driver	Married	SDE	12 months	12	1	No	No	No	SNRI, LITHIUM, BZD	N	Y	22	17	10	3	16
10	Bas989	38	M	Educated	Businessman	Married	RDD with SDE	10 years	5	3	Yes	No	Yes	SSRI, BZD	Y	N	22	20	19	17	11
11	Fat475	40	F	Educated	Ex-army	Married	SDE	5 months	5	1	Yes	No	No	SNRI, BZD	N	Y	25	20	13	6	12
12	Lax679	27	F	Educated	Student	Unmarried	SDE	6 months	6	1	No	No	No	SNRI	Y	N	19	18	18	17	8
13	All232	48	M	Educated	Farmer	Married	BPAD with SDE	5 years	4	2	Yes	No	No	SNRI, ANTIPSYCHOTIC	Y	N	24	20	14	8	12
14	San254	35	M	Uneducated	Housewife	Married	RDD with SDE	12 years	4	5	Yes	Yes	Yes	SNRI, BZD	N	Y	22	19	14	10	13
15	Shi859	45	M	Educated	Businessman	Married	SDE	6 months	6	1	Yes	No	No	SNRI	N	Y	22	19	14	9	11
16	Sav180	36	F	Educated	Farmer	Married	SDE	4 months	4	1	No	No	Yes	SNRI, BZD	Y	N	21	18	15	10	5
17	Mah850	47	F	Educated	Farmer	Married	RDD with SDE	13 years	4	2	Yes	Yes	No	SNRI	Y	N	23	18	13	5	6
18	Bas768	48	M	Educated	Driver	Married	SDE	12 months	12	1	No	No	No	SNRI, BZD	N	Y	22	17	10	3	18
19	Naf699	34	F	Educated	Unemployed	Unmarried	RDD with SDE	4 years	3	2	Yes	No	No	SSRI, BZD	Y	N	20	18	17	17	9
20	Mou926	43	M	Educated	Housewife	Married	SDE	6 months	6	1	No	No	No	SNRI, BZD	N	Y	24	22	20	16	19
21	Bas355	48	M	Uneducated	Housewife	Married	SDE	12 months	12	1	Yes	No	Yes	SNRI, LITHIUM, BZD	N	Y	22	19	16	15	14
22	Nal763	35	F	Educated	Farmer	Unmarried	RDD with SDE	5 years	7	3	Yes	No	No	SNRI, LITHIUM, BZD	Y	N	20	18	16	15	4

23	Shr762	36	F	Educated	Housewife	Married	RDD with SDE	9 years	8	2	Yes	No	Yes	SSRI, LITHIUM, BZD	Y	N	22	20	16	14	9
24	Bal635	42	M	Educated	Businessman	Married	SDE	4 months	4	1	No	No	Yes	SNRI	N	Y	26	22	18	15	19
25	Nag736	46	F	Educated	Housewife	Married	SDE	8 months	8	1	Yes	No	No	SNRI, BZD	Y	N	25	22	19	17	6
26	Raj621	30	M	Educated	Compounder	Married	SDE	8 months	8	1	Yes	No	No	SNRI, BZD	Y	N	26	23	19	14	5
27	Ash921	25	F	Uneducated	Housewife	Married	Dysthymia with SDE	15 years	6	1	Yes	No	Yes	SNRI, BZD	N	Y	24	22	20	19	2
28	Shr218	41	F	Uneducated	Housewife	Married	SDE	15 months	15	1	Yes	No	No	SNRI, BZD	Y	N	20	18	15	14	11
29	Dev913	27	M	Educated	Housewife	Married	RDD with SDE	5 years	3	3	Yes	Yes	Yes	SNRI, LITHIUM, BZD	N	Y	24	22	19	15	17
30	Dun320	39	M	Educated	Unemployed	Unmarried	RDD with SDE	14 years	6	2	Yes	No	No	SSRI, BZD	Y	N	20	18	18	17	11
31	Vee103	42	F	Educated	Housewife	Married	SDE	4 months	4	1	No	No	No	SNRI, BZD	N	Y	24	22	20	15	12
32	Par821	27	F	Uneducated	Housewife	Married	SDE	11 months	11	1	Yes	No	Yes	SNRI, BZD	Y	N	22	19	17	16	8
33	Lax632	48	M	Educated	Farmer	Unmarried	RDD with SDE	4 years	2	3	Yes	No	No	SNRI, ANTIPSYCHOTIC, BZD	Y	N	20	17	15	14	12
34	San327	35	M	Educated	Teacher	Married	RDD with SDE	12 years	3	2	Yes	No	Yes	SSRI, BZD	N	Y	22	20	16	14	8
35	Aru629	41	M	Educated	Teacher	Married	SDE	4 months	4	1	No	No	Yes	SNRI, BZD	N	Y	26	22	18	15	9
36	Sav120	36	F	Educated	Housewife	Married	RDD with SDE	13 years	3	1	Yes	No	No	TCA, LITHIUM, BZD	Y	N	25	22	19	17	5
37	Vid852	47	F	Educated	Farmer	Married	SDE	6 months	6	1	Yes	No	No	SNRI, BZD	Y	N	26	23	19	14	6
38	Bhi953	45	M	Uneducated	Housewife	Married	Dysthymia with SDE	12 years	6	1	Yes	No	Yes	SNRI, LITHIUM, B ZD	N	Y	24	22	20	19	18
39	Sar799	33	F	Uneducated	Housewife	Married	SDE	18 months	18	1	Yes	No	No	SNRI, BZD	Y	N	20	18	15	14	9
40	Mah936	42	M	Educated	Housewife	Married	RDD with SDE	7 years	4	3	Yes	Yes	Yes	SNRI	N	Y	24	22	19	15	19