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Original research article

Efficacy and Safety of Repeated Ketamine Infusion in Treatment Resistant Depression

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Abstract

Introduction: Ketamine infusion was known to be effective treatment in treatment resistant depressed patients in subanasthetic dose as shown by multiple studies. Previous studies suggested that repeated infusion having higher response rate than single infusion.With this rationale, we planned a study a study to see efficacy and safety of repeated infusion in such patients.

Methods and Materials:

This was a single center, prospective, open-label study . After applying inclusion and exclusion criteria 20 patients were recruited and ketamine was infused @ 0.5mg/kg over 60 min under guidance of anaesthetist.Various scales like MADRS , CGI,SSI,BPRS and CADSS were applied to see efficacy and safety of infusion before and after every infusion and mean scores were compared with appropriate statistics.

Results and Conclusions:

In our study, 14 patients (70%) showed response among 20 patients, among responders 10 patient (50%) were remitters. Pre and Post infusion difference between mean MADRS, CGI and SSI scores found signicant while difference between mean BPRS and CADSS scores were not significant. Most of the patient felt self limiting side effect like sedation, dizziness, vertigo, restlessness etc. So ketamine infusion is safer alternative for treatment resistant depression.

Key words: Treatment resistant depression, MADRS, Ketamine, NMDA

Introduction

Globally depression is one of the most significant causes of global disease burden and disability. [1] It is well accepted that 20 -50 % of depressed patients had poor or partial responses to traditional antidepressant [2,3]. Treatment-resistant depression (TRD) or treatment-refractory depression is very challenging to be diagnosed in routine clinical practice. It may also have a broad definition: it can usually be presented as a failure to respond to one antidepressant or two trials with antidepressants from different pharmacological classes in adequate courses, to two antidepressants in combination, or to electroconvulsive therapy (ECT) or can also be presented when there is intolerance to treatment or there is a relapse after initial response to treatment [4]. Most accepted definition of TRD is insufficient treatment response to at least 2 antidepressants trial for adequate duration [5].Such patient have higher relapse rate, more suicidality, diminished quality of life and poor psychosocial outcome. [6, 7]

So there was a need of some pharmacological agent like ketamine for such patients that could help in reducing depressive symptoms.[8] Ketamine, a potent selective N-methyl-d-aspartate (NMDA) receptor antagonist.[9] which has emerged as a promising agent in poor responders and treatment resistant patients [10-12]. The blockade of N-methyl-D-aspartate receptors (NMDA) by ketamine may contribute to antidepressive effects by different mechanisms – It increases synaptic connections in prefrontal cortex via realease of glutamate release at synapse. It increases BDNF synthesis by blocking extrasyneptic NMDA receptors which is responsible for dendritic regrowth.[13-16] Various studies concluded that intravenous ketamine significantly reduces suicidal ideation in depressive patients. [17]

In available literature ketamine was used in both unipolar and bipolar depressive patients. [18,19] In existing literature, ketamine was tried by various routes of administration like intravenous route as single dose and as repeated infusion, intramuscular injection, oral administration, intranasal spray and sublingual route. Apart from intravenous route, others have very poor bioavailability. [20]

The antidepressant effect of a single ketamine infusion may last up to one week, although repeated infusions may maintain these effects for at least 2-3 weeks. So there is need of repeated infusion to achieve good response and remission. [21-23] Several small clinical trials have shown that a single subanesthetic dose of ketamine, produces a quick antidepressant response within 2 to 4 hours, highest impact after 24 hours and effect may last up to 7 days so for long effect multiple infusions may be required. [12,24,25]

There is difference in treatment protocols which is followed by various researchers. Ketamine is used in dose range of 0.1 to 0.5 mg/kg and infused over 40-100 minutes. It was infused as single dose, daily infusion, once in week, twice weekly and alternate day infusion. [10-12,26] However, few side effects include perceptual disturbances, confusion, headache euphoria, dizziness has been reported in previous studies. These adverse effects cease about 80-110 min after an i.v. infusion [27-29] .
In India till date very few studies have corroborated such findings, the present study aimed to assess the efficacy and safety of repeated ketamine infusion in subjects with treatment resistant depression.

Material and Methods:-

Subjects:-

This was a single center, prospective, open-label study conducted at Department of Psychiatry, Sardar Patel Medical College, Bikaner.

Inclusion criteria:
Patients who fulfill the criteria of depressive disorder (single episode or recurrent) as per International Classification of Diseases, Tenth Revision (ICD-10), aged between 18-60 years, of either gender, subjects were psychotropic medication-free for 2 weeks before infusion, refractory to at least two antidepressant medication trials for at least 4 week each in the current episode of depression and provide informed consent for participation.

Exclusion criteria
Where: Bipolar disorder, history of current or past psychotic disorder, history of alcohol use and illicit substance use (except nicotine) within the past 6 months, psychotic symptoms in current episode, history of traumatic brain injury, dementia and significant neurological illness, any disability hampering communication, failure to comply with the study protocol, pregnancy and known case of hypertension, cardiac illness and intrinsic airway disease.

Procedure:-
After taking ethical clearance from institutional ethical and review board, total 32 patients were selected as per inclusion criteria but 12 patients not fulfilled eligibility criteria and rejected due to hypertension (n=3), psychotic features (n=3), concomitant substance abuse (n=3), not gave consent (n=2), history of traumatic brain injury (n=1) so finally 20 patients were recruited for study and provided a written informed consent. Patient had undergone preanaesthetic checkup for ketamine infusion.

Each patient was treated upto four ketamine infusions at 0.5 mg/kg over 60 min after clearance from anaesthetist. Infusions were administered thrice weekly under supervision of anaesthetist in fully equipped room for anesthesia. Baseline Montgomery – Asberg Depression Rating Scale (MADRS) score was assessed on the morning before each infusion, and repeated after 2 hour of infusion and the next morning. If the patient met criteria for remission with the MADRS (a score of 9 or less) on the morning after an infusion or the morning of a next scheduled infusion, then no more infusions were administered. Patient were given no more than 4 infusions regardless of MADRS score on next morning.

Other outcome measures included the Brief Psychiatric Rating Scale (BPRS), the Clinical Global Impression Scale (CGI), the Scale for Suicide Ideations (SSI) and Clinician-Administered Dissociative States Scale (CADSS) were administered at same point times as MADRS.

Acute dissociative effects were measured by Clinician-Administered Dissociative States Scale (CADSS) and Psychotomimetic effects were measured with the four-item positive symptom subscale of the Brief Psychiatric Rating Scale (BPRS) consisting of suspiciousness, hallucinations, unusual thought content, and conceptual disorganization. These effects were measured before infusion, post 2 hour infusion and during post ketamine infusion monitoring period.

Tools:
The tools used for the study were, a semi-structured questionnaire for socio-demographic variables and clinical detailes, Montgomery–Åsberg Depression Rating Scale (MADRS), Brief Psychiatric Rating Scale (BPRS), Scale for suicidal ideation (SSI) and Clinical Global Impression rating scales (CGI) and Clinician-Administered Dissociative States Scale (CADSS).

Montgomery–Åsberg Depression Rating Scale (MADRS) is a ten-item questionnaire which is used to measure the severity of depressive episodes. The overall score ranges from 0 to 60. Response was defined as ≥ 50% improvement from baseline depression score as measured by the Montgomery–Åsberg Depression Rating Scale. Remission was established by a MADRS score ≤ 9. [30]

Brief Psychiatric Rating Scale (BPRS) is used to measure psychiatric symptoms. It consist 24 items and each symptom is rated 1-7. In our study we took only 4 items consisting of suspiciousness, hallucinations, unusual thought content, and conceptual disorganization for evaluation of psychotic symptoms. [31]

Scale for suicidal ideation (SSI) consists of 19 items that assess three dimensions of suicide ideation: active suicidal desire, specific plans for suicide, and passive suicidal desire. Each item is rated on a 3-point scale from 0 to 2. The higher score indicates severity of suicide ideation. We scored the sum of the five items which related to wish to live, wish to die, reasons for living outweighing reasons for dying, desire to kill oneself, and degree of desire to save oneself in a life-threatening situation[32] .

Clinical Global Impression – Severity scale (CGI-S) is a 7-point scale that requires the clinician to rate the severity of the patient's illness. **The Clinical Global Impression – Improvement scale (CGI-I)** is a 7 point scale that requires the clinician to assess how much patient's illness has improved or worsened relative to a baseline state. [33]

Clinician-Administered Dissociative States Scale (CADSS) was a clinician-administered measure of perceptual, behavioral, and attention alterations occurring during dissociative experiences. This scale involved 19 self-report questions and eight observer ratings scored from 0 (not at all) to 4 (extremely) [34].

Statistical analysis:-
Descriptive statistical measures (mean, median, standard deviation and range) were estimated for summarizing the quantitative characteristics related to demographic variables. Paired t test was applied for all quantitative measures. The two sided $p< 0.05$ were considered statistically significant. The data analysis was performed by using licensed SPSS version 21.0 software.

Results:-
Most of the participants were male (60%), belong to upper lower socioeconomic class (50%) and rural areas (55%). Mean age of participants was 44.55 ±12.92 years, mean weight was 57.18 ± 7.94 kg, mean duration of illness was 10.07 ± 7.73 years. Most of them had past psychiatric history (90%), family history of psychiatric illness was absent (65%) and non-significant medical history.

Table 2 shows comparison of MADRS before and after ketamine infusions. Baseline MADRS score and next morning MADRS score after first infusion was 36.40±5.43 and 33.10±6.34 respectively, the difference between these scores was found statistically significant ($t =3.56$; $p=0.002$). MADRS score before and after second ketamine infusions was 32.68±6.60 and 25.21±8.59 respectively, difference was also found significant ($t=6.85$; $p=0.001$). Score before and after third ketamine infusions was 26.64±7.47 and 19.17±11.44 respectively and difference was found significant ($t=6.56$; $p=0.001$). Score Before and after fourth infusions was 27.10 ±5.91 and 20.10±9.44 respectively, difference was also found significant ($t=4.84$; $p=0.001$).

Endpoint MADRS score for all patients was 15.10 ±2.40, its difference with baseline score was found highly significant (t=8.83; p=0.001).

Out of 20 patients, 14 patients (70%) showed response (50% reduction in the baseline MADRS score) from which 10 patients (50%) showed remission (score ≤9 in MADRS). Among remitters 7 patient (70%) needed three infusion, 2 (20%) needed two infusion while rest 1 (10%) needed four infusion. 1 patient dropped out from study after single infusion.

Table 3 shows comparison of CGI scores before and after ketamine infusions. Baseline CGI score and next morning CGI score after first infusion was 5.65±0.48 and 3.85 ± 0.36 respectively, the difference between these two scores was found statistically significant (t =11.56; p=0.001). CGI score before and after second ketamine infusions was 5.26±0.56 and 2.68±1.00 respectively, difference also found significant (t=11.04; p=0.001). Score before and after third ketamine infusions was 4.41±1.00 and 2.23±1.30 respectively and difference was found significant (t=10.16; p=0.001). Score Before and after fourth infusions was 4.50±0.70 and 2.40±1.34 respectively, difference was also found significant (t=6.67; p=0.001). Endpoint CGI for all patients was 1.80 ± 1.24, its difference with baseline score was found highly significant (t=6.49; p=0.001).

Table 4 shows comparison of Pre and post ketamine infusion SSI scores. Baseline SSI score and next morning SSI score after first infusion was 5.95±2.01 and 3.65±1.84 respectively, their difference was found statistically significant (t =2.34; p=0.029). SSI score before and after second ketamine infusions was 5.31±2.02 and 3.15± 2.31 respectively, difference was also found significant (t=6.42; p=0.001). Score before and after third ketamine infusions was 3.29±2.41 and 2.11±2.39 respectively and difference was found significant (t=3.63; p=0.002).. Score Before and after fourth infusions was 3.60±2.06 and 2.00±2.58 respectively, difference also found significant (t=3.53; p=0.006). Endpoint SSI for all patients was 1.35±2.43, its difference with baseline score found highly significant (t=6.86; p=0.001).

As we considered BPRS and CADSS to assess psychotomimetic and dissociative effect of ketamine, 3 (15%) patients had perceptual disturbance in form of visual hallucination and 2 (10%) patients felt disconnected from their body but reversed with in 2 hours. Difference in pre and post infusion BPRS and CADSS scores after every infusion were not found statistically significant.

TABLE 1: Various Socio-demographic variables and clinical details of all patients.

	VARIABLES	**N=20**	**%**	**Mean± (SD)**
Age (Years)	21 - 40	07	35	
	41 - 60	11	55	44.55±(12.29)
	>60	02	10	
Sex	Male	12	60	
	Female	08	40	
Socioeconomic Class	Upper Lower	10	50	
	Lower Middle	07	35	
	Upper Middle	03	15	
Family type	Joint	08	40	
	Nuclear	12	60	

Duration of illness	<1 year 1 year- 10 year 11 year- 20 year >20 year	02 08 08 02	10 40 40 10	10.07±(7.73)
Past Psychiatric history	Present Absent	18 02	90 10	
Medical History	Non Significant Diabetes	19 01	95 05	
Family History	Absent Present	13 07	65 35	
Locality	Rural Urban	11 09	55 45	

TABLE 2: Comparisons of MADRS score pre and post infusion.

MADRS Score	No. of patient (N)	Mean ± SD	t-score	p-value
Baseline (Pre infusion 1) Next morning	20 20	36.4 ± 5.43 33.1 ± 6.34	3.56	**0.002**
Pre infusion 2 Next morning	19 19	32.68 ± 6.60 25.21± 8.59	6.85	**0.001**
Pre infusion 3 Next morning	17 17	26.64 ± 7.47 19.17 ± 11.44	6.56	**0.001**
Pre infusion 4 Next morning	10 10	27.10 ± 5.91 20.10 ± 9.44	4.84	**0.001**
Baseline MADRS Endpoint MADRS	20 20	36.40 ± 5.43 15.10 ± 2.40	8.83	**0.001**

MADRS - Montgomery–Åsberg Depression Rating Scale

TABLE 3: Comparisons of CGI score pre and post infusion.

CGI Score	No. of patient (N)	Mean ± SD	t-score	p-value
Baseline (Pre infusion 1) Next morning	20 20	5.65 ± 0.48 3.85 ± 0.36	11.56	**0.001**
Pre infusion 2 Next morning	19 19	5.26 ± 0.56 2.68 ± 1.00	11.04	**0.001**
Pre infusion 3 Next morning	17 17	4.41 ± 1.00 2.23 ± 1.30	10.16	**0.001**
Pre infusion 4 Next morning	10 10	4.50 ± 0.70 2.40 ± 1.34	6.67	**0.001**
Baseline CGI Endpoint CGI	20 20	5.65 ± 1.34 1.80 ± 1.24	6.49	**0.001**

CGI = Clinical Global Impression Scale

TABLE 4: Comparisons of SSI score pre and post infusion.

SSI Score	No. of patient (N)	Mean ± SD	t-score	p-value
Baseline (Pre infusion 1)	20	5.95 ± 2.01	2.34	**0.029**
Next morning	20	3.65 ± 1.84		
Pre infusion 2	19	5.31 ± 2.02	6.42	**0.001**
Next morning	19	3.15 ± 2.31		
Pre infusion 3	17	3.29 ± 2.41	3.63	**0.002**
Next morning	17	2.11 ± 2.39		
Pre infusion 4	10	3.60 ± 2.06	3.53	**0.006**
Next morning	10	2.00 ± 2.58		
Baseline SSI	20	5.95 ± 2.01	6.86	**0.001**
Endpoint SSI	20	1.35 ± 2.43		

SSI = Scale for Suicidal Ideation

Discussion:-

The present study was aimed to assess efficacy and safety of repeated ketamine infusion in treatment resistant depressed patients. In our study, differences in mean MADRS score before infusion and after infusion were found statistically significant. Similar pattern of response was seen between mean SSI score and mean CGI score before and after ketamine infusions. Previous authors also found similar finding, but sample size, number and method of infusions may be variable. [35-37].

In our study we found response rate (defined by 50 % reduction in MADRS score at any point of time during infusion) was 70 % while remission rate (defined by was MADRS score ≤9 at any point of time) was 50 %. These results were consistent with previous study conducted by Zarate et al in 2006 found 71% response rate and 29% remission rate in 18 patients , treated with 2 doses of ketamine (0.5mg/kg) [12]. An another study conducted by Paulo R. Shiroma et al in 2014 found response rate and remission rate slightly higher than our study that is 92% and 67% by using six infusion protocol[22]. Segmiller *et al.*(2013) found 50% response rate and 33.3% remission rate in a sample of six patients patients.[37]Similar finding was obtained by Rasmussen et al. in 2013 and Murrough et al. in 2013 had a response rate of 80% and 70.8 % respectively by using multiple infusions [21,26]. Yu Han et al (2016) reviewd 9 high-quality studies that included 368 patients were selected to compare the efficacy of ketamine to placebo. The therapeutic effects of ketamine at 24 and 72 h, and day 7 were found to be significantly better than placebo. Response and remission rates in the ketamine group at 24 and 72 h, and day 7 were 52.2% and 20.6%; 47.9% and 23.8%; and 39.8% and 26.2%, respectively.(38) Response and remission rates may differ from study to study due to difference in study protocols

Ketamine infusion not only decreases depressive symptoms but also reduce suicidal ideation. In our study this is evident by reduction in MADRS score as well as in SSI scores. These finding was also consistent with previous studies. Rasmussen et al. in 2013 conducted a study in 11 patients and found correlation between suicidal ideation scale score and MADRS and suggest that drop in suicidality occurred in concert with overall reductions in depressive symptoms [26]. Guha et al in 2012 found that ketamine induced a rapid and dramatic response in reducing suicidal ideation in severly depressed patients, which was statistically significant but relatively ill-sustained [39]. Murrogh et al(2015) found that MADRS-SI score was lower in the ketamine group compared to midazolam group at 24 hour after single ketamine infusion.[40] Ballard et al (2014) stated that Ketamine infusion was associated with significant reductions in

suicidal ideation compared to placebo, when controlling for the effects of ketamine on depression and anxiety. [41]

Regarding the safety of ketamine infusion, as we assessed BPRS score and CADSS score before and after every infusion for psychotomimetic and dissociative effects. There was no significant difference found in mean scores of both scales pre and post infusion after each infusion. In our study, 3 (15%) patients reported perceptual disturbances while 2 (10%) patient felt dissociative effect but these patients recovered with in 2 hours. Almost similar findings were observed in previous studies. Dissociative and perceptual disturbances usually peak at 40 min and gradually resolved by 1-2 hours.(42-44) Approximately 17% - 25 % patients reported transient dissociative symptoms.(44-45) Some of authors did not observed any perceptual disturbances or psychotic symptoms.(45) There was no significant association found between antidepressant response of ketamine and dissociative or psychotomimetic effects . (46)

Conclusion :-

Ketamine seems to have a high potential in the treatment of refractory depression. As effect of single infusion may last for a week only so for sustained effect multiple infusions are helpful. Repeated ketamine infusion can be one of new alternative treatment to electroconvulsive therapy for treatment resistant depression and patient with suicidal ideation.

Limitation & Suggestion:-

Among limitations of the study, we can not generalize the findings as our sample size is small and follow up period was brief. So, in future, further long term follow up study of responded patients with large sample size is required to assess long term or maintenance antidepressant effect of ketamine infusions and establish protocol of ketamine infusions.

Conflict of interest :-

There are no conflicts of interest to be reported for any of the listed authors.

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