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A Case Series

Ketamine in Treatment Refractory OCD – A Case Series

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Abstract

Obsessive-Compulsive Disorder (OCD) is a chronic debilitating neuropsychiatric disorder, affecting 2% of global population and 0.6 % of Indian population. Treatment Refractory OCD (TR-OCD) is defined as poor response to serotonergic drugs, augmenting antipsychotics and behavioural therapy at optimal dose and duration. Various receptors involved in OCD are serotonergic, dopaminergic, glutaminergic (N-Methyl-D-Aspartate - NMDA) and Gamma Amino Butyric Acid receptors. There is significant evidence regarding the role of serotonergic and dopaminergic receptors in neurobiology of OCD. Though the research in the role of glutamate and glutaminergic receptors in OCD is emerging, the current evidence regarding same is still limited. Along with this, research regarding the role of NMDA receptor inhibitors in treatment of OCD is also limited to few case reports. Ketamine is an inhibitor of the NMDA receptor. Ketamine has been used in treatment resistant depression. However, there is dearth of literature regarding use of ketamine in TR-OCD. Here we present 3 cases of TR-OCD responding to ketamine. The possible role of glutaminergic receptors in neurobiological mechanism of OCD is also discussed.

Keywords: OCD, Treatment refractory, Glutamate, Ketamine

Introduction

Obsessive compulsive Disorder (OCD) is characterized by the presence of obsessions and/or compulsions. Obsessions are intrusive and unwanted repetitive thoughts, urges, or impulses that often lead to a marked increase in anxiety or distress. Compulsions are repeated behaviours or mental acts that are done in response to obsessions, or in a rigid rule-bound way. Some patients may have only obsessions or only compulsions, but in most cases both obsessions and compulsions are present [1,2]. OCD is found to occur in a uniform manner across all the socio-demographic strata and geographical areas. The lifetime prevalence of OCD is found to be around 2-3% [2]. Approximately one quarter of cases have onset by age 10, with early onset more common in males. Onset after 30 is rare [1]. It leads to a significant socio-occupational impairment due to not only the original illness but also due to associated psychiatric comorbidities. Despite the presence of both psychotherapeutic and pharmacological management modalities, nearly half of all patients fail to respond to treatment

adequately and about 30% have refractory OCD [3].

Treatment-refractory OCD (TR-OCD) can be defined as failure of least three therapeutic trials of SRIs (with clomipramine being one of the SRI trials), the use of at least two atypical antipsychotics as augmentation strategies, and treatment with cognitive behavioral therapy while on a therapeutic dose of an SRI, with a demonstration of < 25% reduction in Y-BOCS score, or still showing considerable impairment from their illness [4].

OCD was once central to psychodynamic thinking, but it is now an exemplar par excellence of a neuropsychiatric disorder in so far as its underlying Neurocircuitry is to some extent understood. A range of neurotransmitter systems contribute to OCD, including serotonergic, dopaminergic, glutamatergic, and GABAergic systems [5,6]. Most recently, there has been interest in additional systems, including the glutamatergic system in OCD, with evidence that some glutamatergic agents may be useful in this condition [7].

We present here 3 cases of treatment refractory OCD responding to ketamine therapy.

Case 1:

A 20-year-old unmarried male, belonging to LSES, a student, with no significant medical, family or personal history and no past history suggestive of psychiatric illnesses, presented to psychiatry OPD with complaints of recurrent intrusive thoughts regarding dirt and contamination and compulsive behaviour of washing hands and bathing repeatedly (10-15 times per day) and most of this washing rituals would last around 1.5-2 hours. The patient would find these thoughts distressing and ego-dystonic and would try to resist it but would be unsuccessful most of the times. Total duration of illness was 4 years and had a continuous deteriorating course. Initial Yale Brown Obsessive Compulsive Score (YBOCS) (8) was 35 which indicated severe intensity of OCD. Diagnosis of OCD with fair insight as per DSM-5 (2) was made. Treatment trials of escitalopram (30 mg/day), fluoxetine (80 mg/day), clomipramine (225 mg/day), venlafaxine (150 mg/day), mirtazapine (30 mg/day), augmentation with risperidone (2 mg/day), aripiprazole (5 mg/day) and multiple sessions of Exposure and Response Prevention Therapy (ERP) were given.This treatment regimen was continued for almost a year and a maximum improvement of 20% were reported with a decrease in YBOCS to 28.

With the presence of the above- mentioned symptoms along with severe socio-occupational and academic decline and a significant distress with the repeated thoughts, patient was considered for Ketamine therapy with continuation of treatment with a SSRI, TCA, SSRI, anti-psychotic, BZD and ERP. Ketamine Infusion Therapy was initiated on inpatient Basis after taking patient's consent, at an initial rate of 0.5 mg/kg and optimised to 1 mg/ kg (patient weight=52 kg) YBOCS done weekly showed an improvement in scores. CBT and pharmacotherapy were continued, and the YBOCS score reduced to 21 which suggested 40% improvement over a period of 2 months. Patient was followed up for next 6 months with once-a-month Ketamine infusion at 1 mg/kg as a maintenance dose along with pharmacological and psychological management and had continued to report an improvement of at least 45-50% with an overall improvement in socio-occupational and academic performance.

Case 2:

An 18-year-old unmarried male, belonging to MSES, a student, with no significant medical, family or personal history and no past history suggestive of psychiatric illnesses, presented to psychiatry OPD with

complaints of recurrent intrusive thoughts regarding symmetry and orderliness and compulsive behaviour of arranging and rearranging things repeatedly (5-6 times/ day) and most of the times would take out objects from his cupboard, arrange them in a particular manner. At times he would re-arrange the articles around the house if they were kept in a manner not acceptable to him. He also would keep the objects in a particular manner, arrange them in an increasing order, according to colour or in patterns. The patient would find these thoughts distressing and ego-dystonic and would try to resist it but would be unsuccessful most of the times. Total duration of illness was 2 years and had a continuous deteriorating course. Initial YBOCS was 28 which indicated moderate intensity of OCD. Diagnosis of OCD with partial insight as per DSM-5 was made. Treatment trials of sertraline (250 mg/day), fluoxetine (80 mg/day), clomipramine (225 mg/day), venlafaxine (150 mg/day), lamotrigine (200 mg/day), augmentation with risperidone (1 mg/day), aripiprazole (2.5 mg/day) and multiple sessions of Exposure and Response Prevention Therapy (ERP) were given. This treatment regimen was continued for almost 10 months and a maximum improvement of 15-20% were reported with a decrease in YBOCS to 20.

With the presence of the above- mentioned symptoms along with severe socio-occupational and academic decline and a significant distress with the repeated thoughts, patient was considered for Ketamine therapy with on-going treatment of an SSRI, TCA, SSRI, anti-psychotic, BZD and ERP. Ketamine Infusion Therapy was initiated on inpatient Basis after taking patient's consent, at an initial rate of 0.5 mg/kg and optimised to 1.5 mg/ kg (patient weight=60 kg) YBOCS done weekly showed an improvement in scores. CBT and pharmacotherapy were continued, and the YBOCS score reduced to 18 which suggested almost 45% improvement over a period of 3 months. Patient was followed up for next 9 months with once-a-month Ketamine infusion at 1.2 mg/kg as a maintenance dose along with pharmacological and psychological management and had continued to report an improvement of at least 55-60% with an overall improvement in socio-occupational and academic performance. The insight developed overtime to fair insight with a regular follow up and compliance.

Case 3:

A 23-year-old unmarried male, belonging to MSES, a student, with no significant medical, family or personal history and no past history suggestive of psychiatric illnesses, presented to psychiatry OPD with complaints of recurrent intrusive thoughts regarding images of running cars and obscene images. The patient would find these images distressing and ego-dystonic and would try to resist it but would be unsuccessful most of the times. Total duration of illness was 3.5 years and had a continuous deteriorating course. Initial YBOCS was 28 which indicated moderate intensity of OCD. Diagnosis of OCD with fair insight as per DSM-5 was made. Treatment trials of sertraline (250 mg/day), fluvoxamine (200 mg/day), clomipramine (225 mg/day), venlafaxine (150 mg/day), lamotrigine (200 mg/day), mirtazapine (30 mg/day), memantine (5 mg/day) and augmentation with risperidone (1 mg/day), aripiprazole (2.5 mg/day) and multiple sessions of Cognitive Behaviour Therapy (CBT) were given. This treatment regimen was continued for almost 14 months and a maximum improvement of 15-20% were reported with a decrease in YBOCS to 20.

With the presence of the above- mentioned symptoms along with severe socio-occupational and academic decline and a significant distress with the repeated thoughts, patient was considered for Ketamine therapy with on-going treatment of an SSRI, TCA, SSRI, anti-psychotic,

BZD and ERP. Ketamine Infusion Therapy was initiated on inpatient Basis after taking patient's consent, at an initial rate of 0.5 mg/kg and optimised to 1.5 mg/ kg (patient weight=65 kg) YBOCS done weekly showed an improvement in scores. CBT and pharmacotherapy were continued, and the YBOCS score reduced to 18 which suggested almost 45% improvement over a period of 3 months. Patient was followed up for next 9 months with once-a-month Ketamine infusion at 1.2 mg/kg as a maintenance dose along with pharmacological and psychological management and had continued to report an improvement of at least 65-70% with an overall improvement in socio-occupational and academic performance.

Discussion

Obsessive compulsive disorder (OCD) is a common, chronic and mostly a debilitating disorder. Treatment-refractory OCD (TR-OCD) can be defined as failure of least three therapeutic trials of SRIs (with clomipramine being one of the SRI trials), the use of at least two atypical antipsychotics as augmentation strategies, and treatment with cognitive behavioral therapy while on a therapeutic dose of an SRI, with a demonstration of < 25% reduction in Y-BOCS score, or still showing considerable impairment from their illness [4].

The use of SSRIs at a higher dose, in case of Major Depressive Disorder is usually associated with greater side effects than the efficacy, but evidences suggest that the increased doses in case of OCD is associated with greater efficacy than lower or medium doses. Also, treatment of OCD requires more duration of treatment than that for MDD. [8] The first line treatment for management of OCD is exposure and response prevention (ERP) and Serotonin Reuptake Inhibitors (SRI). Second line management may include augmentation with Tricyclic Anti-depressants Serotonin-Nor epinephrine Reuptake Inhibitors, Antipsychotics, NMDA antagonists, Lamotrigine and Benzodiazepines [9, 10].

The receptors involved in OCD are broadly Serotonin receptors, dopamine receptors, glutamate receptors or N-Methyl-D-Aspartate (NMDA) receptors, GABA receptors [5]. While extensive studies are done in the role of serotonin, dopamine and nor-epinephrine receptors, very limited work is done on the role of glutaminergic receptors in OCD. Recently there is emerging evidence regarding the role of glutamatergic system in the neurobiology of OCD based on the following (a) genetic studies (SLC1A1, SAPAP3, SLITRK5, which play a role in encoding the neuronal glutamate transporter EAAT3), (b) the involvement of glutamatergic system in connections forming Cortico-striatal-thaloamo-cortical circuit and (c) elevated levels of Glutamate in Cerebro Spinal Fluid [7,11].

Glutamate is an amino acid which serves as the brain's primary excitatory neurotransmitter. They cause depolarisation of the post-synaptic cell, leading to electrical firing, hence leading to excitatory effects. This action is primarily carried by 2 receptors such as NMDA and AMPA, which are ligand gated ion channels. When these 2 receptors bind to glutamate, they open and allow cationic currents to pass through membrane and thus change the electrical state of cell. There are multiple subtypes of both these receptors which are acted upon by multiple medications [7,12,13].

Ketamine has proven to be a potent non-competitive antagonist of NMDA receptor. While it is clinically used as an anaesthetic agent, it also has strong abuse potential. The psychiatric manifestations of ketamine are based on the effects of ketamine at sub-anaesthetic doss, which are psychotomimetic, dissociative and have an almost immediate anti-depressant effect that may last up to few weeks after single dose administration. The plasma half-life of

the drug is alpha: 10-15 minutes; beta: 2.5 hours. It is metabolised by CYP450, 2B6, 2C9 and 3A4. [12,13].

Ketamine has been used in treatment resistant depression. However, there is dearth of literature regarding use of ketamine in TR-OCD limited to case reports and series. Our case series adds further to the existing limited evidence. There is a need for further research regarding use of ketamine in TR-OCD and the role of NMDA receptors in OCD. It also instils a need for developing guidelines regarding the duration and frequency of ketamine infusion therapy in TR-OCD. [14]

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