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Rapid Antidepressant Action of Ketamine in Psychiatric Patients with Suicidality - a Case Series

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Abstract Ketamine, a non-competitive NMDA receptor antagonist with rapid antidepressant action, is a novel approach in modulating glutamate receptors for management of treatment-resistant major depressive disorder. It clinically engenders meaningful advances in depression therapeutics. This case series highlights the role of low dose intravenous ketamine infusion i.e., 0.5 mg/kg dissolved in 100 ml normal saline and given over a period of 40 minutes in patients of depression who were contemplating suicide.

Keywords: *Ketamine, N-methyl D-Aspartate antagonist (NMDA), major depressive disorder (MDD), mammalian target of rapamycin (mTOR), brain derived neurotrophic factor (BDNF), Eukaryotic Elongation Factor 2 (eEF 2) kinase*

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1. Introduction

Major depressive disorder (MDD) is going to be the second most leading cause of years lived in disability by the year 2020 as per the World Health Organization (WHO) Health survey report [1]. A range of antidepressant agents are available, but 30% to 40% of patients do not respond to initial treatment and non response rate is even higher in depressed patients in bipolar disorder. In patients, who experience symptomatic relief after conventional antidepressant drug treatment, these improvements are generally not evident for 3 to 4 weeks. A monoamine neurotransmitter system (e.g. nor-epinephrine, dopamine, or serotonin) is the pharmacological mechanism underlying almost all current antidepressant agents. Indeed, the lag period in onset of action for several weeks is a major limitation which results in considerable morbidity and higher risk for suicidal behaviour [2]. Converging evidence from in vivo brain imaging studies, postmortem investigations and gene expression studies implicates abnormalities in glutamatergic signaling in the pathophysiology of depressive disorders [3,4].

Ketamine, a non-competitive NMDA receptor antagonist has a rapid antidepressant action within hours of a single sub-anaesthetic intravenous infusion [5,6] and decreases suicidality [7,8]; efficacious and safe [9,10,11] as reported in several small studies and case reports, thus representing a paradigm shift in therapeutic approaches for treatment- resistant major depressive disorder [12,14]; treatment-resistant bipolar depression [15] and obsessive compulsive disorder [8].

The spontaneous neurotransmission "at rest" causes robust trafficking of Vps 10 p-tail-interactor-1a (vti1a) synaptic vesicle to fuse with the presynaptic membrane as compared to more abundant vesicular SNARE synaptobrevin 2 (also called VAMP 2) and modulates action potential firing in neurons. Non-competitive NMDA receptor antagonist (ketamine) "at rest" deactivates eukaryotic elongation factor 2 (eEF 2) kinase, resulting in reduced phosphorylation and desuppression of rapid dendritic protein translation, including brain-derived neurotrophic factors (BDNF), which contribute to synaptic plasticity that mediates long term effects of the drug [17,18,19]. Synaptogenesis in response to mammalian target of rapamycin (mTOR) activation could be hypothesized to contribute ketamine's acute and sustained effects in depressed patients for 7 days to 2 weeks by increasing (mTOR) expression [20].

The repeated long administration of ketamine may have neurotoxic effects when the dose exceeds the therapeutic relevant range, causing reversible vacuolation in the posterior cingulated and retrosplenial cortex of rats [21]. This is not the universal phenomenon as other more selective NMDA antagonists e.g., eliprodil and Ro 63-1908 which are nicotinic receptor (NR2B) subunit antagonists have not reported vacuolation in rats [22]. NR2B antagonist Ro 25-6981 has antidepressant like activity and traxoprodil, an NR2B antagonist, has demonstrated expression of brain-derived neurotrophic factor (BDNF) which triggers the neuroplastic changes

that hypothetically represent the final common pathway of antidepressant action [23].

A case series of psychiatric patients who had depression and suicidal tendency is reported. They were prescribed ketamine 0.5 mg/kg infusion (dissolved in 100 ml of normal saline) over a period of 40 minutes as per the procedure documented earlier in the literature for difficult to treat or treatment-resistant patients [5,6,7,10,11,12,13,14]. Various scales were administered e.g., psychopathology was assessed on brief psychiatric rating scale (BPRS)[26]; depression on Montgomery Asberg Depressive Rating Scale (MADRS) [27]; obsessive compulsive disorder on Yale-Brown Obsessive and Compulsive Scale (YBOCS) [28]; perceptual and dissociative changes on Clinician- Administered Dissociative States Scale (CADSS) [29]; and clinical outcome on Clinical Global Impression- Severity (CGI-S) and Clinical Global Impression- Improvement (CGI-I) Scale.

2. The Cases

2.1. Case 1

A 33 year old male, married graduate reported in the outdoor patient department unit of Psychiatry, Government Medical College, Rajindra Hospital, Patiala with symptoms of sadness of mood, describing his world as pale, stale and gloomy, with decreased appetite and sleep. He was having hopelessness, worthlessness and suicidal ideation, and a death wish of jumping in front of the train; but not completing the act. These symptoms were gradual in onset and worsened with time, during the last six months. He denied hearing any voices or self referential gestures, delusion of sin, guilt, poverty and nihilism. There was no past psychiatric, medical illness, substance abuse and family history of any psychiatric illness. Mental status examination showed depressed mood, appropriate affect, and low volume speech, slow in rate and rhythm, coherent and comprehensibility with no echolalia. Patient's thoughts were slow in progression and goal directed, there was no loosening of association, thought insertion, broadcasting, withdrawal or blocking. His higher mental functions were normal; attention was aroused, but showed difficulty in concentration, memory and calculation with delayed responses. Judgement, insight to illness and contact with reality was intact. He was diagnosed on ICD-10 Classification of Mental and Behavioural Disorders, as F 32.2 Severe depressive episode without psychotic symptoms. His score on MADRS at the baseline was 35 and CGI –S score was 6. The sub-anaesthetic dose of ketamine i.e., 0.5 mg/kg dissolved in 100 ml of normal saline was given intravenously over a period of 40 minutes. During infusion, the most common side effects observed were dizziness, blurred vision, nausea, poor coordination, poor concentration, restlessness, and dissociative symptoms (i.e., feeling outside one's body or perceiving that time is moving more slowly) and transient raise of blood pressure. The psychopathology of the symptoms was assessed on BPRS and severity on CGI-S with score of 41 and 4 respectively, indicating moderate illness. After two hours, patient was reassessed on MADRS which was 10, BPRS and CGI- I score of 19 and 1 respectively, indicating very much improvement after therapeutic intervention.

2.2. Case 2

A 33 year old bachelor reported with symptoms of OCD (F 42.2) of over 10 years duration with comorbid bipolar affective disorder, current episode of moderate depression (F 31.3) for the last 3 months, characterized predominantly by obscene thoughts leading to guilt feelings and consequent depression. His depression became intense over the last few months along with suicidal thoughts. In the past, he had history of psychiatric illness with two episodes of mania and one episode of depression that remitted with medications. There was no history of any substance abuse or medical illness and family history of psychiatric disorder. He was, therefore, titrated on fluoxetine 40 mg/day, clomipramine SR 150 mg/day and divalproex sodium 1500 mg/day during the past one month. The unbearable guilt feelings caused by his obsessive blasphemous thoughts of spitting on photos of deities and sexual thoughts about them, forced him to attempt suicide, by slashing his wrist with a knife. He was rushed to the emergency department and timely surgical intervention got him saved. He was still harbouring suicidal thoughts, YBOCS score was 36; MADRS was rated at 21 and CGI – S score for illness was 6. ECT was considered but he refused to give consent. He was counselled for rapid antidepressant action of sub-anaesthetic dose of ketamine i.e., 0.5 mg/kg dissolved in 100 ml of normal saline and given over a period of 40 minutes which he readily consented. During infusion, the most common side effects were nausea, blurring of vision, dizziness, perspiration, ringing in ears, poor coordination, poor concentration, restlessness, and dissociative symptoms (i.e., feeling disconnected from the body, outside one's body or perceiving that time is moving more slowly, things seems unreal, seeing things as if in tunnel, losing track of what is going on) and transient raise of blood pressure. The psychopathology of the symptoms was assessed on BPRS and severity on CGI-S with score of 47 and 4 respectively, indicating moderate illness. After two hours of infusion, he was reassessed on YBOCS, MADRS, BPRS, and CGI-I scales scoring 28, 11, 23 and 2 respectively, indicating much improvement.

2.3. Case 3

A 35 year old, self employed bachelor farmer, suffering from treatment-resistant depression for the last 7 years, had reported with a recent worsening of his symptoms due to death of his mother with guilt feeling that he could not take care of her ailing mother at the terminal end of her life. He had death wish that life was not worth living and planed to end his life by consuming poison. He described his mood as sad with feeling of despondency, lassitude, hopelessness, worthlessness and suicidal ideas. He was diagnosed on ICD-10 as F 33.2 recurrent depressive disorder, current episode severe depression without psychotic symptoms. He was prescribed drugs which were gradually titrated to maximum therapeutic levels i.e., dosulepin 450 mg /day, pramipexole 1.5 mg/day, modafinil 200 mg/day, clonazepam 1.5 mg/day. His MADRS score was 34 with a high score on the suicidality and CGI- severity score of 5. As he did not like to inform

his family about death wish and not willing for ECT, he was taken up for sub-anaesthetic ketamine infusion i.e., 0.5 mg/kg dissolved in 100 ml of normal saline and given over a period of 40 minutes to induce a quick relief from depression. He reported nausea, dizziness, salivations, perceptual changes and on CADSS items his scores were 3, 4 respectively, indicating effects to be considerable and extreme in the following areas, 'as if looking at the things from outside body; feels separated from what is happening; as if spectator or observer; feels disconnected from the body; body change, seeing things as if tunnel/wide angle lens; things happening quickly; as if looking through fog; sound changed in intensity and special sense of clarity. He reported raised blood pressure which subsided gradually within about 2 hours and the efficacy index score of 7, indicates that therapeutic effects were moderate and side effects significantly interfere with functioning. However, after 2 hours of ketamine infusion, his MADRS score significantly dropped down to 14 and CGI-I score was 2 indicating much improvement. There were no other side effects and BPRS, CADSS items scored were also normal.

3. Discussion

Treatment for MDD has a range of antidepressant agents, but 30% to 40% of patients do not respond to initial treatment. Monoamine neurotransmitter requires a lag period in onset of action for several weeks resulting in considerable morbidity and higher risk for suicide. Suicidality is a major cause of morbidity and mortality in psychiatric practice and co-morbid depression either in unipolar or bipolar disorder can significantly contribute among many completed suicides. This unmet need can be resolved by ketamine, a non-competitive, glutamatergic NMDA receptor antagonist which has rapid antidepressant effects [9,10,11,12].

In Case 1, severe depression with suicidality, the MADRS score of 35, CGI-S score of 6 before the start of ketamine infusion therapy and after 2 hours MADRS score of 10 and CGI-I score of 1 showed very much improvement. His efficacy index score was 2 indicating therapeutic effects were marked and side effects did not significantly interfere the functioning. These findings were similar as reported by Price et al., [7] which showed that suicide ratings dropped significantly within a day of treatment with ketamine (n=26); thrice-weekly ketamine infusions across a 12-day period were associated with sustained fall in suicidality scores (n=9). The authors considered that the attenuation of suicidality was likely to be a result of the antidepressant effect. However, there were transient psychoactive and hemodynamic effects which were consistent with those in previous reports and clinical experience [9,10,11,12].

In Case 2, obsessive compulsive disorder and bipolar depression with suicidality also showed improvement in depression, OCD scores as assessed on MADRS, YBOCS and severity on CGI-S scale with baseline score of 21, 36 and 6. After 2 hours of ketamine infusion, the scores were 11, 28 and CGI-I score of 2 respectively, indicating much improvement. Efficacy index of 5 showed therapeutic effect to be of moderate with no side effect. These findings were similar to antidepressant activity which was observed within hours of a single sub-anaesthetic intravenous infusion (0.5 mg/kg) and intramuscular ketamine (0.5 mg/kg) for treatment-resistant depression; unipolar depression; OCD and bipolar depression [5-15]. The adverse effects during infusion of ketamine were dizziness, nausea, blurring of vision, dissociative symptoms, poor concentration, tunneling of vision and sense of bodily change. The rise in blood pressure during ketamine may be due to stimulation of cardiovascular system by circulating catecholamine, producing changes in heart rate and cardiac output as reported by Haas and Harper, 1992 [24] and treated by giving premedication with clonidine and attenuation of neuropsychiatric effects of ketamine with lamotrigine [25].

In Case 3, treatment- resistant depression with suicidality showed sudden decrease in depression as assessed on MADRS, CGI-S scores from 34, 7 to 14 and CGI-I score of 2, indicating marked therapeutic effects and side effects do not require any intervention; they were mild and remitted within about 2 hours. Aan het Rot et al., [10] administered a single ketamine (0.5 mg/kg) infusion to 10 patients with treatment-refractory depression; a day later, MADRS scores in nine patients showed >50% attenuation. These nine patients received five more ketamine infusions across the next 10 days. At the end of the ketamine course, there was 85% attenuation in MADRS ratings in the sample.

However, during infusion of ketamine in Case 3, patient manifested symptoms of perceptual changes, dissociative symptoms of depersonalization and derealization, which were due to pharmacodynamic nature of ketamine and resolved spontaneously. There are possibilities of neurotoxic effects, except in high doses causing reversible vacuolation which is not uncommon in animal studies but extrapolation on humans needs sufficient rigorous clinical trials [22,23].

4. Conclusion

Ketamine infusion (0.5 mg/kg) is associated with antidepressant and ant suicidal effects. It has a wide margin of safety. The benefits develop within 1-2 hours of the infusion. Adverse effects are confusion, dizziness, perceptual disturbances which usually last for not more than 2 hours. Infusion of ketamine in sub-anaesthetic doses may, therefore, be a useful antidepressant measure in patients with suicidality.

5. Limitation of Study

Although the above treatment reduces depression and suicidality for patients in extreme need yet, rigorous double blind randomized control trials are needed to generalize these findings.

6. Implication/Salient Features of this Study

This study gives an alternative approach to ECT for immediate intervention of depression with suicidality by subanaesthetic low dose ketamine infusion which is safe and efficacious.

7. Source of Support

Nil.

8. Conflict of Interest

None declared.

References

[1] The World Health Report, *Mental Health: New Understanding, New Hope*, Geneva, World Health Organization, 2001.

[2] Stahl, S.M, *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 3rd ed. Cambridge: Cambridge University Press; 2008. pp 520-521.

[3] Hashimoto, K, Emerging role of glutamate in the pathophysiology of major depressive disorder, *Brain Res Rev*, 61. 105-123. 2009.

[4] Sanacora, G., Zarate, C.A., Krystal, J.H. and Manji, H.K, Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders, *Nat Rev Drug Discov*, 7. 426-437. 2008.

[5] Liebrenz, M., Borgeat, A., Leisinger, R. and Stohler, R, Intravenous ketamine therapy in a patient with a treatment-resistant major depression, *Swiss Med Wkly*, 137. 234-236. 2007.

[6] Machado-Vieira, R., Salvadore, G., Diazgranados, N. and Zarate, C.A. Jr, Ketamine and the next generation of antidepressants with a rapid onset of action, *Pharmacol Ther*, 123. 143-150. 2009.

[7] Price, R.B., Nock, M.K., Charney, D.S. and Mathew, S.J, Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression, *Biol Psychiatry*, 66. 522-526. 2009.

[8] Harihar, C., Dasari, P. and Srinivas, J.S, Intramuscular ketamine in acute depression: A report on two cases, *Indian J Psychiatry*, 55. 186-188. 2013.

[9] Berman, R.M., Cappiello, A., Anand, A., Oren, D.A., Heninger, G.R. and Charney, D.S, Antidepressant effects of ketamine in depressed patients, *Biol Psychiatry*, 47. 351-354. 2000.

[10] Aan het Rot, M., Collins, K.A., Murrough, J.W., Perez, A.M., Reich, D.L., Charney, D.S. el al., Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression, *Biol Psychiatry*, 67. 139-145. 2010.

[11] Murrough, J.M., Losifescu, D.V., Chang, L.C., Al Jurdi, R.K. et al., Antidepressant efficacy of ketamine in treatment-resistant major depression: A two site randomized controlled trial, *Am J Psychiatry*, 170. 1134-1142. 2013.

[12] Zarate, C.A. Jr., Singh, J.B., Carlson, P.J., Brutsche, N.E., Ameli, R., Luckenbaugh, D.A. et al., A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression, *Arch Gen Psychiatry*, 63. 856-864. 2006.

[13] Rao, T.S.S. and Andrade, C, Innovative approaches to treatment – refractory depression: The ketamine story, *Indian J Psychiatry*, 52. 97-99. 2010.

[14] Mathew, S.J., Shah, A., Lapidus, K., Clark, C. et al., Ketamine for treatment –resistant unipolar depression: current evidence, *CNS Drugs*, 26. 189-204. 2012.

[15] Diazgranados, N., Ibrahim, L., Brutsche, N.E., Newberg, A., et al., A randomized add-on trial of N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression, *Arch Gen Psychiatry*, 67. 793-802. 2010.

[16] Ramirez, D.M., Khvotchev, M., Trauterman, B. and Kavalali, E.T, Vti 1a identifies a vesicle pool preferentially recycles at rest and maintains spontaneous neurotransmission, *Neuron*, 73. 121-134. 2012.

[17] Autry, A.E., Adachi, M., Nosyreva, E., Na, E.S., Los, M.F. et al., NMDA receptor blockade at rest triggers rapid behavioral antidepressant responses, *Nature*, 475. 91-95. 2011.

[18] Sutton, M.A. and Schuman, E.M, Dendritic protein synthesis, synaptic plasticity and memory, *Cell*, 127. 49-58. 2006.

[19] Ege, T.K. and Lisa, M.M, Synaptic mechanisms underlying rapid antidepressant action of ketamine, *Am J Psychiatry*, 169. 1150-1156. 2012.

[20] Li, N., Lee, B., Liu, R.J., Banasr, M. et al., mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists, *Science*, 329. 959-964. 2010.

[21] Olney, J., Labruyere, J. and Price, M.T, Pathological changes induced in cerebro-cortical neurons by phencyclidine related drugs, *Sciences*, 244. 1360-1362. 1989.

[22] Higgins, G.A., Ballard, T.M., Huwyler, J., Kemp, J.A. and Gill, R, Evaluation of the NR2B selective NMDA receptor anatagonist R0 63-1908 on rodent behavior: evidence for involvement of NR2B NMDA receptors inhibition, *Neuropharmacology*, 44. 324-341. 2003.

[23] Machado-Vieira, R., Yuan, P., Brutsche, N., Diazgranados, N., Luckenbaugh, D., Manji, H.K. et al., Brain-derived neurotrophic factor and initial antidepressant response to an N-methyl-D-aspartate antagonist, *J Clin Psychiatry*, 70. 1662-1666. 2009.

[24] Haas, D.A. and Harper, D.G, Ketamine: a review of its pharmacologic properties and use in ambulatory anaesthesia, *Anesth Prog*, 39.61-68. 1992.

[25] Anand, A., Charney, D.S., Oren, D.A. et al., Attenuation of the neuropsychiatric effects of ketamine with lamotrigine, *Arch Gen Psychiatry*, 57. 270-276. 2000.

[26] Overall, J.E. and Gorham, D.R, The Brief Psychiatric Rating Scale (BPRS), *Psychol Rep*, 10. 799-812. 1962.

[27] Montgomery, S.A. and Asberg, M, A new depression scale designed to be sensitive to change, *Br J Psychiatry*, 134. 382-389. 1979.

[28] Goodman, W.K., Price, L.H., Rasmssen, S.A. et al., The Yale-Brown Obsessive Compulsive Scale-I: Development, use and reliability, *Arch Gen Psychiatry*, 46. 1006-1011. 1989.

[29] Bremner, J.D., Krystal, J.H., Putnam, F.W., Southwick, S.M. et al., Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS), *J Trauma Stress*, 11. 125-136. 1998.