

# Haloperidol: A Novel Use in Ketamine Induced Postoperative Fulminant Psychosis

Shahla Haleem<sup>1</sup>, Muazzam Hasan<sup>2</sup>, Nida Fatima<sup>3</sup>, Md Kashif Jamal<sup>4</sup>

Department of Anaesthesiology and Critical care, J. N. Medical College, A.M.U., Aligarh 202002, U.P., India

**Abstract:** We report a case of severe/fulminant psychosis in an intellectually disabled healthy teenage female operated for the fracture shaft of the femur after post polio residual para-paresis under spinal anaesthesia. For intra-operative sedation, injection ketamine was used in subanaesthetic doses following midazolam premedication. Postoperatively she developed severe psychosis for which injection diazepam and midazolam were unsuccessful to manage the psychological crisis. Finally, ketamine induced unmanageable fulminant psychosis was controlled by injection haloperidol.

**Keywords:** Ketamine, Haloperidol, Glutamate, Psychosis, Anaesthesia.

## 1. Introduction

Psychological reactions following ketamine anesthesia is not an uncommon issue, usually evident when the medication wears off. The "emergence reactions" have described a form of neurocognitive impairment, including confusion, hallucinations or psychosis or delirium or, agitation, and muscle tremors. Exaggerated psychiatric symptoms are matters of serious concern for the patient as well as treating physician. Chain of events following cognitive dysfunction lead to the grave consequences requires urgent attention careful consideration and management.

Ketamine, recognized as a potent psychedelic drug, provokes imaginative, dissociative states, and psychotic symptoms as well as severely impairs semantic and episodic memory when used in sub-anesthetic doses, owing to its NMDA-antagonistic action<sup>[1,2]</sup>. Being competitive antagonist of NMDA receptor; contributes to the physiopathology of behavioral effects in healthy humans. Usually, drug induced psychoactive side effects are less apparent and controlled with psychological support and consolation. Severe form of psychotic symptoms requires various pharmacological interventions.

## 2. Case History

A well built (~50kg) 17 years old female was posted for orthopaedic surgery for fracture shaft of femur. She had post polio residual paraparesis with intellectual disability. She was looking comfortable and following commands. The above mentioned patient was planned for CRIF with intertrochanteric nailing under spinal anaesthesia.

She was planned for surgery under Spinal anaesthesia by the consultant anesthetist. All the monitors (pulse-oximeter for pulse rate & oxygen saturation, NIBP & ECG) were attached and Inj midazolam 1.5 mg was given intravenously as a premedication for sedation and amnesia. Preloading was done with 10 ml/kg of ringer lactate solution. Under all aseptic precautions L<sub>3,4</sub> intervertebral space was identified and spinal needle was inserted, after the free flow of CSF Bupivacaine (12.5 mg) Injection was given in the subarachnoid space.

Adequate anaesthesia was achieved and surgery was started. As the patients' IQ was subnormal, she was unable to stay in a neutral position on the operating table and became restless after an hour time. Inj midazolam was repeated 1.5 mg i.v but the patient could not be sedated properly. Inj ketamine in the dose of 0.5mg/kg was given and repeated when required, to sedate and anesthetize her properly.

A total dose of 50 mg ketamine was used to sedate during the entire surgery (2.5 hours). After completion of surgery patient was shifted to post-op room with normal vitals. She was comfortable in the post-op room, but started unconsolable cry and agitation after some time

Injection ketorolac 30 mg was given for pain relief. But she was still agitated, delirious and crying. Injection midazolam 2mg was given, but there was no improvement in her condition. She was still crying and shouting continued, Injection diazepam 10 mg was also given slowly intravenously. In spite of all efforts, she was agitated yet again just after 15 minutes of injection diazepam. Enough time (>3 hrs) was elapsed between the ketamine medication and continuous uncontrolled psychological distress. Suspecting a schizophrenic, psychotic spell consultant anesthetist advised for haloperidol injection. The patient responded immediately to the slow intravenous Injection of Haloperidol 5.0 mg. There was rapid improvement in the patient's condition with the prompt control over agitation and crying. She was monitored in the post-op room for next one hour and was shifted to ward with normal mental functions and stable vital parameters.

## 3. Discussion

Ketamine and phencyclidine (PCP) induced neurologic conditions are not an infrequent occurrence in clinical setting<sup>[3, 4]</sup>. The anesthetic drug, ketamine has many appealing properties in awkward clinical scenarios. In anaesthetic practice it is commonly used in pediatric population for induction, maintenance and procedural sedation, and analgesia. In adult patients ketamine is used as a sort of rescue medicine for induction of anaesthesia in hypotensive (shock) patients in emergency or supplementation of regional anaesthesia after weaning off the effects of neuraxial blockade. It is seen that ketamine

induced psychotic symptoms are most commonly observed in adult patients [5].

In spite of its diverse uses in the field of aesthetic practice the subanesthetic doses of ketamine could produce the behavioral symptoms and cognitive deficits even in normal volunteers.

Noncompetitive **NMDA glutamate receptor** antagonists can produce a transient state of NMDA receptor hypofunction (NRH) in the brain, a mechanism that could be psychotogenic and can lead to schizophrenia-like symptoms [1, 6]. Thus, glutamate abnormalities may disturb brain function and underpin psychotic symptoms and cognitive impairments [7]. Furthermore the glutamate hypothesis proposed by *Goff & Coyle* [8], which is one of the leading neuro-chemical theories of schizophrenia, suggests that phencyclidine and other glutamate antagonist drugs induce symptoms similar to those of schizophrenia. [8]

Effect analysis of ketamine using proton magnetic resonance spectroscopy (1H-MRS) has found an increase in cortical glutamate and glutamine levels in the anterior cingulate cortex [9].

The unwanted affective symptoms and cognitive deficits produced by ketamine have different quantitative and qualitative responses. The acute ketamine administration is considered widely as a valid model of positive, negative and cognitive symptoms of schizophrenia as the delta power is increased after acute ketamine administration. [10]

Therefore, considering the schizophrenic side effect, Haloperidol, a typical antipsychotic was considered. It controls the symptoms of acute psychosis, aggression, agitation by increasing glutamate release in striatum and prefrontal cortex. This elevation in glutamate may explain the ability of haloperidol to reverse the behavioral alterations elicited by NMDAR antagonists like ketamine [Fig.1]. [11, 12]

Recent evidence, suggests that most of the currently known NMDA antagonists have a broader receptor profile than originally thought [12]. Besides exerting an antagonistic effect on NMDA receptors, they have agonistic effects on dopamine D2 receptors. Haloperidol being a D2 antagonist may counteract the disruptive effects of ketamine on psychophysiological parameters. Oranje et al [12] has found that the disruptive effects of ketamine on processing negativity could be prevented by pre-treatment with Haloperidol.

Thus haloperidol may be used as a preferred drug in patients with ketamine induced acute psychosis. Use of haloperidol to treat ketamine induced psychosis has also been supported by other case reports [13]. The authors also suggest injection haloperidol should also be the part of armamentarium of emergency drugs kept in post operative room to control the schizophrenia like side effects of drugs. Furthermore, the health provider need to be aware its side effects and limitations before use. Caution is required in the special situation of bipolar disorder, mania, seizure, last trimester of pregnancy & lactation, and heart or thyroid disease [14].

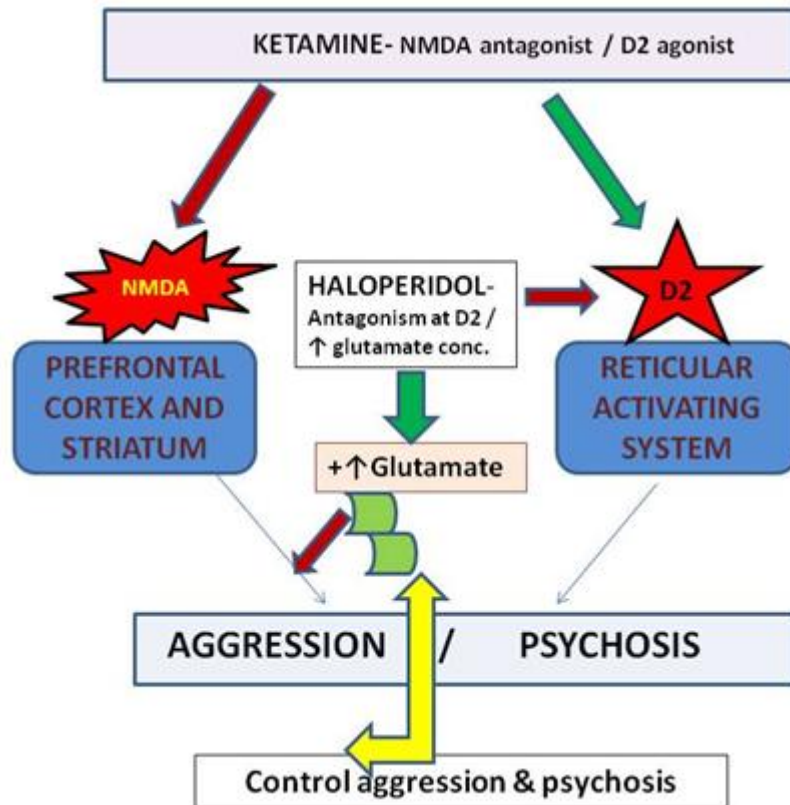
However, further studies and research are recommended to have a better understanding of the mechanisms involved, as it is also pointed out to be having risk of arrhythmia, hypotension and sudden cardiac death, etc especially at higher dosages and in elderly patients.

## References

- [1] Krystal JH, Karper LP, Seibyl JP, et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry* 1994;51:199–214.
- [2] Morgan CJ, Mofeez A, Brandner B, Bromley L, Curran HV. Acute effects of ketamine on memory systems and psychotic symptoms in healthy volunteers. *Neuropsychopharmacology*. 2004;29:208–218.
- [3] Celia J. A. Morgan and H. Valerie Curran Ketamine Use: A Review. *Addiction*. 2012;107:27-38.
- [4] Kothari D, Mehrotra A, Jain A K, and Dixit S. Role Of Promethazine In Post Ketamine Emergence Phenomenon - A Clinical Evaluation. *Indian J. Anaesth*. 2003;47:456-457.
- [5] Newcomer JW, Farber NB, Jevtovic-Todorovic V, Selke G, Melson AK, Hershey T, et al. Ketamine-induced NMDA receptor hypofunction as a model of memory impairment and psychosis. *Neuropsychopharmacology* 1999;20:106–181.
- [6] Malhotra AK, Pinals DA, Adler CM, Elman I, Clifton A, Pickar D, Breier A. Ketamine-induced exacerbation of psychotic symptoms and cognitive impairment in neuroleptic-free schizophrenics. *Neuropsychopharmacology*. 1997;17:14 1–150.
- [7] Merritt K, McGuire P and Egerton A. Relationship between Glutamate Dysfunction and Symptoms and Cognitive Function in Psychosis *Front Psychiatry* 2013;4:151.
- [8] Goff D and Coyle JT. The emerging role of glutamate in the pathophysiology an treatment of schizophrenia. *Am J Psychiatry* 2001;158:1367 -1377.
- [9] Stone JM, Dietrich C, Edden R, Mehta MA, De Simoni S, Reed LJ, Krystal JH, D Nutt and Barker GJ. Ketamine effects on brain GABA and glutamate levels with 1H-MRS: relationship to ketamine-induced psychopathology. *Mol Psychiatry*. 2012;17:10.1038.
- [10] Frohlich J, Van Horn JD. Reviewing the ketamine model for schizophrenia. *J Psychopharmacol* 2014;28:287–302.
- [11] Anderson MP, Pinault D, O'Brien TJ, Jones NC. Chronic administration of antipsychotics attenuates ongoing and ketamine induced increases in cortical  $\gamma$  oscillations. *Int J Neuropsychopharmacol* 2014;17:1895-1904.
- [12] Oranje B, Gispens-de Wied CC, Westenberg HG, Kemner C, Verbaten MN, Kahn RS. Haloperidol counteracts the ketamine-induced disruption of processing negativity, but not that of the P300 amplitude. *Int J Neuropsychopharmacol* 2009;12:823-32.

- [13] Glen M. Atlas, Maano Milles. Haloperidol for the Treatment of Ketamine-Induced Emergence Delirium. *J Anesth Clin Pharmacology* 2007;23:65-67.  
[14] PRODUCT INFORMATION [Internet]. Available from:

<https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2011-PI-03532-3>



**Figure 1:** Haloperidol reverses the ketamine induced NMDAR antagonism by increasing glutamate concentration and antagonizes D2 receptor

