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Review Article

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USE OF KETAMINE IN STATUS EPILEPTICUS, A REVIEW ARTICLE

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ABSTRACT

Status epilepticus (SE) is defined as any seizure that lasts more than 5 minutes, or recurrent seizures without a regain of consciousness. Refractory status epilepticus (RSE) is described by a continuous seizure despite first- and second-line agents. In the management of SE, there is a general agreement regarding the first and second lines of management. However, in RSE there is no definitive algorithm that dictates its management approach. Ketamine has shown promising efficacy and safety in the management of refractory and super-refractory status epilepticus cases. Recent studies recommended an earlier administration of KE in RSE, as it is currently being administered only after failing of conventional anaesthetics.

KEYWORDS: Ketamine, Status Epilepticus, Refractory status epilepticus.

INTRODUCTION

Status epilepticus (SE), a life-threatening neurological emergency, is previously defined as an acute episode of abnormal excessive or synchronous neuronal activities for 30 minutes or more, or intermittent seizures over 30 minutes without a complete regain of consciousness.[1] Due to the advances in the field of neurology along with a comprehensive understanding of the pathophysiology, the SE currently defined as a seizure that lasts more than 5 minutes or repetitive seizure without fully regaining consciousness in between.[2]

Refractory status epilepticus (RSE) which requires an immediate transfer of patients to an intensive care unit, is describe by a continuous seizure despite first- and second-line agents.[3] Furthermore, if SE does not respond or recurs for 24 hours or longer or recurs with the withdrawal of general anaesthesia is labelled as super refractory status epilepticus.[3]

In the management of SE, there is a general agreement regarding the first and second lines of management.[4] However, in RSE there is no definitive algorithm or protocols exist that dictates its management approach.[3, 5–7] Therapeutic measured used in the management of RSE include an electroencephalography (EEG) monitoring if available and the use of anaesthetics: propofol, midazolam, and thiopental sodium.[5, 7]

Pathophysiology of Status Epilepticus and Ketamine

On a neurochemical level, seizure is a condition results from an excess excitation and reduced inhibition of neurotransmitters. Glutamate is commonly known for its excitatory effect, along with its subtype; the *N*- methyl- d- aspartate (NMDA) receptors. In contrast to Gamma-aminobutyric acid (GABA), which is commonly known for its inhibitory effect. A key mechanism of a continuous seizure activity is internalization of GABA receptors and increased expression of NMDA receptors to the synapse. Over time, the inhibitory effects become less effective, whereas the excitatory actions of glutamate are increased.[8,9,10] Use of NMDA-receptor antagonists such as ketamine (KE), in the treatment of SE has been studied and experimental models have demonstrated its effect on the control of prolonged SE,[11, 12] Moreover, a combination of KE and benzodiazepines, which enhances the binding of GABA to its receptor, does greatly increase the efficacy of KE.[13, 14]

The half-life of KE is approximately 2 to 3 hours. It gets metabolised mainly in the liver by cytochrome P450 3A and cytochrome P450 2B6 isoenzymes into the active metabolite: nor-ketamine. KE is both hydrophilic and lipophilic, therefore, this allowing it to be extensively distributed in the body and to be administered conveniently via various routes. The oral route of administration has a poor bioavailability due to extensive first-pass metabolism which also makes it more liable to drug-drug interaction. In addition, the maximum plasma concentration (Tmax) is longer with the oral form than intravenous form; 15-30 minutes in contrast to 1-5 minutes with the intravenous form.[15,16,24] Common side effects of KE include hallucinations, ptyalism, nausea and vomiting.[15,16]

Based on its clinical safety and efficacy profile, along with it being currently the only NMDA receptor antagonist licensed, it might be considered as the anaesthetic agent of choice in specific complicated situations and as an out-of-hospital medication option for SE.[16,17,18]

Evidence Based Efficacy of Ketamine in Status Epilepticus:

A retrospective study done by Gaspard, aiming to report the effective dose and time to intervene with KE concluded the following by reviewing patients' medical records and EEG results between 1999 and 2012.

- Seizures ultimately resolved in 57% of cases.
- Approximately 45% of the cases of RSE were controlled with ketamine use.
- When ketamine was administered on the 8th day post SE onset, after 7 failed medications or, with an infusion rate less than 0.9 mg/kg/h, no likely responses were noted.[21]

Similarly, additional study demonstrated the efficacy and safety of intravenous ketamine in 9 paediatrics patients' with RSE between 2009 and 2011. A control of RSE was achieved in 6 patients with no serious adverse reactions reported.[22]

In addition, the use of oral KE in paediatrics patient with non-convulsive RSE (NCSE), including Lennox–Gastaut syndrome, pseudo-Lennox syndrome, progressive myoclonic epilepsy and myoclonic-astatic epilepsy, concluded the resolution of seizure within 24–48 hours after the initiation of ketamine in all patients without apparent side effects, despite the low bioavailability of the oral form.[23]

Furthermore, regarding its use in RSE, recent studies recommended an earlier administration of KE in RSE, as it is currently being administered only after failing of conventional anaesthetics.[3, 19, 20]

CONCLUSION

Status epilepticus being a medical emergency and ketamine has shown promising efficacy and safety in the management of refractory and super-refractory status epilepticus cases. A lack of consensus about the use of ketamine is due to fewer studies of ketamine use in patients of status epilepticus. Ketamine should be considered as a preferred choice in the management of status epilepticus consider its good safety profile, fast duration of action, and proven effectiveness as demonstrated in the previous studies.

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