IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 23, Issue 9 Ser. 7 (September. 2024), PP 01-03
www.iosrjournals.org

Use Of Ketamine In Refractory Status Epilepticus With Hemodynamic Instability

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Abstract
The use of benzodiazepines, such as midazolam, as a last-resort treatment for refractory status epilepticus is widely practiced, particularly in patients who are hemodynamically stable. However, as the dosage of this anti-epileptic agent is increased, it potentiates γ-aminobutyric acid (GABA) activity, which can lead to hypotension and subsequently necessitate the administration of vasopressor agents, especially in cases involving hemodynamic instability, as illustrated by this case where a young man who arrived at the emergency department with complaints of epileptic seizures and was already on regular anti-epileptic medications. During a seizure episode in the department, he was administered intravenous Lorazepam according to standard protocol to stop the seizure, and then placed on an IV infusion of Midazolam. However, his hemodynamics became unstable due to the side effects of the benzodiazepines administered. To address this instability, the decision was made to initiate an infusion of Ketamine along with a low dose of Midazolam. This combination successfully terminated the epileptic activity and stabilized his hemodynamics. In these instances, either concurrent or standalone administration of N-methyl-D-aspartate (NMDA) receptor antagonists might prove beneficial for managing refractory status epilepticus. For example, ketamine infusion can inhibit the reuptake of catecholamines into the systemic circulation, thereby aiding in the maintenance of blood pressure in hemodynamically unstable patients. The initial application of a combined third-line therapy, which involves blocking NMDA receptors while simultaneously enhancing GABAergic activity, appears promising for the management of refractory status epilepticus.

Date of Submission: 09-09-2024 Date of Acceptance: 19-09-2024

I. Introduction

The administration of anesthetics such as midazolam (last resort medication) becomes necessary to control seizure activity in refractory status epilepticus (RSE). However, the use of higher doses of anesthetics, which potentiate γ-aminobutyric acid (GABA) activity, often leads to hypotension, a critical side effect requiring vasopressor agents. Concurrent administration of N-methyl-D-aspartate (NMDA) receptor antagonists, like ketamine, may be beneficial in managing prolonged refractory SE while maintaining stable blood pressure due to inhibition of catecholamine reuptake in systemic circulation [1]. In this case study, we had one such patient who was found to be a suitable candidate for using ketamine infusion along with low-dose midazolam. This combined therapy effectively suppressed epileptic activity with reduced hemodynamic side effects, requiring lower doses of midazolam when used alongside ketamine, where ketamine is associated with decreased use of vasopressors and maintain hemodynamic stability [2]. The initial use of a combined third-line therapy, blocking NMDA receptors while enhancing GABAergic activity, shows promise in managing RSE. Further research is needed to explore its efficacy across various etiologies of SE [3].

II. Case Presentation

A 24-year-old male was brought in by colleagues, allegedly found unresponsive in the washroom. The patient was brought immediately to the Emergency Department, with a total time elapsed of 1 hour since the onset of the event. On arrival, the patient was noted to be frothing from the mouth and was drowsy but oriented to time, person, and place. Pertinent secondary examination revealed minimal bleed noted at the lateral upper 1/3rd of the tongue. The patient, known to have a seizure disorder for 10 years, was on oral Levetiracetam 500 mg twice daily. During the stay in the Emergency Department, the patient was triaged to level 3, received Intra-Venous (IV) Levetiracetam 2 gm and IV fluid Ringers Lactate 100 ml/hour. Around the 3-hour mark since the onset of the first seizure episode, the patient had two episodes of generalized tonic-clonic seizures (GTCS) lasting less than a minute each, for which IV Lorazepam 6 mg was given. Despite stabilization efforts, the patient experienced persistent clonic jerks.In view of unstable hemodynamics, patient was started on IV Midazolam 3mg/hour infusion. About 30 minutes elapsed and patient was still noted to have recurrent tonic clonic jerks despite ongoing IV Midzolam infusion. IV Ketamine infusion was then initiated at 90 mg/hr, which effectively ceased the clonic jerks. The patient was shifted to the ICU with ongoing IV Midazolam infusion at 3 mg/hour and IV Ketamine infusion at 90 mg/hour. Vital signs stabilized, and the patient was discharged on the 5th day post-extubation.

III. Discussion

In the case presentation, a 24-year-old male with a history of seizure disorder presents with unresponsiveness and frothing from the mouth, requiring immediate medical attention. Despite being on Levetiracetam, the patient experiences generalized tonic-clonic seizures (GTCS) in the ED, leading to the initiation of lorazepam. However, persistent clonic jerks and hemodynamic instability necessitate further intervention. Ketamine infusion is initiated alongside low-dose midazolam, resulting in the cessation of clonic jerks and stabilization of the patient's condition.

In patients experiencing refractory status epilepticus (RSE), the effectiveness of gamma-aminobutyric acid (GABA)ergic agents diminishes as the duration of the seizure extends [4]. During status epilepticus, specific signal transduction pathways become activated, which in turn alter the GABA-A receptors and reduce their functional efficacy [5]. Additionally, an increase in N-methyl-D-aspartate (NMDA) receptors has been observed in cases of prolonged or refractory status epilepticus [6]. Medications commonly utilized for treating refractory status epilepticus, such as benzodiazepines and barbiturates, may prove ineffective in patients with unstable hemodynamics, potentially leading to a worsening of hypotension [7]. Conversely, treatment with ketamine has been associated with a reduction in seizure burden among patients with super-refractory status epilepticus (SRSE). Moreover, high-dose infusions of ketamine are linked to decreased requirements for vasopressors and do not result in increased intracranial pressure [2].

This case highlights the successful use of ketamine as an adjunctive therapy in managing RSE, particularly in patients with hemodynamic instability. By blocking NMDA receptors and enhancing GABAergic activity, ketamine effectively controls seizure activity while minimizing the hemodynamic side effects associated with higher doses of midazolam alone. The prompt initiation of ketamine infusion in this case demonstrates its potential to improve outcomes in RSE patients, emphasizing the importance of considering alternative treatment modalities in challenging clinical scenarios. Further research and prospective studies are warranted to validate these findings and elucidate the optimal dosing and safety profile of ketamine in this context.

IV. Conclusion

Early institution of drugs that enhance GABA activation by blocking the NMDA receptor, in combination with low dosage midazolam, is effective for patients with hemodynamic instability. Research indicates ketamine infusion is often followed by seizure termination and has fewer adverse effects for patients in shock compared to midazolam, warranting further prospective studies for stronger evidence. Adequate fluid resuscitation and the use of vasopressors are essential when using drugs that may cause hypotension in patients requiring immediate treatment.

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