Case Report

Intravenous ketamine for treatment of super-refractory convulsive status epilepticus with septic shock: A report of two cases

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Abstract

Refractory and super-refractory status epilepticus is a life-threatening neurological emergency, associated with high morbidity and mortality. Treatment should be aimed to stop seizure and to avoid cerebral damage and another morbidity. Published data about effectiveness, safety and outcome of various therapies and treatment approaches are sparse and are mainly based on small case series and retrospective data. Here we report successful management of two cases of super-refractory status epilepticus refractory to anesthetic therapy with midazolam and complicated by septic shock, managed successfully with ketamine infusion.

Keywords: Ketamine, septic shock, super-refractory status epilepticus

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Introduction

Patients who continue to experience seizures after receiving adequate dose of an initial benzodiazepine followed by a second acceptable anti-epileptic drug (AED) is considered refractory. When bolus intermittent therapy or AED fails, continuous infusion of anesthetic agents is recommended.[1] Super-refractory status epilepticus is defines as status epilepticus that continues or recurs 24 h or more after the onset of anesthetic therapy, including those cases where status epilepticus recurs on the reduction or withdrawal of anesthesia.[2] Around 10–15% of patients with status epilepticus admitted to hospital will become super-refractory.[3] The reported incidence of death is 35%, and severe neurological deficit is 13%. Various therapeutic options like anesthetic drugs, AEDs, magnesium, pyridoxine, steroids, immunotherapy, ketogenic diet, hypothermia, neurosurgery, electrical stimulation therapy and cerebrospinal fluid drainage have been tried with variable success. Evidences supporting the management of super-refractory seizures is poor due to lack of randomized or controlled studies and is mainly derived from case reports and retrospective series.[4]

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist, not associated with cardiorespiratory depression.[5] It has been reported to be used successfully in hemodynamically compromised patients.[6] Studies have demonstrated efficacy and safety of ketamine for the treatment of refractory status epiepticus (RSE).[7,8] Here we report the successful management of two cases of super-refractory status epilepticus in patients with septic shock using ketamine infusion.

Case Reports

Case 1

A 23-year-old lady, around 50 kg was a known case of seizure disorder since 10 years. Despite on her regular anti-epileptic medications, she presented with convulsive status epilepticus, which did not respond to intravenous Lorazepam bolus and loading dose of Phenytoin. Dose of her regular medications were maximized (phenytoin, sodium valproate, levetiracetam and phenobarbital). Laboratory investigation reports were normal. Serum

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phenytoin level was therapeutic and NMDA receptor IgG antibodies were not detected in serum. She was admitted to intensive care unit (ICU) and started on midazolam infusion, which was titrated up to 20 mg/h. The seizure was not controlled even after 36 h of midazolam infusion. Patient was intubated and required Noradrenaline infusion at 0.15 μg/kg/min for the management of hypotension due to septic shock due to urinary tract infection. Ketamine 50 mg was administered as a bolus and continued at 100 mg/h. Over the next 48 h, convulsive seizure episodes progressively decreased. Midazolam and noradrenaline were gradually tapered and stopped. Over the following 24 h, the patient was free of convulsive seizures. Ketamine infusion was stopped, and electroencephalogram (EEG) showed no seizure activities. Her level of consciousness progressively improved over next 36 h. She was weaned off the ventilator and extubated.

Case 2

A 30-year-old lady (35 kg), known case of chronic kidney disease grade V, on regular maintenance hemodialysis, was admitted to ICU following desaturation during hemodialysis. She was intubated and was on mechanical ventilatory support. On 4th day of ICU admission, she developed convulsive seizures that did not respond to midazolam bolus and phenytoin loading. She was started on midazolam infusion up to 18 mg/h. Phenytoin, sodium valproate, levetiracetam and clobazam were started as maintenance anti-epileptic agents at maximum therapeutic dose. Convulsive seizures persisted even after 24 h of midazolam infusion. Except for elevated creatinine level (320 μmol/L), other laboratory investigation reports were normal. Computed tomography of head and magnetic resonance imaging of brain did not reveal any abnormalities. In the mean time, she developed septic shock, due to Acinetobacter ventilator associated pneumonia (VAP), requiring noradrenaline infusion up to 0.2 μg/kg/min. Ketamine bolus 35 mg followed by 70 mg/h was administered. Frequencies of convulsive seizures decreased progressively followed by total absence of convulsive seizures over next 24 h. EEG showed no seizure activities. Midazolam was tapered and stopped. Her noradrenaline requirement decreased to 0.1 μg/kg/min. After the next 24 h free of clinical seizure, ketamine was decreased and stopped. Her level of consciousness improved, but her inotropic requirement increased, and the patient expired after 3 days due to multiorgan dysfunction following septic shock.

Discussion

Super-refractory status epilepticus is difficult to treat and is associated with significant morbidity and mortality. In patients with RSE, the efficacy of γ-aminobutyric acid (GABA) ergic agents decline as the duration of seizure increases.[9] GABA receptor trafficking causes failure of inhibitory control, increase in neuronal excitation and persistence of status epilepticus despite the presence of GABAergic agents. As seizure progresses, GABAergic drugs lose their potency and require such high doses that they produce toxic adverse effects.[10] On the other hand, number of NMDA receptors increases.[11] Ketamine was shown to be effective in controlling RSE when used early. No likely response was observed when infused at dose lower than 0.9 mg/kg/h, when introduced at least 8 days after seizure onset, or after the failure of seven or more drugs.[7]

In both of our patients, ketamine was initiated within 48 h of onset of refractory seizure at the loading dose of 1 mg/kg followed by infusion at 2 mg/kg/h. Ketamine was started when four anti-epileptic medications and midazolam infusion failed to control the seizure. Episodes of convulsive seizure progressively decreased over 24–48 h after starting ketamine infusion. Midazolam was successfully tapered in both cases, and subsequent EEG demonstrated absence of seizure. In both patients, level of consciousness improved. Both the patients required noradrenaline infusion to manage hypotension due to septic shock. Ketamine infusion helped in decreasing the requirement of noradrenaline in both cases. In first case, it was tapered and stopped, but in the second case, it was initially tapered, but later, patient deteriorated due to acinetobacter VAP and the dose had to be increased again. As demonstrated in our case, ketamine has been shown to confer hemodynamic stability in patients with shock.[6,8] Another advantage of ketamine is easy availability and low cost. Ketamine has been theoretically attributed to cause cerebral atrophy when used for prolonged period.[2] But recent retrospective study has shown it to be safe when used at dose of up to 10 mg/kg/h for up to 27 days.[7]

Conclusion

Ketamine can be a safe, effective, reaidly available and economic therapeutic agent for the management of super-refractory status epilepticus in patients with hemodynamic instability. Larger randomized studies are needed to test the safety and efficacy.

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