

CASE REPORT



Dexmedetomidine as an antiepileptic in super refractory status epilepticus

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ABSTRACT

Refractory and super-refractory status epilepticus (SRSE) is a life-threatening neurological emergency, associated with very high morbidity and mortality. Treatment should be aimed to stop seizure and to avoid cerebral damage and morbidity related to it. The term SRSE is reserved for the patients who continue to have seizures despite the use of general anesthetic agents, or for whom seizures recur when therapy is tapered or withdrawn. A variety of treatment modalities are present, almost entirely based upon open observational studies or case reports. Therapy includes anesthesia, antiepileptic drug therapy, hypothermia, ketogenic diet, other medical, immunological, and physical therapies. In our case the patient's seizure subsided after starting dexmedetomidine infusion while other antiepileptics had been completely stopped except valproic acid.

Key words: Status epilepticus; Super refractory status epilepticus; Dexmedetomidine; Neurocritical care

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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 intermittent therapy or AED fails, continuous infusion of anesthetic agents is recommended¹ Super-refractory status epilepticus (SRSE) is defined as status epilepticus that continues or recurs 24 h or more after the onset of anesthetic therapy, including those cases where status epilepticus (SE) recurs on the reduction or withdrawal of anesthesia.² Around 10-15% of patients with SE admitted to hospital will become super-refractory.² 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. Evidence supporting the management of SRSE is poor due to lack of randomized or controlled studies and is

mainly derived from case reports and retrospective studies. We report this case because a very surprising response was found after starting dexmedetomidine in this patient as seizure were effectively controlled after its use. No other case report or study has reported this effect which may support the use of dexmedetomidine in SRSE.

CASE REPORT

A 12 years old male child presented to emergency department with sudden onset of high grade, continuous fever and headache for 2 days. There were no body aches, burning micturition, rash or trauma. Family history and drug toxicity were ruled out. The neurological examination revealed no cranial nerve involvement, focal changes, or meningism. Within 24 h of onset of fever, he developed generalized tonic clonic convulsions (GTC) lasting less than 2 min, then followed by altered sensorium and frequent episodes of fits of GTC type. Emergency personnel terminated the initial seizures with intravenous

lorazepam. The patient was admitted to intensive care unit (ICU) because of frequent fits. Our ICU uses a standard protocol for evaluation and treatment of SE. So we managed the patient based on such protocol. Endotracheal intubation was passed after inj. thiopentone 5 mg/kg and inj. rocuronium 1 mg/kg with rapid sequence technique (RSI) and mechanical ventilation started, which was adjusted to maintain SpO₂ of $\geq 95\%$ and/or PaO₂ ≥ 80 mmHg and eucapnia (PCO₂ 35–40 mmHg). As the first line AEDs i.e. diazepam and phenytoin failed to achieve the clinical remission of SE, an infusion of thiopental was used to maintain the patient in an electrographic burst-suppression state, while parenteral antiepileptic medications e.g. phenytoin, valproic acid and levetiracetam, were titrated to therapeutic doses.

Extensive laboratory analyses, including virological, bacterial, fungal, immunological tests were performed on blood and CSF. Contrast enhanced CT of head revealed relatively well-defined, non-enhancing, near CSF-density, extra axial, hypodense lesion in right ambient cistern (possibility of small arachnoid cyst). A lymphocytic pleocytosis (> 5 cells/ μ l), a mildly elevated protein concentration, a normal glucose concentration was detected in CSF; other investigations were normal. Brain MRI was carried out 3 days after SE onset, and its report revealed multiple patchy areas of edema in the bilateral deep periventricular areas with meningeal thickening and pial vascular congestion suggestive of meningitis. Therefore, a presumptive diagnosis of meningo-encephalitis with SE was considered. Acyclovir was empirically added to antibiotics (ceftriaxone, vancomycin) and steroids. The tapering down of the maximal dose of intravenous anesthetic agents was tried but SE recurred. So the doses of valproic acid, and levetiracetam was again increased up to maximum limit. Then other groups of AEDs like phenobarbital, clobazam, lacosamide, topiramate, oxcarbazepine were gradually added.

The patient developed venous thrombosis in right internal jugular vein and axillary vein, probably due to prolonged infusion of thiopentone.¹⁰ It was managed with low molecular weight heparin. Thiopentone infusion was stopped and midazolam infusion was started which became ineffective in three days, so we had to start propofol infusion.

Follow-up brain MRI studies performed at 4 weeks demonstrated no abnormality. EEG revealed burst of generalized slow waves with associated spike and slow wave discharge < 2 Hz lasting for 0.5 – 1 sec continuous, followed by alternate of amplitude for 0.5 sec suggestive of generalized discharge with burst suppression. The fits were partially controlled by anesthetic drugs. Tracheotomy was done on 14th day after admission. Complications associated with antiepileptic drugs, continuous fits

and mechanical ventilation e.g. hypotension, liver failure, renal failure, coagulation abnormalities, ventilator associated pneumonia, etc. were managed accordingly. After 45 days, the patient again developed severe sepsis, which was managed as per surviving sepsis guidelines. After the patient recovered from sepsis and became hemodynamically stable, we decided a new strategy to control the patient's continuous fits and wean off the ventilator. We stopped all AEDs except inj. valproic acid 1500 mg in three divided doses and inj. lorazepam bolus if seizure occurred. Dexmedetomidine infusion was also started at 0.7 μ g/kg after the bolus of 1 μ g/kg over 20 min for sedation. After starting dexmedetomidine no seizure developed for the next 24 h. But movement disorder like choreiform and dystonic movement of limbs and face became more prominent, hence tab trihexyphenidyl 10 mg tds started and continued with dexmedetomidine infusion. As per FDA protocol we stopped dexmedetomidine after 24 h, but it had to restart again as the seizure recurred. During the next 4 days no seizure episode was noticed and the extrapyramidal symptoms also subsided. Gradually the patient improved dramatically. Except for mild confusion. Mild degree facial muscle twitches, myopathy and signs of ICU psychosis were also noticed. Physiotherapy, valproic acid and clobazam were continued. We weaned him from mechanical ventilation after 55 days and the tracheostomy tube was decannulated on 57th day. He started speaking, swallowing and walking normally and was shifted to the pediatric ward after 60 days of admission for further rehabilitation.

DISCUSSION

It is well-know that early stage established SE can be managed with benzodiazepine, phenytoin, phenobarbital or valproic acid as per severity and duration of seizures. When it becomes refractory we might have to use general anesthetic agents to control it. SRSE is the most advanced condition of SE.² Usually SRSE develops in patients who have had severe brain insult due to infection, trauma, stroke or any immunological cause.³ Sometimes, the precipitating factor is absent. Most of the cases in which fever is the precipitating factor, SRSE develops after 1-2 days of onset of fever.⁴

On the basis of the research by Lowenstein and Aldrege et al., approximately 10-15% of SE can be converted into SRSE.⁵ The aim for the management of the SRSE is to control the seizure, neuroprotection and reduction of the chances of systemic complications. Effect of conventional AEDs in SRSE is unexplained and dubious. Thiopentone, propofol, and midazolam are the most commonly used anesthetic agents in SRSE. In our case, thiopentone appeared to be most effective anesthetic agent to control seizure at a dose

which was sufficient to cause burst suppression. Krishnamurthy KB and co-workers suggest that phenobarbitone is associated with lower risk of acute failure, breakthrough seizure and withdrawal seizure than either propofol or midazolam⁶. Use of midazolam infusion in burst suppressive dose become ineffective due to tachyphylaxis.⁷ Thiopentone and midazolam infusions had had their side effects.⁸ Iyer et al. quoted high chances of propofol infusion syndrome in SRSE patients if used for more than 24 h.⁹ Gradually we added other AEDs having different mechanisms of action (phenytoin, valproic acid, levetiracetam, lacosamide and clobazam) upto the maximum allowed dose. Despite of all these AEDs and sedative infusion, patient developed seizures whenever we stopped or tapered off the dose. We also tried for ketogenic diet, immunoglobulin and hypothermia to control the seizures without success. Multiple attempts at weaning from ventilator and seizure control failed. We were not able to measure the serum AED levels due to logistic problems.

Finally, when the patient recovered from the last

episode of sepsis, all AEDs were stopped other than valproic acid to ensure the use of single antiepileptic drug at maximum dose and injection lorazepam bolus if seizure occurred. As an adjunct to dexmedetomidine weaning dexmedetomidine infusion was started for its neuroprotective effect.¹⁰⁻¹² Surprisingly, the patient's seizures subsided after 2 cycles of 24 h of dexmedetomidine infusion. The ineffectiveness of all other antiepileptic drugs remains unexplained. The role of dexmedetomidine in the control of SE and SRSE needs some controlled studies to confirm or rule out.

Till date there is no authentic study of the role of dexmedetomidine in preventing or treating SRSE. Hence, there is a need of few prospective randomized studies to confirm or rule out this incidental finding.

Conflict of interest: None declared by the authors.

Authors' contribution: All authors contributed equally in the management of the case and preparation of the manuscript

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