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The use of ketamine to treat neonatal refractory status epilepticus in a resource limited setting

B Jason Brotherton, MD, MS[1]*; Arthur Partikian, MD[2]

[1]AIC Kijabe Hospital, PO Box 20, Kijabe, Kenya

[2]Keck School of Medicine of USC & LAC+USC Medical Center, USA

***Corresponding Author(s): B Jason Brotherton**

AIC Kijabe Hospital, PO Box 20, Kijabe, Kenya

Tel: +1-901-356 2669; Email: jb042107@gmail.com

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Abbreviations: SE: Status Epilepticus; RSE: Refractory Status Epilepticus; AED: Antiepileptic Drug; HIE: Hypoxic-ischemic Encephalopathy; NBU: Newborn Unit; CPAP: Continuous Pulmonary Airway Pressure; WHO: World Health Organization; EEG: Electroencephalogram

Abstract

Seizures occur in the neonatal period more than any other time in human life. Status Epilepticus (SE), although poorly defined for neonates, is a seizure lasting more than 30 minutes, or multiple distinct episodes of seizure without a return to neurologic baseline within a 30-minute timeframe. Refractory Status Epilepticus (RSE) is the persistence of seizure activity despite administration of first and second line Antiepileptic Drugs (AED). Neonatal seizures in the resource limited setting are not uncommon and are due most frequently to Hypoxic Ischemic Encephalopathy (HIE), stroke, or infection. Resource limited settings are defined as settings where the capability to provide care for life-threatening illness is limited to basic resources, including oxygen and trained staff. These settings are often limited in their AED regimen, and in their ability to effectively monitor the cardiorespiratory status of a convulsing patient. Ketamine is a drug commonly used in resource limited settings for conscious sedation and as an anesthetic. It has been used to treat refractory seizures in adolescents and adults. This report details the second case in the literature using ketamine to successfully treat a neonate with RSE in a resource limited setting.

Introduction

Seizures occur more frequently in the neonatal period than any other period of human life [1]. There is no consensus definition for SE in neonates; the criteria for children and adults are often applied. RSE also lacks a consensus definition but is considered a rare phenomenon occurring when seizure activity continues despite maximum doses of first and second line agents.

In Sub-Saharan Africa, neonatal seizures are thought to be due most frequently to either HIE, stroke, or neonatal infections [2]. Geiling et al defined a resource limited setting as settings where the capability to provide care for life-threatening illness is limited to basic resources, including oxygen and trained staff [3]. In these resource limited settings, many facilities do not have an extensive AED regimen. Phenobarbital and phenytoin are commonly the only two AEDs available.

Through several case reports and a couple of retrospective reviews, ketamine has shown promise in the treatment of SE and RSE in both children and adults [4]. Currently, there is one

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case report in the literature detailing the use of ketamine to treat RSE in a neonate [5]. This is the second case report detailing the use of intravenous ketamine to successfully treat neonatal RSE.

Case report

Baby Boy P was born at our mission hospital to a primigravid, 24-year-old woman at 38 weeks and 5 days via emergency cesarean section for arrest of labor and fetal distress. The mother had 5 prenatal visits, but no prenatal ultrasound. Her pregnancy was uneventful, and she received no treatment for any genitourinary infections. Testing for HIV and syphilis, using VDRL, were negative. Her membranes had ruptured less than 8 hours prior to delivery.

A floppy baby was delivered with APGAR scores of 4, 5, and 5 at 1, 5, and 10 minutes of life, respectively. Positive pressure ventilation with bag-valve mask was required for resuscitation, but there was no indication for chest compressions or drug administration. After initial resuscitation and stabilization, the baby was admitted with a diagnosis of birth asphyxia.

Vital signs on admission: Axillary temperature, 35° Celsius; heart rate, 168 beats per minute; respiratory rate, 70 breaths per minute; oxygenation, 94% on 5 liters/minute of oxygen delivered via nasal CPAP. Birth weight was 3.2 kg.

Initial exam revealed a hypotonic, full-term appearing infant with acrocyanosis. Pulse rate was rapid with strong brachial and femoral pulses. No murmur was auscultated. Respiratory effort was increased with nasal flaring, subcostal retractions, and expiratory grunting. Neurologic exam revealed symmetric hypotonia of all extremities, slow palmar and plantar grasp reflexes, equivocal Babinski reflex, and absent Moro reflex. There were no abnormal pigmentation or other neurocutaneous stigmata.

Finger stick glucose was 4.1 mmol/L (72 g/dL). We gave intravenous ampicillin 50 mg/kg twice daily, gentamycin 7.5 mg/kg once daily, and dextrose 10% solution at 60 mL/kg for the first 24 hours of life.

At around 12 hours of life, repetitive focal seizures started, consisting of right upper extremity clonic movements that would secondarily generalize after 30 seconds. The clinical seizures lasted 1-2 minutes each. During these episodes, the patient became apneic resulting in desaturation to the 60s. The facility does not have cardiopulmonary monitoring so continuous evaluation for bradycardia was not possible. However, bradycardia was not appreciated on chest auscultation during the apneic events. Moreover, the hospital did not have access to EEG monitoring.

He was treated with a bolus of intravenous phenobarbital, 20 mg/kg, two minutes into his second witnessed convulsion. He required two subsequent doses of 10 mg/kg each (total of 40 mg/kg [13]); one about 30 minutes after the initial bolus, and the second almost an hour after the initial bolus. Phenytoin, 20 mg/kg intravenously, was given at around 15 hours of life, but also proved ineffective with seizure activity persisting.

Due to the focal nature of the seizures, the patient received empiric acyclovir 20 mg/kg by orogastric tube (intravenous formulation not available) every 8 hours. Despite receiving adequate doses of two anticonvulsants and empiric antimicrobial coverage, he continued to seize without a return to baseline. Neurologic exam between clinical seizures was significant for diffuse hypotonia and no response to stimulus. The patient received a dose of intravenous calcium gluconate to treat for possible hypocalcemia with no resolution of seizure activity.

Having no other anticonvulsants to treat SE in a neonate, a trial of intravenous ketamine was given at around 20 hours of life. The patient received a bolus of 2 mg/kg followed by a continuous infusion of 10 mcg/kg/min. This dosing was obtained from the only case report in the literature by Tarocco [5] and colleagues that used intravenous ketamine to successfully treat RSE in a neonate with a brain malformation.

Within 5 minutes of starting the infusion his seizures ceased, as well as the associated episodes of apnea and desaturation. He remained on the 10 mcg/kg/min infusion for 72 hours. During this time, the patient also received phenobarbital 5 mg/kg/day, the three antimicrobials, and intravenous fluids. He sustained no adverse cardiopulmonary events, nor did he display evidence of increased intracranial pressure (i.e. bulging fontanelle, posturing, vomiting).

After 72 hours, the infusion was stopped, and he was monitored clinically as he slowly became more alert. Over the next 24-48 hours he began to have age appropriate movements and was weaned from CPAP on hospital day 4.

Given the severity of his presentation, no lumbar puncture was performed. Additionally, the facility, like others in a similar setting, does not have the capability to reliably perform blood or CSF cultures. Therefore, the patient was empirically treated for bacterial meningitis with 14 days of antibiotics and HSV encephalitis with 21 days of acyclovir.

By day 10 of life, he remained seizure free and displayed no focal neurologic deficits. At this time, the maintenance phenobarbital was discontinued with no return of seizure activity. He was cup-fed until day 14 of life when he started to breastfeed.

At discharge, on hospital day 23, he was breastfeeding, gaining weight, and had had no further seizure activity. His neurologic exam was dramatically improved with a strong sucking reflex, improved tone, spontaneous limb movements, symmetric Moro, and bilateral Galant reflexes.

He returned to the clinic for follow up at one week, four weeks and six weeks after discharge. The patient remains seizure free but will require close follow-up to assess for his neurologic development after the birth asphyxia and RSE.

Discussion

The developing neonatal brain is more hyperexcitable and thus susceptible to seizure activity for several reasons. Insults, such as global ischemia and hypoxia increase the risk of seizures. Animal studies have shown that as seizures continue, inhibitory $GABA_A$ receptors become less responsive to medications and even internalize. Additionally, there is an increase in the number of excitatory, glutaminergic NMDA receptors on the cell surface. This phenomenon has a direct effect on neural cells in generating paroxysmal depolarization shifts and prolonging seizures [6].

Phenobarbital and phenytoin are the first line agents recommended by the WHO for the treatment of neonatal seizures in resource limited settings and are on their list of essential medicines [7,8]. In this context, once recommended doses have been administered, potential underlying causes of seizures (i.e. hypoglycemia, infections, electrolyte abnormalities) are addressed. Additionally, many of these facilities do not possess cardio-

pulmonary monitoring equipment, mechanical ventilators, or EEG. The lack of equipment can limit the use of other effective medications such as benzodiazepines if available. The absence of EEG monitoring can negatively impact the timely diagnosis and treatment of neonatal seizures and their distinction from non-epileptic movements or other paroxysmal phenomena.

This case highlights the common practices in treating seizures and SE in resource limited settings. It also describes the use of another medication found on the WHO Essential Medicines list that is commonly used as an anesthetic [8].

Ketamine, a glutaminergic NMDA receptor antagonist, has been described in a few retrospective studies and case reports for the treatment of SE or RSE, but these cases focused mainly on adult and pediatric patients. Ketamine has been proposed as a potential AED due to its ability to block the hyperexcitatory NMDA receptors and its acceptable side effect profile [9].

The largest retrospective review by Gaspard et. al [10] evaluated the records and EEGs of 58 patients experiencing RSE at 10 different medical centers over a 13-year period. These patients were aged 7 months to 74 years and comprised 60 distinct RSE episodes. Of the 60 episodes, 57% were controlled with the administration of ketamine. Their overall findings suggested ketamine may be safe and effective for the treatment of RSE but should be studied further.

A systemic review by Zeiler [11] and colleagues searched the literature for the use of NMDA antagonists to treat RSE. They found 23 studies, all using ketamine, that met their inclusion/exclusion criteria. Of the adult patients, 56.5 % had complete electrographic seizure cessation. The pediatric response rate was 63.5%. Only two adult patients had arrhythmias related to ketamine. In the pediatric patients, nine experienced hypersalivation and one had elevated liver enzymes.

In addition to the known side effects of laryngospasm, risk for apnea, and sympathomimetic effect such as tachycardia, there have been areas of concern for the use of ketamine in neonates based upon animal models. Several animal studies have shown that ketamine induced onset of neuronal apoptosis, as well as the alteration of neurogenesis during fetal development of mice and rhesus macaque [14,15]. The exact pathophysiologic mechanisms are under investigation, but a leading opinion is the antagonistic effect of ketamine on the NMDA receptors inhibits the crucial role of glutamate signaling that naturally results in synaptic development and neuronal survival [16]. More studies are clearly needed in this regard.

Conclusion

Seizures and SE are not uncommon in the neonatal period, especially in the resource limited setting. Progression of SE to RSE further complicates treatment when medications and cardiopulmonary support are limited. This report highlights the second case of the use of ketamine to treat neonatal RSE. Much of the information regarding ketamine as an AED in humans is from case reports and a few retrospective studies. However, its use appears to be promising with minimal short-term adverse effects, but more studies are warranted to determine long-term outcomes. The first randomized control trial evaluating ketamine's effectiveness is underway [12]. This is encouraging for those caring for SE in the resource limited context where AEDs are limited, and monitoring capability is sparse.

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