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Paradoxical Response to Midazolam in an Extremely Premature Neonate with Refractory Seizures

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Abstract

Background: Neonatal seizures present a complex challenge in clinical management, particularly in extremely premature infants. Benzodiazepines, such as midazolam, are commonly used in seizure management, but rare paradoxical responses leading to seizure exacerbation have been documented.

Patient: We report a case of refractory status epilepticus in an extremely premature neonate born at 25 weeks and three days of gestation, with comorbidities including hyaline membrane disease, germinal matrix hemorrhages, and *E. coli* bacteremia with meningitis and ventriculitis. Initial treatment with phenobarbital, Levetiracetam, and fosphenytoin was ineffective, prompting the initiation of a midazolam infusion. Although initial boluses transiently suppressed seizures, midazolam paradoxically worsened them over time, with seizures becoming more prolonged and occurring in back-to-back clusters. This effect was confirmed via continuous video EEG, emphasizing the likely proconvulsant response to midazolam in this patient.

Results: Electroencephalographic monitoring revealed significant alterations in seizure patterns following midazolam initiation, illustrating its potential to exacerbate seizures in certain neonatal cases.

Conclusion: This case highlights the need for vigilance when managing neonatal seizures, particularly in extremely premature infants. Clinicians should remain aware of the potential for paradoxical responses to midazolam and consider alternative therapeutic strategies promptly to achieve effective seizure control and minimize harm.

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Background

Neonatal seizures can be a significant challenge in neonatal intensive care, especially among extremely premature infants, where the delicate balance of neurological integrity is paramount [1]. Management of these seizures often necessitates pharmacological intervention to mitigate the risk of neurological injury. Traditionally, phenobarbital and phenytoin/fosphenytoin have been the cornerstone medications despite their efficacy ranging from only 50% to 80% [1,2]. While barbiturates and benzodiazepines are commonly employed as first-line anticonvulsants, their use in immature brains may paradoxically lead to neuronal excitation [3].

Midazolam, a short-acting benzodiazepine, has been utilized since the early 1990s for the treatment of status epilepticus in children [4]. However, its role in neonatal seizures remains poorly defined, with limited data on its efficacy and long-term neurological outcomes in this population [3]. Moreover, emerging evidence suggests that midazolam may exacerbate seizure activity in some instances, highlighting the complexity of pharmacological management in neonatal seizures [5-7].

Herein, we present a clinical case of an infant born at 25 weeks gestational age who developed seizures within the first 48 hours of life. Despite the administration of midazolam for refractory seizures, the infant experienced worsening seizure activity, prompting a reassessment of pharmacological management strategies. This case underscores the importance of further research to elucidate optimal treatment strategies and minimize adverse outcomes in neonatal seizures.

Description of the Case

The infant, born vaginally at 25 weeks and three days of gestation to a gravida 1, para 1 mother who had received appropriate prenatal care, presented following preterm labor. At delivery, the Apgar scores were 4 and 7 at 1 and 5 minutes, respectively. Positive pressure ventilation was

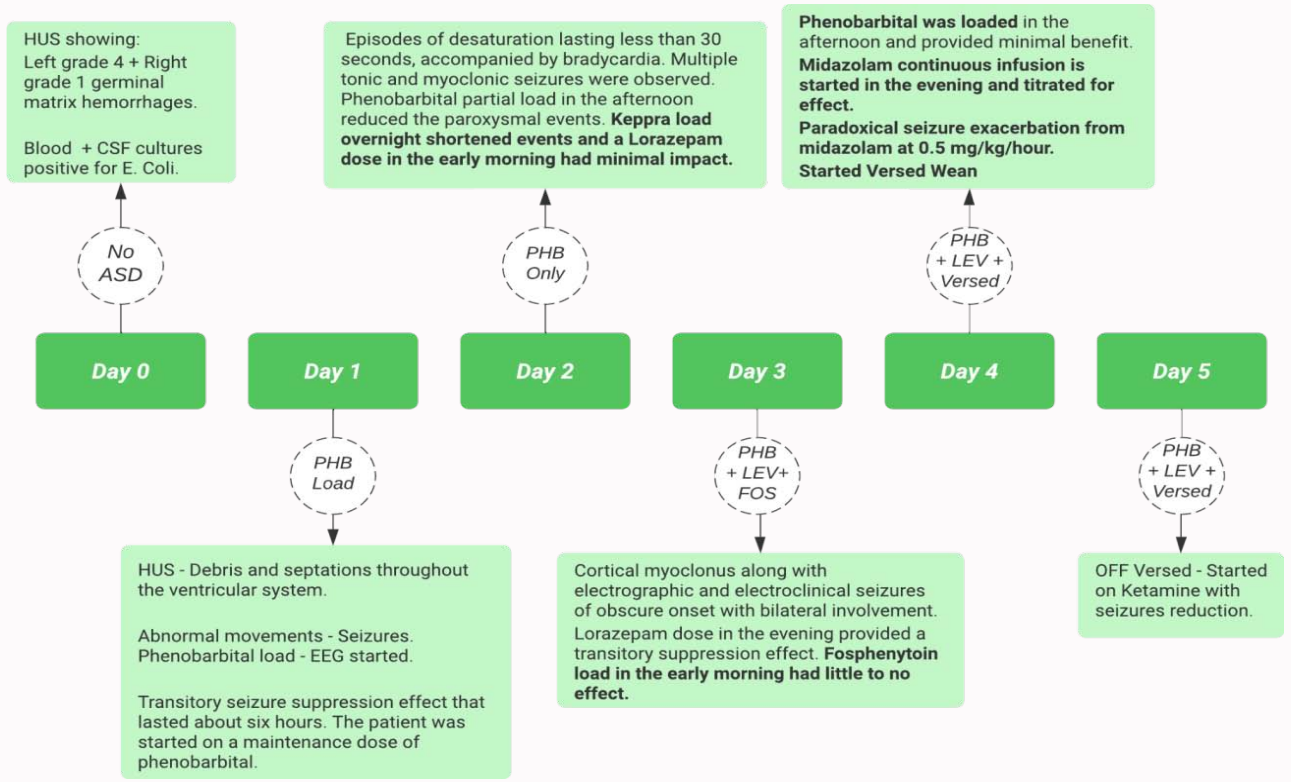

Figure 1: Diagram of the patient's hospital course, with Day 0 marking the onset of observed seizure-like activity.

initiated, and the infant was subsequently transferred to the NICU. She was diagnosed with hyaline membrane disease and managed with intubation, surfactant therapy, budesonide, and caffeine. Figure 1 illustrates a diagram of the patient's hospital course, with Day 0 marking the onset of observed seizure-like activity.

On day three of life, a head ultrasound (HUS) was performed, revealing a grade four on the left side and a grade one on the right-side germinal matrix hemorrhages. On the eleventh day of life, given a concern for sepsis, a blood culture was collected and returned positive for the growth of *Escherichia coli* (*E. coli*); CSF studies were also concerning for meningitis, so she was started on meningitis dosing of antibiotics. On the thirteenth day of life, another HUS was conducted, which showed that the germinal matrix hemorrhages had continued along with increased debris and septations throughout the ventricular system. The patient experienced episodes of oxygen desaturation as low as 60%, accompanied by bradycardia with a heart rate of 40 beats per minute, and at times, upper limb stiffening was noted. Neurology was consulted, leading to the initiation of video electroencephalography (EEG). Overnight, she experienced several seizures with myoclonic, tonic, and clonic elements, with the longest seizure lasting five minutes, both electrographic and electroclinical, of obscure onset with bilateral involvement. A phenobarbital loading dose was administered, which led to a transitory resolution of the seizure that lasted about six hours. The patient was started on a maintenance dose of phenobarbital. The next day, she had seizures characterized by desaturations lasting less than 30 seconds, accompanied by bradycardia. Also, multiple tonic and myoclonic seizures were observed. Phenobarbital partial load in the afternoon reduced the seizures. Levetiracetam loading dose overnight shortened the duration of the seizures, and a Lorazepam dose in the following early morning had minimal impact. She was started on a maintenance Levetiracetam dose but, throughout the day, continued to have myoclonic seizures along with electrographic and electroclinical seizures of obscure onset with bilateral upper and lower extremities involvement; a lorazepam dose in the evening provided a transitory suppression effect. Fosphenytoin load in the early morning had little to no effect. Given the persistence of the seizures, phenobarbital was loaded in the afternoon and provided minimal benefit.

Midazolam continuous infusion was started in the evening and titrated for effect. Within a few hours of Midazolam initiation, the seizures' electrographic appearance became much more defined, with rhythmic theta activity in the right, left, or mid-central areas with evolution in frequency and location - now involving the neighboring regions (Figure 2 illustrates a right central and midline seizure after Midazolam). Seizures also became more prolonged, ranging between one to ten minutes. With each bolus of midazolam, the seizures initially responded favorably but then recurred and, at times, were repetitive. At this time, all the seizures were electrographic only. This led to the initiation of ketamine infusion and weaning of midazolam drip. Seizures responded well to Ketamine drip and remained controlled. She went home from the neonatal intensive care unit at 45 weeks and two days corrected gestational age.

Discussion

Neonatal seizures can pose significant challenges in clinical management, particularly in extremely premature infants [8]. Pharmacotherapy plays a crucial role in seizure control, with benzodiazepines commonly used as initial agents [2] followed by either phenobarbital or fosphenytoin. However, our case highlights a previously known rare but critical phenomenon: the paradoxical exacerbation of seizures following midazolam administration. This paradoxical effect, characterized by intensified and prolonged

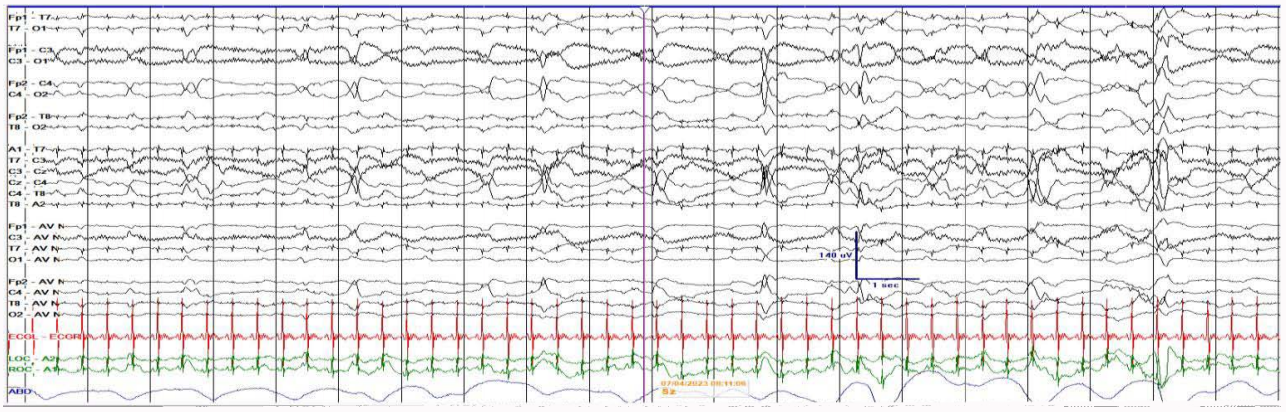

Figure 2: Right central and midline seizure on Midazolam infusion.

seizures, is consistent with prior reports in the literature, though it has not been frequently reported. Montenegro et al. described four newborns, all preterm and 2 of them being 26 weeks and 27 weeks gestational age, like our patient who developed seizures as a result of midazolam administration [9]. Gupta et al. also reported two preterm neonates at 33-week and 34-week gestational age who developed myoclonic seizures a few seconds after the bolus administration of intravenous midazolam [7]. In 1991, Anker et al. were already describing premature neonates with a gestational age below 32 weeks having decreased heart rate and arterial blood pressure directly following an intravenous bolus injection of 0.2mg/kg midazolam, as well as some involuntary epileptiform movements lasting for 15-30 seconds [10].

Myoclonic seizures seem to be the prevailing seizure type in those reports [7,11], which is different from our patient's presentation; though she initially had tonic, clonic, and myoclonic seizures, once on Midazolam drip, she only had subclinical seizures. Zaw et al. described three cases of midazolam-induced, myoclonic-like abnormal movements in term infants, and flumazenil was used to reverse it in one case [11].

Several non-epileptic adverse events have also been described following midazolam administration [5,6,9,12]; Paroxysmal automatic movements were described by Ishizaki et al. as drum-beating and pedaling motions in three full-term neonates following intravenous bolus injections (0.1-0.3 mg/kg/dose) or drip infusions (0.2 mg/kg/h) of midazolam used for sedation, these movements did not have an electrographic correlate [13].

The mechanisms underlying such paradoxical responses remain unclear but may involve alterations in GABAergic signaling and excitatory neurotransmission. Midazolam acts by binding to gamma-aminobutyric acid A (GABA-A) receptors. There is a limited synthesis of GABA in the newborn cortex. It is probable that an imbalance of the GABA subunit (agonist) and benzodiazepine subunit (modulators) with longer half-lives (6.25 h) of midazolam creates an excitatory influence, thereby causing seizure-like activity [6].

Conclusion

This case underscores the importance of vigilance in the pharmacological management of neonatal seizures, particularly in extremely premature infants. Clinicians should be aware of the potential for paradoxical exacerbation of seizures by midazolam, which highlights the need for a nuanced approach to pharmacological intervention in this vulnerable patient population. Hence, prompt recognition and alternative therapeutic strategies may be necessary to ensure optimal seizure control and mitigate potential harm.

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