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Case Series of Midazolam-Induced Seizures-Like Activity in Five Neonates

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Abstract

An intravenous administration of midazolam may result in seizure-like activity or movement. This report describes five neonates who developed seizure-like movements after intravenous midazolam injection. The patients presented between 2019 and 2022. The abnormal movements occurred shortly after intravenous bolus administration of midazolam. None of our patients experienced seizure-like movements after receiving midazolam infusions. The seizure-like movements were aborted either spontaneously or by antiseizure medications. Also, we did not observe any seizure recurrence in any of the infants during the later stages of their treatment. Since this adverse effect might be related to the speed of the bolus administration, intravenous midazolam must be given as a slow bolus over 2-3 minutes followed by a slow flush of normal saline. To prevent midazolam's potential adverse effect on newborns, neonatal caregivers must be aware of it.

***Keywords*:** Midazolam; Injection, intravenous, Seizures; Infant, Newborn; Hypnotics and Sedatives.

Introduction

Midazolam is a short-acting benzodiazepine with a rapid onset of action and a short half-life.[1] It is used frequently in the neonatal intensive care unit (NICU) for the treatment of seizures,

procedural sedation, and sedation in ventilated infants.[2] The effects of midazolam are produced by binding to neurotransmitter receptors activated by gamma-aminobutyric acid (GABA). GABA-A receptors are responsible for most of the central nervous system's inhibitory neurotransmission. Benzodiazepines act on GABA-A receptors by binding to a specific site.[3] Since infants may experience moderate to severe pain, agitation, and irritability in the NICU, using sedation to keep them comfortable during painful medical interventions is useful.[4] Midazolam has several serious known adverse reactions e.g., respiratory depression, and hypotension.[3] Other side effects known as paradoxical reactions to midazolam are, e.g., hyperexcitability, restlessness and myoclonic jerks. Seizures or seizure-like activity have been reported following rapid bolus administration of midazolam.[1,5,6] Seizure-like activity or myoclonic jerks are rare side effects of midazolam. We describe five cases of seizure-like abnormal movements in neonates intending to raise awareness among neonatologists and other neonatal health practitioners of this rare adverse reaction to midazolam. Parental consent was obtained for this publication.

Settings

The neonates described in this study were admitted to a level III-IV NICU located within an academic center, with perinatal services and an average birth rate of 5,000 births per year. This NICU also is a referral unit for complex neonatal cases from other secondary or peripheral hospitals. Approximately 450-500 neonates of varying gestational ages are admitted per year to this NICU. Midazolam at a dose of 0.1mg/kg/dose is sometimes used for procedural sedation and the management of agitation for mechanically ventilated neonates. Before administration, midazolam is diluted in normal saline by adding 5 mg of midazolam to 4 ml of normal saline to produce a 1 mg:1 ml dilution. It is normally administered by the bedside nurse intravenously as a slow bolus, followed by a slow 2 ml flush of normal saline.

Case 1:

The first case study is a newborn male infant born at 37 weeks of gestation, weighing 2540 g, born to non-consanguineous parents, and a G4P3 mother by caesarian section. The mother had late latent syphilis, treated with Penicillin G. The infant was shifted to the NICU for a workup to rule out congenital syphilis. He was admitted in stable condition in room air and the physical

examination was unremarkable. The syphilis screening serology was positive, but the rapid plasma reagent (RPR) was negative. On day 2 of life, midazolam 0.1mg/kg was given for procedural sedation before a lumber puncture (LP). The dose was given intravenously through a peripheral cannula, as a slow bolus, followed by a 2 ml flush of normal saline pushed slowly, before the procedure. The infant had stable vital signs (heart rate 133/minute, respiratory rate 55/minute, oxygen saturation 99%, mean blood pressure [MBP] 59 mmHg). During the LP, he had clonic jerks of the upper limbs, so the procedure was aborted. He received a loading dose of intravenous levetiracetam 20mg/kg because the abnormal movements continued for more than five minutes. However, the abnormal movements continued after the levetiracetam loading, so a half-loading dose of levetiracetam 10 mg/kg was given after which the abnormal movements stopped. The vital signs after the event were heart rate 128/minute, respiratory rate 34/minute, oxygen saturation 97%, and MBP 63 mmHg. A septic workup was performed, and since it was negative, he received cefotaxime, and acyclovir for 72 hours. Treponema Pallidum hemagglutination was positive with a titer of 640. Syphilis IgM was <0.90 (negative). The brain ultrasound was normal. A routine electroencephalogram (EEG) was done after the episode and showed no epileptic discharges. The baby received penicillin-G for 10 days. The seizure-like movement did not recur, and at follow-up at six months of age, no seizures or neurodevelopment deficits were documented.

Case 2:

The second case study is a newborn male neonate, late preterm at $36^{4/7}$ weeks of gestational age, born to a G7P3A3 mother with gestational diabetes, on metformin. He was born via normal vaginal delivery with Apgar scores of 6 and 9 at 1 and 5 minutes respectively, and a birth weight of 3320 g. He was admitted to the NICU with respiratory distress, presumed neonatal sepsis, hypoglycemia, and right shoulder dystocia. He was placed on a high-flow nasal cannula (HFNC) for 48 hours and then weaned to room air. Antibiotics were commenced for suspected neonatal sepsis. On the 10^{th} day of life, a LP was planned, and the infant received IV midazolam 0.1mg/Kg for procedural sedation. The dose was given through a peripheral cannula as a slow bolus followed by a flush of 2 ml of normal saline. The vital signs were stable (heart rate 155/minute, respiratory rate 34/minute, oxygen saturation 98%, MBP 71 mmHg). While doing the LP, he immediately developed clonic movements of his 4 limbs that lasted for two minutes,

associated with apnea, and grimacing. The vital signs after the event (heart rate 200/minute, respiratory rate 28/minute, oxygen saturation 88%; during the LP, the infant was on room air, but after the procedure, he required a high-flow nasal cannula, MBP 66 mmHg). Antibiotics were upgraded to meningitis doses, and acyclovir was started. The EEG was normal with no epileptic discharges. The herpes simplex virus (HSV) polymerase chain reaction (PCR), and Varicella zoster PCR were negative, so acyclovir was stopped. The neonate received antibiotics for 7 days, and he was discharged on day 16 of life. He had no recurrence of abnormal movements. A follow-up in the clinic at five months of age showed normal growth and development, and the neurological examination was normal.

Case 3:

The third care study is an extreme male preterm neonate born at 25 weeks gestational age to a G4P3 mother who received dexamethasone, and antibiotics. The infant was born via cesarean section because of a breech presentation and cord prolapse; he had a birthweight of 800 g, and Apgar scores 8 and 9 at 1 and 5 minutes, respectively. He was intubated at birth and given one dose of endotracheal surfactant. His NICU course was complicated with stage II necrotizing enterocolitis at the post-menstrual age of 34 weeks. The blood culture was reported positive for methicillin-resistant staphylococcus aureus (MRSA). On day 69 of life, an LP was arranged to evaluate for meningitis. He was given midazolam intravenously (0.1 mg/kg) for procedural sedation before the LP. The dose was given through a peripheral cannula as a slow bolus, followed by a flush of 2 ml of normal saline. The vital signs before the procedure were: heart rate 129/minute, respiratory rate 55/minute, oxygen saturation 100%, and MBP 50mmHg. Shortly after the administration of the dose, the infant developed clonic seizure-like movements of the four limbs, lasting for two minutes. He was loaded with levetiracetam. His vital signs after the abnormal movements were heart rate 174/minute, respiratory rate 49/minute, oxygen saturation 96%, and MBP 45mmHg. The abnormal movements did not recur, and the repeated blood culture was negative. A cerebrospinal fluid (CSF) bacterial culture as well as a viral PCR were negative. The brain ultrasound and magnetic resonance imaging (MRI) were normal. He received antibiotics for 14 days. The Levetiracetam was discontinued one week before discharge at the post-menstrual age of 36 weeks. At the last post-discharge follow-up at 19 months of age,

he had no history of recurrence of abnormal movements. He showed appropriate development for his corrected age.

Case 4:

The fourth case study is an extreme preterm male neonate born at 24 weeks gestational age, with a birth weight of 800 g. The parents were non-consanguineous, and the mother was a G6P3L3A2, with a history of gestational diabetes mellitus (GDM) on diet. He was born via a breech vaginal delivery. His Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. He was electively intubated after birth, and he received two doses of endotracheal surfactant therapy. He was extubated on day 12 of life and given non-invasive positive-pressure ventilation. However, he experienced an extubation failure within 24 hours and was reintubated on day 13 of life. On day 16 of life, he was given a dose of intravenous midazolam (0.1mg/Kg) for sedation, since he was agitated on the ventilator despite being on a good dose of morphine infusion. The dose was given through a PICC line as a slow bolus, followed by a flush of 2 ml of normal saline over two minutes. The vital signs were stable (heart rate 145/minute, respiratory rate 45/minute, oxygen saturation 99%, and MBP 33mmHg). Within seconds of the midazolam dose, he developed seizure-like clonic abnormal movements involving all 4 limbs, associated with bradycardia. He received a loading dose of phenobarbitone (20 mg/Kg). The vital signs after the abnormal movement were stable (heart rate 135/minute, respiratory rate 35/minute, oxygen saturation 98%, and MBP 35mmHg). Subsequently, he had no further abnormal movements. The septic work-up revealed a positive tracheal aspirate culture for Acinetobacter *baumannii*, which was treated with appropriate antibiotics. His EEG and brain ultrasound were normal, and there was no seizure recurrence. He received a midazolam infusion of 10 microgram/Kg/hour for 72 hours without any complications. He was discharged home on nasogastric feeding due to oro-motor weakness and oral feeding difficulties.

Case 5:

The fifth case study is an extreme preterm male born at 25 weeks, twin II, conceived via in-vitro-fertilization (IVF), born by an emergency cesarean section to a 53-year-old mother. His Apgar scores were 8 and 9, at 1 and 5 minutes, respectively, and his birth weight was 790 g. He was intubated at birth and received a total of two doses of endotracheal surfactant therapy. On day 10

of life, he was desaturating, and fighting against the high-frequency oscillatory mechanical ventilation despite being on a good dose of morphine infusion. A dose of intravenous midazolam (0.1mg/Kg) was given for sedation through a PICC line, as a slow bolus, followed by a slow flush of 2 ml of normal saline. `Within a few seconds of administration of midazolam, he developed clonic seizure-like movements. The vital signs before the abnormal movement were stable (heart rate 125/minute, respiratory rate 35/minute, oxygen saturation 98%, and MBP 38mmHg). He was loaded with phenobarbitone (20 mg/kg), and the seizure-like movements resolved within 2 minutes of the loading. His vital signs after the event were also stable (heart rate 165/minute, respiratory rate 53/minute, oxygen saturation 92%, and MBP 38mmHg). There was no seizure recurrence, and he was discharged home at the post-conceptional age of 36 weeks.

Discussion:

Midazolam is a commonly used sedative in neonatal intensive care units.[1,7] In addition to its sedative-hypnotic actions, midazolam also is used to treat refractory neonatal seizures and less frequently for anesthesia.[3] Respiratory depression and hypotension are serious well-known adverse reactions to midazolam. Paradoxical reactions to midazolam, e.g., hyperexcitability, agitation, and seizures, also have been described.[5,6]

In this study, we present five neonates who developed seizure-like movements within seconds to minutes after the intravenous bolus administration of midazolam. It is worth mentioning that the cases occurred over four years (2019-2022): patient #1 had the episode in January 2021, patient # 2 in May 2022, patient #3 in August 2019, patient # 4 in April 2022 and patient # 5 in July 2022. No other causes of seizures could be identified by appropriate investigations performed in the five patients. We believe that the seizure-like events were induced by intravenous midazolam bolus administration due to the temporal association between the commencement of the intravenous midazolam bolus and the onset of seizure-like movements in all cases. Furthermore, there were no other etiologies could be identified in any of the five patients. The seizure-like movements responded to anti-seizure medications, a finding that was previously described.[5] In addition, there were no further events documented on long-term follow-up in any of the five patients. Moreover, the Uppsala Monitoring Centre causality assessment (WHO-UMC) was

checked for every patient and showed probable for all patients except patient # 3, who had a certain causality term. When the Naranjo Probability Scale was used, four patients were probable on the scale except for patient # 3, who had definitive scoring.[7]

The distinction between seizure and seizure-like activity is challenging since both may manifest as motor activity that involves the upper and lower extremities. A seizure is a temporary disturbance in brain activity that usually is caused by increased electrical activity due to an imbalance between excitatory and inhibitory inputs. On the other hand, seizure-like activity is abnormal motor or behavioural activities that resemble seizure. In addition, these seizure-like activities are not caused by the same abnormal brain electrical activity.[8] A normal EEG doesn't exclude seizure especially if the EEG was not done during the abnormal movements. Even though some of our patients did receive anti-seizure medications to help abort the events, it is still difficult to ascertain with certainty whether the events were actual seizures or seizure-like activities.

Also, midazolam-induced seizure-like movements were described in term and preterm neonates. For example, Montenegro MA et al. (2001) reported on four preterm neonates (34, 30, 27, and 26 weeks gestation) who developed similar clonic seizures-like movements after the administration of IV midazolam bolus for sedation.[9] The authors ruled out possible etiologies that could be associated with neonatal seizure, including hypoglycemia, hypocalcemia, infection, polycythemia, CNS malformations, and hemorrhagic or ischemic lesions.[9] In addition, Ozcan et al. (2015) described a similar adverse reaction in a preterm neonate.[10] More recently, Gupta MK et al. (2018), described two preterm infants (34 and 33 weeks gestation) who developed myoclonic seizure-like movements following IV midazolam administration.[11] In both studies, appropriate investigations were done to rule out any possible seizure etiologies.

Moreover, this adverse reaction does not only affect preterm neonates because Zaw et al. (2012) reported on three term neonates who developed myoclonic-like abnormal movements after receiving IV midazolam. Of interest, one of them was treated with flumazenil.[12]

An explanation of why an anti-seizure medication may induce seizures has not yet been delineated. However, the rapid administration of midazolam could be the cause of the occurrence of seizure-like movements, since this adverse effect only occurred after intravenous bolus injection and not during continuous infusion. Van den Anker et al. (1992) proposed that since midazolam decreases arterial blood pressure and heart rate in preterm infants, a reduced cerebral blood flow may be the underlying pathogenesis.[6] However, this hypothesis is a speculation and a possible direct impact on the CNS cannot be excluded. Another explanation proposed by Ishizaki Y. et al. (2011) is that the abnormal movements induced by the midazolam have no epileptic origin, but rather related to a brainstem release phenomenon induced by midazolam.[13] Since it is difficult to determine why an ant-seizure medication may induce seizures, more basic medical science research is needed to establish the cause of such a phenomenon.

Neonatal formularies recommend that midazolam boluses be administered slowly. The recommended duration of administration varies from 2-3 to 10 minutes.[14-17] In our NICU, IV midazolam is administered after dilution with normal saline to 1mg:1ml. The dose is administered by the bedside nurse, supposedly by slow bolus as per the formulary recommendations. However, no specific duration was specified. Thus, individual variation probably existed with respect to the rate of administration. The exact duration of the administration of the dose in each of the cases could not be determined since it was not routinely documented in the electronic records. However, after observing these cases and reviewing the literature, we emphasized the practice of injecting IV midazolam bolus slowly over 2-3 minutes duration, followed by a slow flush of 2 ml of normal saline over 2 minutes. Since then, we have not observed any similar cases. Therefore, we believe that our five patients received a rapid administration of the IV midazolam bolus, which played an important role in the occurrence of this rare adverse event.

Conclusion

Although uncommon, seizures-like movements can be a side effect of midazolam intravenous injection. Although its underlying pathogenesis is not well determined, it may be related to the rapid administration of injection midazolam. Intravenous midazolam is recommended to be administered with caution by slow IV injection over 2-3 minutes followed by a slow flush of

normal saline, and rapid injection must be avoided. Caution should also be exercised in preterm infants, especially the extreme preterm. Neonatologists and NICU nurses should be aware of this rare adverse event in order to prevent it.

Authors' contribution:

HAM proposed the idea of the project. HS made the initial draft of the article. Subsequently, all authors contributed equally to the final version article. All authors approved the final version of the manuscript.

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