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

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13

14 **Abstract**

15 An intravenous administration of midazolam may result in seizure-like activity or movement.

16 This report describes five neonates who developed seizure-like movements after intravenous
17 midazolam injection. The patients presented between 2019 and 2022. The abnormal movements

18 occurred shortly after intravenous bolus administration of midazolam. None of our patients

19 experienced seizure-like movements after receiving midazolam infusions. The seizure-like

20 movements were aborted either spontaneously or by antiseizure medications. Also, we did not

21 observe any seizure recurrence in any of the infants during the later stages of their treatment.

22 Since this adverse effect might be related to the speed of the bolus administration, intravenous

23 midazolam must be given as a slow bolus over 2-3 minutes followed by a slow flush of normal

24 saline. To prevent midazolam's potential adverse effect on newborns, neonatal caregivers must

25 be aware of it.

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

27 Sedatives.

28

29 **Introduction**

30 Midazolam is a short-acting benzodiazepine with a rapid onset of action and a short half-life.¹ It

31 is used frequently in the neonatal intensive care unit (NICU) for the treatment of seizures,

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

46

47 *Settings*

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

57

58 *Case 1:*

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

63 examination was unremarkable. The syphilis screening serology was positive, but the rapid
64 plasma reagent (RPR) was negative. On day 2 of life, midazolam 0.1mg/kg was given for
65 procedural sedation before a lumbar puncture (LP). The dose was given intravenously through a
66 peripheral cannula, as a slow bolus, followed by a 2 ml flush of normal saline pushed slowly,
67 before the procedure. The infant had stable vital signs (heart rate 133/minute, respiratory rate
68 55/minute, oxygen saturation 99%, mean blood pressure [MBP] 59 mmHg). During the LP, he
69 had clonic jerks of the upper limbs, so the procedure was aborted. He received a loading dose of
70 intravenous levetiracetam 20mg/kg because the abnormal movements continued for more than
71 five minutes. However, the abnormal movements continued after the levetiracetam loading, so a
72 half-loading dose of levetiracetam 10 mg/kg was given after which the abnormal movements
73 stopped. The vital signs after the event were heart rate 128/minute, respiratory rate 34/minute,
74 oxygen saturation 97%, and MBP 63 mmHg. A septic workup was performed, and since it was
75 negative, he received cefotaxime, and acyclovir for 72 hours. *Treponema Pallidum*
76 hemagglutination was positive with a titer of 640. Syphilis IgM was <0.90 (negative). The brain
77 ultrasound was normal. A routine electroencephalogram (EEG) was done after the episode and
78 showed no epileptic discharges. The baby received penicillin-G for 10 days. The seizure-like
79 movement did not recur, and at follow-up at six months of age, no seizures or neurodevelopment
80 deficits were documented.

81

82 *Case 2:*

83 The second case study is a newborn male neonate, late preterm at 36^{4/7} weeks of gestational age,
84 born to a G7P3A3 mother with gestational diabetes, on metformin. He was born via normal
85 vaginal delivery with Apgar scores of 6 and 9 at 1 and 5 minutes respectively, and a birth weight
86 of 3320 g. He was admitted to the NICU with respiratory distress, presumed neonatal sepsis,
87 hypoglycemia, and right shoulder dystocia. He was placed on a high-flow nasal cannula (HFNC)
88 for 48 hours and then weaned to room air. Antibiotics were commenced for suspected neonatal
89 sepsis. On the 10th day of life, a LP was planned, and the infant received IV midazolam
90 0.1mg/Kg for procedural sedation. The dose was given through a peripheral cannula as a slow
91 bolus followed by a flush of 2 ml of normal saline. The vital signs were stable (heart rate
92 155/minute, respiratory rate 34/minute, oxygen saturation 98%, MBP 71 mmHg). While doing
93 the LP, he immediately developed clonic movements of his 4 limbs that lasted for two minutes,

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

103

104 *Case 3:*

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

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

126

127 *Case 4:*

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

149

150 *Case 5:*

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

155 of life, he was desaturating, and fighting against the high-frequency oscillatory mechanical
156 ventilation despite being on a good dose of morphine infusion. A dose of intravenous midazolam
157 (0.1mg/Kg) was given for sedation through a PICC line, as a slow bolus, followed by a slow
158 flush of 2 ml of normal saline. Within a few seconds of administration of midazolam, he
159 developed clonic seizure-like movements. The vital signs before the abnormal movement were
160 stable (heart rate 125/minute, respiratory rate 35/minute, oxygen saturation 98%, and MBP
161 38mmHg). He was loaded with phenobarbitone (20 mg/kg), and the seizure-like movements
162 resolved within 2 minutes of the loading. His vital signs after the event were also stable (heart
163 rate 165/minute, respiratory rate 53/minute, oxygen saturation 92%, and MBP 38mmHg). There
164 was no seizure recurrence, and he was discharged home at the post-conceptual age of 36
165 weeks.

166

167 **Discussion:**

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

173

174 In this study, we present five neonates who developed seizure-like movements within seconds to
175 minutes after the intravenous bolus administration of midazolam. It is worth mentioning that the
176 cases occurred over four years (2019-2022): patient #1 had the episode in January 2021, patient #
177 2 in May 2022, patient #3 in August 2019, patient # 4 in April 2022 and patient # 5 in July 2022.
178 No other causes of seizures could be identified by appropriate investigations performed in the
179 five patients. We believe that the seizure-like events were induced by intravenous midazolam
180 bolus administration due to the temporal association between the commencement of the
181 intravenous midazolam bolus and the onset of seizure-like movements in all cases. Furthermore,
182 there were no other etiologies could be identified in any of the five patients. The seizure-like
183 movements responded to anti-seizure medications, a finding that was previously described.⁵ In
184 addition, there were no further events documented on long-term follow-up in any of the five
185 patients. Moreover, the Uppsala Monitoring Centre causality assessment (WHO-UMC) was

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

189
190 The distinction between seizure and seizure-like activity is challenging since both may manifest
191 as motor activity that involves the upper and lower extremities. A seizure is a temporary
192 disturbance in brain activity that usually is caused by increased electrical activity due to an
193 imbalance between excitatory and inhibitory inputs. On the other hand, seizure-like activity is
194 abnormal motor or behavioural activities that resemble seizure. In addition, these seizure-like
195 activities are not caused by the same abnormal brain electrical activity.⁸ A normal EEG doesn't
196 exclude seizure especially if the EEG was not done during the abnormal movements. Even
197 though some of our patients did receive anti-seizure medications to help abort the events, it is
198 still difficult to ascertain with certainty whether the events were actual seizures or seizure-like
199 activities.

200
201 Also, midazolam-induced seizure-like movements were described in term and preterm neonates.
202 For example, Montenegro MA et al. (2001) reported on four preterm neonates (34, 30, 27, and
203 26 weeks gestation) who developed similar clonic seizures-like movements after the
204 administration of IV midazolam bolus for sedation.⁹ The authors ruled out possible etiologies
205 that could be associated with neonatal seizure, including hypoglycemia, hypocalcemia, infection,
206 polycythemia, CNS malformations, and hemorrhagic or ischemic lesions.⁹ In addition, Ozcan et
207 al. (2015) described a similar adverse reaction in a preterm neonate.¹⁰ More recently, Gupta MK
208 et al. (2018), described two preterm infants (34 and 33 weeks gestation) who developed
209 myoclonic seizure-like movements following IV midazolam administration.¹¹ In both studies,
210 appropriate investigations were done to rule out any possible seizure etiologies.

211
212 Moreover, this adverse reaction does not only affect preterm neonates because Zaw et al. (2012)
213 reported on three term neonates who developed myoclonic-like abnormal movements after
214 receiving IV midazolam. Of interest, one of them was treated with flumazenil.¹²

215

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

227

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

241

242 **Conclusion**

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

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

250

251 **Authors' contribution:**

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

255

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259

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