

Delayed Onset Seizures after Inguinal Herniotomy in a Premature Infant: a Case Report

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Summary: Nag DS, Samaddar DP, Mahanty PR, Sengupta A – Delayed Onset Seizures after Inguinal Herniotomy in a Premature Infant: a Case Report.

We report a case of a premature neonate born at 34 weeks and operated at 6 weeks of age developing unexplained seizures 10 hours after the end of surgery under single shot caudal epidural analgesia with bupivacaine and lidocaine combined with general anesthesia.

Keywords: Seizures; Infant, Premature; Anesthesia, Caudal; Postoperative Period.

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INTRODUCTION

A 3.5-kilogram male infant was taken up for an elective left inguinal herniotomy at 6 weeks of age. The premature infant was born at 34 weeks of gestation by an emergency Caesarean Section due to intrauterine fetal distress. Following birth, he developed neonatal sepsis and was managed for ten days in the nursery. Since then the infant had an uneventful period and was subsequently cleared from a pre-anesthetic outpatient and pediatric clinics for an elective inguinal herniotomy at 40 weeks of post-conceptual age. In keeping with the recent trends of preoperative investigation protocols, only a hemoglobin level¹ was done which reflected mild anemia (9.7 g.dL⁻¹).

Preoperatively, a written explained consent was obtained from the child's mother for the surgery, anesthesia and permission for using the observations for publication and advancement of medical knowledge and education with the understanding that the patient's identity will remain confidential.

Anesthesia was induced with halothane, nitrous oxide and oxygen. Tracheal intubation was done with a 3.0 mm uncuffed tube after securing intravenous access. Anesthesia was maintained with atracurium and fentanyl along with halothane, nitrous oxide and oxygen. Post intubation, the infant was positioned in lateral position and caudal epidural was

administered with 1.8 mL of bupivacaine 0.25% and 1.7 mL of lidocaine 1% (Total volume of 3.5 mL, and total dose of 4.5 mg bupivacaine and 17 mg lidocaine). The surgery was associated with an estimated blood loss of about 5 mL. Recovery was uneventful following reversal of neuromuscular blockers. Trachea was extubated and the infant was awake and pain free at the end of surgery. An intraoperative blood sugar testing by glucometer revealed a blood sugar level of 163 mg.dL⁻¹. While 85 mL of Lactated Ringer's solution was infused intra-operatively, the infant was postoperatively maintained on 14 mL per hour of normal saline until accepting oral feeding. The infant received intravenous ceftriaxone 125 mg 12 hourly and an oral dose of 50 mg acetaminophen every 8 hours. The first dose of oral acetaminophen was administered four hours after recovery from the effect of anesthesia.

Postoperative monitoring was done in the Pediatric Intensive Care Unit (PICU) by skilled nursing staff and monitors capable of both storage and retrieval of information. Continuous pulse oxymetry, electrocardiogram (ECG) and impedance pneumography showed no episode of apnea, hypoxia (oxygen saturation below 90%) or ECG abnormality in the postoperative period. The infant voided urine spontaneously within two hours and tolerated oral feeding four hours after recovery from anesthesia.

Ten hours after the end of surgery and twelve hours after administration of caudal epidural analgesia, the child appeared excessively jittery with increased tone in all limbs and progressed to frank tonic generalized seizures. Saturation rapidly dropped to 70-80%. Oxygen was supplemented by face mask; empirically 5 mL of calcium gluconate diluted to 5% was administered intravenously and intravenous phenobarbitone 70 mg was given over 20 minutes after blood sugar by glucometer was found to be 124 mg.dL⁻¹. No episode of apnea, defined as cessation of respiration for at least 15 seconds, desaturation to less than 90%, or bradycardia was noted before the onset of seizures. The axillary temperature ranged from 98.4°F to 99°F (36.7°C to 37.2°C) during the stay in PICU up to the onset of seizures.

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When seizures did not subside, intravenous phenobarbitone 70 mg was repeated over 20 minutes followed by 70 mg of phenytoin intravenously over 20 minutes. Intramuscularly 0.5 mL of 50% magnesium sulphate was given empirically. When seizures persisted despite these efforts, midazolam infusion was started at $1.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and seizures started resolving when midazolam was increased to $2 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Sodium valproate was also administered at 50 mg 12 hourly through a nasogastric tube.

The infant required mechanical ventilation due to persistent hypoxia refractory to supplemental oxygen.

After the onset of seizures blood sugar, serum calcium, magnesium and electrolytes, along with prothrombin time (PT), platelet count, fibrinogen level, septic screen and metabolic screen and an arterial blood gas (ABG) were measured. Since fontanels were not bulging, lumbar puncture was done and cerebrospinal fluid (CSF) was sent for examination. Clinical examination of the chest and cardiovascular system and a chest roentgenogram failed to reveal additional findings.

All investigations including serum calcium, magnesium, electrolytes, blood sugar, transaminases and CSF were normal, except for a raised PT with an international normalized ratio (INR) of 2.1. The hemoglobin had also dropped from $9.7 \text{ g}\cdot\text{dL}^{-1}$ to $6.9 \text{ g}\cdot\text{dL}^{-1}$.

The infant was started on Vitamin K 2 mg and given a transfusion of 50 mL of packed red blood cells (PRBCs). An activated partial thromboplastin time (PTT) was subsequently performed and was 35.6 seconds (Control of 18.0 seconds). The infant received then 50 mL of fresh frozen plasma (FFP).

A subsequent detailed history revealed that the infant had received prophylactic vitamin K injection at birth, was exclusively breast fed and the mother had a negative TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes) screen during her antenatal period.

Over the following two days midazolam drip was slowly tapered and the infant was successfully weaned after 56 hours on mechanical ventilation.

Due to the unavailability of cranial ultrasound in the PICU, a cranial computed tomography (CT) scan could only be performed 5 days after the onset of convulsions, once the infant was weaned from mechanical ventilation and doing well. The CT scan with and without contrast did not reveal any abnormality. A subsequent electroencephalogram (EEG) also failed to demonstrate any significant and specific changes. The infant's PT/INR and PTT also became normal with therapy.

Subsequent magnetic resonance imaging (MRI) was not done considering the safety issues involved in subjecting the premature infant to possible need for sedation or exposure to anesthetics to prevent movement in a cold noisy environment where monitoring can be challenging.

The infant was doing well and was discharged on oral valproate 50 mg 12 hourly and multivitamins with normal findings on subsequent follow-up over the last 6 months.

DISCUSSION

Inguinal herniotomy is one of the commonest procedures performed in pediatric surgery. In keeping with present con-

servative guidelines², only a hemoglobin level was done. Although exclusive regional anesthesia (spinal or caudal) has been preferred to general anesthesia in ex-premature infants, in absence of large prospective controlled studies, we did not want to subject our patient to a potentially stressful awake procedure³. Due to the reported incidence of postoperative apnea in preterm infants up to at least 44-46 weeks of post-conceptual age⁴, close monitoring was planned for the infant in the postoperative period in a PICU.

Despite the popularity of sevoflurane for induction in pediatrics, halothane still remains as one of the preferred alternatives for induction in neonates and infants⁵. Bupivacaine and lidocaine combination was used for caudal analgesia for rapid onset and prolonged postoperative pain relief. Oral acetaminophen was used for post operative analgesia for having a safe therapeutic profile⁶. Supplementary analgesia with opioids was not necessary for the following 10 hours, possibly due to the analgesic effect of caudal bupivacaine.

The reported incidence of postoperative convulsions is between 3.1:10,000 and 0.005-12.6% in high risk groups like post carotid endarterectomy, craniotomy or open heart surgery⁷.

A less accentuated biphasic shape of the plasma concentration curve has been reported in infants after caudal bupivacaine in infants while the time (T_{max}) to reach peak plasma concentration (C_{max}) is around 30 minutes⁸. Premature and term neonates are predisposed to the adverse effects of lidocaine due to the delayed maturation of drug metabolizing enzymes⁹. Prolonged elimination half life and decreased protein binding also predisposes the premature neonates to the adverse effects of lidocaine. Estimation of plasma local anesthetic concentrations probably would have been more informative, but could not be done due to lack of facilities. Nevertheless, there are no published reports of convulsions due to local anesthetics 12 hours after a single bolus injection.

Although there are several case reports of convulsions on bolus doses of local anesthetics¹⁰, systemic toxicity of local anesthetics causing convulsions 12 hours after a single shot of caudal bupivacaine or lidocaine seem unlikely.

Infants who are 55 weeks postconceptual age and younger are generally at great risk of postoperative apnea, and anemia further increases the risk¹¹. Therefore continuous postoperative monitoring was planned for the case. Despite postoperative monitoring with pulse oxymetry, continuous ECG and impedance pneumography with recording and retrieval facility, it failed to detect any apneic episode. MRI could have thrown more light on the cause of convulsion, but it was not planned due to its safety concerns.

Routine metabolic screening which included renal and liver functions, calcium, phosphate, magnesium, glucose, acid-base status, ammonia, lactate, pyruvate, paired CSF and plasma glucose, and urine for reducing substance and amino acids were all within normal limits for our laboratory and age. This, combined with a normal growth and development even 6 months after discharge, ruled out metabolic causes, including inborn errors of metabolism and mitochondrial diseases, as a possible cause of seizures.

Infective causes of convulsions were also not considered due to a negative septic screen and CSF examination. A normal EEG also made epilepsy syndromes improbable.

After exclusion of metabolic causes, a drop in hemoglobin level associated with increased PT and PTT, normal platelet and fibrinogen levels, sudden convulsions led us to a clinical suspicion of intracranial hemorrhage¹². Prematurity, exclusive breast feeding, neonatal sepsis and antibiotic therapy, all indicated towards late onset vitamin K deficiency in newborn leading to acute intracranial hemorrhage¹³.

Although cranial ultrasound is the first imaging modality when intracranial hemorrhage is suspected, several studies have shown computed tomography (CT) imaging to be superior over ultrasound for detecting of intracranial hemorrhage¹⁴. Lumbar puncture is advised if CT finding is normal, inconclusive, or not consistent with the clinical presentation. In our case, the CSF examination had already excluded a sub-arachnoid bleed.

While relying on imaging facility, the fact that all imaging modalities have low negative predictive value (NPV) should be taken into consideration. Irrespective of the modality of imaging, Blankenberg et al.¹⁵ have reported NPVs of 53% and 59% at 2-month and at 2-year follow-up, respectively.

In this case, despite strong clinical suspicion of vitamin K deficient bleeding (VKDB) imaging modalities failed to substantiate the diagnosis. Only a hemoglobin level was done as routine preoperative testing as per the advocated guidelines¹⁶ as less than 30% hematocrit has been found to be the predisposing factor for postanesthetic apnea in premature infants¹⁷.

Although it is reported that a neither normal coagulation profile nor a negative history of "easy bruising" reliably predicts surgical bleeding¹⁸, our experience with this case suggests the need for a preoperative PT and activated PTT to exclude vitamin K deficient bleeding in infants and neonate susceptible to it. Neonates and infants with prematurity, inadequate Vitamin K prophylaxis after birth, (especially in exclusively breast fed), antibiotic therapy, chronic diarrhea, cystic fibrosis, biliary atresia, celiac disease, alpha 1-antitrypsin deficiency and abetalipoproteinemia are most vulnerable to VKDB. The fact that the risk of intracranial hemorrhage in late hemorrhagic disease of newborn is reported to be 50-80%¹⁹ makes preoperative exclusion even more relevant.

REFERÊNCIAS / REFERENCES

1. Coté CJ – Preoperative preparation and premedication. *Br J Anesth*, 1999;83(1):16-28.
2. Steward DJ – Screening tests before surgery in children. *Can J Anesth*, 1991;38:693-695.
3. William JM, Stoddart PA, Williams SA et al. – Post-operative recovery after inguinal herniotomy in ex-premature infants: comparison between sevoflurane and spinal anesthesia. *Br J Anesth*, 2001;86: 366-371.
4. Welborn LG – Postoperative apnea in the former preterm infant: a review. *Paed Anesth*, 1992;2:37-44.
5. O'Brien K, Robinson DN, Morton NS – Induction and emergence in infants less than 60 weeks post-conceptual age :comparison of thiopental, halothane, sevoflurane and desflurane. *Br JAnesth*, 1998;80:456-459.
6. Korpela R, Meretoga OA – Comment. *Anesthesiology*, 2000;92(4): 1202-1203.
7. Akavipat P, Rungreungvanich M, Lekprasert V et al. – The Thai Anesthesia Incidents Study (THAI Study) of perioperative convulsion. *J Med Assoc Thai*, 2005;88(Suppl 7):S106-S112.
8. Eyres RL, Bishop W, Oppenheim RC et al. – Plasma bupivacaine concentrations in children during caudal epidural analgesia. *Anesth Intens Care*, 1983;11:20-22.
9. Kearns GL, Abdel-Rahman SM, Alander SW et al. – Developmental pharmacology-Drug disposition, action and therapy in infants and children. *N Engl J Med*, 2003;349:1157-1167.
10. Matsumiya N, Dohi S, Takahashi H et al. – Cardiovascular collapse in an infant after caudal anesthesia with a lidocaine-epinephrine solution. *Anesth Analg*, 1986;65:1074-1076.
11. Coté CJ, Zaslavsky A, Downes JJ et al. – Postoperative apnea in former preterm infants after inguinal herniorrhaphy. A combined analysis. *Anesthesiology*, 1995;82:809-822.
12. Pichler E, Pichler L – The neonatal coagulation system and the vitamin K deficiency bleeding - a mini review. *Wien Med Wochenschr*, 2008;158(13-14):385-395.
13. Sutor AH, Dages N, Niederhoff H – Late form of vitamin K deficiency bleeding in Germany *Klin Padiatr*, 1995;207:89-97.
14. Blankenberg FG, Norbash AM, Lane B et al. – Neonatal intracranial ischemia and hemorrhage: diagnosis with US, CT, and MR imaging. *Radiology*, 1996;199:253-259.
15. Blankenberg FG, Loh NN, Bracci P et al. – Sonography, CT, and MR imaging: a prospective comparison of neonates with suspected intracranial ischemia and hemorrhage. *AJNR Am J Neuroradiol*, 2000;21(1):213-218.
16. O'Conner ME, Drasner K – Preoperative laboratory testing of children undergoing elective surgery. *Anesth Analg*, 1990;70:176-180.
17. Welborn LG, Hannallah RS, Luban NLC et al. –Anemia and postoperative apnea in former preterm infants. *Anesthesiology*, 1991;74:1003-1006.
18. Borzotta AP, Keeling MM – Value of the preoperative history as an indicator of hemostatic disorders. *Ann Surg*, 1984;200:648-652.
19. Flood VH, Galderisi FC, Lowas SR et al. Haemorrhagic disease of the newborn despite vitamin K prophylaxis at birth. *Paediatr Blood Cancer*, 2008;50:1075-1077.