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Therapeutic Hypothermia Treatment for an Infant with Hypoxic-Ischemic Encephalopathy and Gastroschisis: A Case Report

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Abstract

Gastroschisis is a congenital, typically isolated, full-thickness abdominal wall defect in which the abdominal contents, usually only the small intestine, remain outside the abdominal cavity. It is commonly detected on fetal ultrasonography, and has generally excellent survival and outcomes, though these can be decreased in cases of complicated gastroschisis. We present the case of a female infant with a prenatal diagnosis of gastroschisis who required a prolonged and complex resuscitation after delivery. In addition to her gastroschisis, she presented with a history and physical examination consistent with severe hypoxic-ischemic encephalopathy and was treated with therapeutic hypothermia (TH) without further compromise to her bowel. In addition, careful consideration of neuroprotection, fluid status, bowel viability, and hemodynamics were undertaken in her care. She was discharged home on full enteral feeds, with only mild language and gross motor delays at 6 months of age. To our knowledge, there are no reports in the literature of the use of TH in the setting of unrepaired simple gastroschisis.

Keywords
- gastroschisis
- hypoxic-ischemic encephalopathy
- therapeutic hypothermia
- neonatal intensive care unit
- pediatric surgery

Case Presentation

A female neonate was born at $37^{3/7}$ weeks' gestation with a prenatal diagnosis of gastroschisis to a 23-year-old primigravida with negative prenatal screening laboratory results. The mother had presented to the hospital approximately 4 hours prior to delivery with contractions and with suspected preterm prolonged rupture of membranes, with leaking of fluid for the past 5 days, confirmed with low amniotic fluid index on bedside ultrasound. She was found to be dilated to 5 cm, with repetitive variable decelerations noted on fetal heart rate (HR) tracing. When examined by the delivering obstetrician, a terminal deceleration was noted and mother was taken to the operating room (OR) for emergent primary C-section under general anesthesia. No antenatal steroids, latency antibiotics, or magnesium was administered prior to delivery.

The neonate was born with a birth weight of 2,040 g (1.6th percentile) and was small for gestational age. Thick meconium was noted on uterine incision. She was delivered apneic

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and with low tone. Delayed cord clamping was not done. She was brought to the warmer and the exposed intestines were placed in a sterile plastic bowel bag. She was apneic and no HR was detected, so positive pressure ventilation was initiated. She was intubated by 3.5 minutes of life but no color change was noted on the carbon dioxide detector. She was reintubated successfully at 8 minutes of life. HR during this time had increased to 60 beats per minute (bpm), then improved to the 80s. At 10 minutes of life, the HR was lost and chest compressions were started. Endotracheal tube (ETT) was suctioned twice with no improvement in HR. Epinephrine was given via the ETT at 14 minutes of life, with improvement in HR to 70s. Chest compressions were paused at this time but resumed after HR fell below 60. A second dose of epinephrine was given via the ETT at 22 minutes of life. A low-lying umbilical venous catheter (UVC) was placed at 26 minute of life and a third dose of epinephrine was given via the UVC at 27 minutes of life. A 25-mL normal saline bolus was also given. By 30 minutes of life, HR was in the 120s and compressions were stopped. Apgar scores were 0, 0, 0, and 3. The exposed intestines in the bag were intermittently moistened with sterile saline during this time. UVC became dislodged during adjustment and was removed. The stabilized neonate was moved to a transporter at 48 minutes of life and transported to our Level IV neonatal intensive care unit (NICU) in the attached quaternary care children's hospital.

On admission, the neonate was noted to be unresponsive, with absent spontaneous movements, flaccid tone, and no suck, gag, or Moro reflexes present. No dysmorphic features were noted and the neonate had a normal cardiac examination. The exposed intestines in the bag appeared pink and healthy. A peripherally inserted central catheter (PICC) line and peripheral arterial line were placed. The neonate was placed on high-frequency oscillatory ventilation. Umbilical cord blood gases were not obtained; however, neonate's first arterial blood gas was 7.08/28/81/8/−20, with lactate of 17.85. Given the extensive and prolonged resuscitation in the delivery room requiring intubation, chest compression and epinephrine, low Apgar scores, and Sarnat examination consistent with severe hypoxic-ischemic encephalopathy (HIE) (e.g., hypotonia, no gag or suck reflex, nonreactive pupils), therapeutic hypothermia (TH) was initiated per unit protocol and continued for 72 hours. The decision to proceed with cooling in the setting of unrepaired gastroschisis was based on time-sensitive benefits of cooling on neurodevelopmental outcomes, and the feasibility of delayed closure in gastroschisis patients. The neonate was started on a morphine infusion for sedation and pain control. Per our unit's protocol, video electroencephalogram was placed and she was noted to have seizures on monitoring. She received two phenobarbital loads and one of levetiracetam and started on maintenance phenobarbital.

Pediatric surgery was immediately notified of the neonate's delivery and a silo was placed at bedside shortly after admission to the NICU. The bowel was noted to be matted but without frank ischemia or perforations. Although mother was group B *Streptococcus* negative, broad-spectrum empiric antibiotic coverage with ampicillin and cefepime were started immediately, given mother's prolonged rupture of membranes without latency antibiotics.

After this period of initial stabilization in the NICU, the neonate had an acute pulmonary hypertensive crisis overnight, and was started on inhaled nitric oxide (iNO) and a sildenafil infusion. An echocardiogram showed severe right ventricular hypertension, mild right atrial and right ventricular dilation, and moderately diminished right ventricular function. The neonate also developed hemodynamic instability on day of life (DOL) 1, requiring an epinephrine infusion and then hydrocortisone, which was started on DOL 3. Total fluids were tightly controlled to a maximum of 110 mL/kg/d in the first day of life, managed with the input of the surgeons and NICU hemodynamic team to maintain a balance between adequate fluid volume resuscitation and preventing bowel edema in preparation for serial reductions in the silo. In addition to her maintenance intravenous fluid infusions, the neonate received fresh frozen plasma, cryoprecipitate, and platelets to correct coagulopathy in the first day of life.

Neonate was subsequently rewarmed on DOL 3 after completing the cooling protocol. No further seizures were noted for the remainder of cooling or rewarming. Her pulmonary hypertension improved and she was weaned off sildenafil on DOL 2, then off iNO on DOL 3. Her systemic hypotension also resolved, and she was weaned off her epinephrine infusion on DOL 4 and off hydrocortisone on DOL 6. Serial reduction was delayed until DOL 2 and continued until DOL 7. She was taken to the OR for closure of the abdominal wall defect on DOL 8 without complication. Ampicillin and cefepime were continued for 7 days. The blood culture collected on admission remained negative. The morphine drip that had been started shortly after admission had been continued for her serial reductions and postoperative recovery, and she was weaned off without complication or evidence of withdrawal on DOL 13.

After a period of awaiting return of bowel function, the neonate's Salem Sump was removed on DOL 30 and trophic feeds were initiated the next day. Feeding volumes were advanced by 10 mL/kg/d without complications and the infant reached full feeds on DOL 45 (15 days later), mostly via gavage.

The infant had remained intubated throughout cooling, serial bowel reduction, and gastroschisis closure in the postoperative period. She was extubated successfully to high-flow nasal cannula on DOL 33 following a course of periextubation dexamethasone, then was weaned to room air on DOL 39.

The infant continued to make steady improvements throughout her admission. Subsequent echocardiograms showed improvement and resolution of pulmonary hypertension and cardiac function. Her PICC remained in place for 43 days without complications or infection. She maintained appropriate growth velocity, improving her z-score at birth of −2.16 to −1.29 at discharge, with an average daily weight gain of 28 g/d during her last week of admission. She did not demonstrate feeding intolerance indicative of stricture or other complications of gastroschisis. By discharge, she was stable in room air and without seizures on phenobarbital.

She did, however, refer bilaterally on her discharge hearing screen. She continued to work on her oral feeding skills until discharge, taking 40 to 50% of her feeding volume PO and was discharged home with a nasogastric tube in place. One week later, at one of her follow-up appointments, her nasogastric tube was discontinued. Her developmental evaluation, scored using the Bayley Scales of Infant and Toddler Development-Fourth Edition (Bayley-4), at her first high-risk infant follow-up visit at 6 months of age, showed mild receptive and expressive language delay and mild gross motor delay. She was found to have silent aspiration on a modified barium swallow study at 8 months of age and a nasogastric tube was placed shortly after at her gastroenterology follow-up appointment. She continues to receive speech and physical therapy.

Discussion

Gastroschisis is one of the most common congenital abdominal wall defects, with an incidence of approximately 3 to 4 per 10,000 live births and rising.[1] Prenatal detection rates are greater than 90%[1] in developed counties and allow for timely preparation for delivery at a center equipped to handle complex neonatal surgery.[2] Gastroschisis is typically an isolated defect and survival is excellent, exceeding 90%; however, morbidity is more common in cases of complex gastroschisis,[3] defined as gastroschisis complicated by associated findings of atresia, necrosis, or perforation.[4]

In HIE, hypoxia resulting from decreased placental perfusion and delivery of oxygen and glucose leads to a decrease in fetal cardiac output, which in turn reduces cerebral perfusion.[5] Decreased cerebral blood flow can subsequently lead to HIE, for which TH has emerged as the standard of care to mitigate this neurologic insult.[6] Further, HIE is associated with changes in intestinal blood flow velocities. Sakhuja et al found that celiac and mesenteric artery flow remained low during TH and rose significantly after rewarming, which may suggest that cooling has a protective effect against reperfusion injury of the gastrointestinal system.[7] We report here the first documented case in which TH was used in an infant with a prenatal diagnosis of gastroschisis who was also diagnosed with HIE following a prenatal hypoxic event and extensive resuscitation in the delivery room.

Once the infant was stabilized and transferred to the NICU, a multidisciplinary team worked quickly to minimize injury and maintain perfusion to both the intestine, and more importantly, the brain. Multiple studies have shown that the optimal window to start TH for infant with HIE is within 6 hours of birth.[8] Our patient was started on active cooling immediately on arrival to the NICU. Protection of the bowel and preserving bowel viability was also a consideration. The infant had already been placed in a plastic drawstring bag in the delivery room and a silo was placed by the surgery team at the bedside very soon after arrival to the NICU. Careful management of fluids and hemodynamics to maintain appropriate cerebral perfusion,[9] prevent cerebral edema,[5] and improve the outcomes in gastroschisis management was a priority in the first day of life.[10] Fluid intake of 60 to 70 mL/kg/d is appropriate for an infant undergoing TH,[11] as fluid restriction has not been found to reduce the composite outcome of death or neurodevelopmental disability and was associated with higher rates of shock and acute kidney injury,[12] but should be individualized for each patient.[11] For our patient, we maintained a total fluid goal of 100 to 110 mL/kg/d in the first day of life, with close monitoring of urine output and electrolytes, and with use of bedside targeted neonatal echocardiogram to guide selection of the most appropriate pressor to maintain goal blood pressure, in this case, epinephrine.

Primary closure, when possible, is performed in the first few hours following birth[13] but surgical management of gastroschisis can vary depending on associated bowel findings and comorbidities. If primary closure is not possible or safe (for whatever reason), delayed closure after staged reduction with silastic silo can be used. Once the silo is placed, gradual reduction of the intestine is performed once or twice per day as tolerated, with the goal, in our institution of closure in 3 to 4 days. Given the instability of our patient and concurrent TH, primary closure was not pursued and the surgical team opted for a silo, which can be placed relatively quickly at bedside. Even then, initial reduction was delayed by a day due to continued hypotension and clinical instability. Our patient had her abdominal closure on DOL 8. Consensus is lacking in terms of optimal timing of gastroschisis closure, but one study by Gurien et al showed that outcomes for primary versus staged closure are equivocal,[14] and a meta-analysis by Kunz et al showed that staged repair with silo was associated with improved outcomes in terms of ventilator days, time to first feed, and infection rates.[15] While one study by Hawkins et al showed there was no significant difference in mortality or time to tolerance of full enteral feeds if reduction time with a silo was limited to less than 5 days as compared with immediate closure,[16] this did not seem to impact her outcomes with regard to bowel viability, success of gastroschisis closure, or ability to achieve and tolerate enteral feeds.

This infant had multiple reasons for concern for bowel viability and function: a prolonged resuscitation, hypotension, delayed closure, and possibly from TH itself. The amount and area of exposed bowel in gastroschisis already predisposes the infant to increased risk for hypothermia and fluid losses, which increases morbidity.[17] We attempt to mitigate this risk by immediately covering the bowel in plastic wrap and warm saline in the delivery room then promptly closing or placing the intestines in a silo. Whole-body cooling decreases the central temperature of the infant to 33 to 35°C, which could also potentially affect bowel perfusion and viability. Some studies have also suggested that there is an increased risk of infection and delayed surgical wound healing with intraoperative hypothermia, which could possibly be extrapolated to TH as well.[18] Our patient did not have any infectious complications or wound healing.

Conclusion

This case illustrates that the neonatal intestine and brain are remarkably plastic and resilient despite early insults to both

organs. It is feasible to treat an infant with hypoxic insult with cooling per protocol without deviation or modification so as to optimize their chance for good neurodevelopmental outcome without sustaining significant morbidity to the intestine. Cooling may have even helped with bowel recovery by preventing reperfusion injury. Further, the necessary delay in closure of gastroschisis in this instance does not appear to have affected the infant's outcomes despite any potential compromise to the intestine.

Conflict of Interest
None declared.

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