PedsCases Podcast Scripts

This is a text version of a podcast from Pedscases.com on "**Neuroprotection from acute brain injury in preterm infants- CPS podcast.**" These podcasts are designed to give medical students an overview of key topics in pediatrics. The audio versions are accessible on iTunes or at www.pedcases.com/podcasts.

Neuroprotection from acute brain injury in preterm infants- CPS podcast

Developed by Dr. Larissa Shapka, Dr. Michelle Ryan, Dr. Thierry Lacaze-Masmonteil, and Dr, Korshid Mohammad for PedsCases.com.
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Introduction:

Hello, my name is Larissa Shapka and I'm a paediatric resident at the University of Toronto. This podcast was produced by PedsCases and the Canadian Paediatric Society (CPS). The goal of this podcast is to summarize the CPS Position Statement titled "Neuroprotection from acute brain injury in preterm infants." The podcast was developed with Drs. Michelle Ryan, Thierry Lacaze-Masmonteil and Khorshid Mohammad, the principal authors of the statement. Dr. Ryan is a Neonatologist at the Montreal Children's Hospital in Montreal, and Dr. Lacaze-Masmonteil is a Neonatologist at the University of Calgary. Dr. Mohammad is a Neonatologist, NICU lead of the Neuro-Critical Care Program in Calgary, and chair of the Canadian Neonatal Brain Health Working Group at the University of Calgary. For additional information and to view the complete CPS statement, please visit www.cps.ca. The script for this podcast can be viewed at www.pedcases.com.

Acute brain injury is a common morbidity associated with extreme prematurity and can have serious sequelae. Currently, strategies for reducing the incidence of acute brain injuries in preterm infants vary between centres. Thus the Canadian Pediatric Society produced a statement that summarizes the evidence on neuroprotection strategies and aims to provide clinicians with a standardized approach to this key topic to optimize clinical care. Please note that the discussion in the podcast focuses on infants born at or less than 32+6 weeks gestation unless otherwise stated.

Objectives:

By the end of this podcast, listeners should be able to:

1. Identify preterm neonates at risk of acute brain injury.
2. Highlight mechanisms leading to acute brain injury in these neonates.
3. Identify the critical time period for incurring brain injury.
4. Describe neuroprotection strategies in the antenatal, perinatal, and postnatal periods.

We will begin with a clinical case to provide some context, and return to it throughout this podcast to apply what we learn. Let's get started.

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Case:

You are working in the Neonatal Intensive Care Unit (NICU) at a tertiary care centre. The obstetrical team has asked you to see Ms. Browne, who has preterm premature rupture of membranes (PPROM). She is at 26+0 weeks gestation and they would like you provide counseling about prematurity. Ms. Browne is very worried, and has expressed concern about the likelihood of her baby developing a brain injury and having poor developmental outcomes. As you prepare to go see her, you realize you need a bit of a refresher on this topic!

Background and pathophysiology:

In Canada, approximately 21% of infants born at or before 32+6 weeks gestational age will have findings consistent with parenchymal lesions or intraventricular hemorrhage on brain ultrasound. These injuries can occur due to ischemia and reperfusion which causes infarction and/or hemorrhage. Why is it that these preterm infants have such a high incidence of acute brain injury? Extremely preterm infants have delicate cerebral vessels and immature autoregulatory systems, which means that fluctuations in blood flow can lead to ischemia and hemorrhage.

Two of the most common forms of acquired brain injuries in preterm infants are germinal matrix hemorrhage- intraventricular hemorrhage, more commonly referred to simply as intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL). In preterm infants, intraventricular hemorrhages usually arise from the germinal matrix located next to the lateral ventricles. There is wide variation in the clinical presentation of IVH, and some infants can initially appear asymptomatic. Diagnosis is made based on imaging findings, and IVH are classified into 4 grades of severity based on the extent of bleeding, ventricular dilation, and involvement of brain parenchyma. The other common preterm brain injury is periventricular leukomalacia (PVL), which refers to necrosis of white matter in a characteristic distribution on neuroimaging. The etiology is often ischemia, however PVL may also arise from infection or cytokine exposure. PVL can be classified into cystic and non-cystic forms. Depending on severity, both IVH and PVL are associated with poor motor and cognitive outcomes, seizures, and visual disturbances. Specifically, they can both cause cerebral palsy in surviving preterm infants.

The first 72 hours after birth are considered the highest risk time for brain injury to occur. Known as the “critical window,” this is a time period in which neuroprotective interventions can change outcomes. We will review strategies that can be used in this critical window, as well as those applicable to antenatal, perinatal, and postnatal periods as a whole.

Antenatal strategies:

Interventions prior to birth that protect against acute brain injury include the administration of maternal corticosteroids and magnesium sulphate, as well as timely and preventive treatment for chorioamnionitis. Let’s review each of these in more detail.

Maternal corticosteroids:

Corticosteroids have been shown to promote the maturation of organs in animal models. Specifically, they seem to promote vasoconstriction in the brain, which may protect against

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injury. However it is not just the administration of maternal corticosteroids that matters, but also the timing of when they are given. Studies have shown that for optimal fetal neuroprotective effect, corticosteroids should be given between 48 hours to 7 days before delivery.

Based on this, the Canadian Paediatric Society recommends that women routinely receive a course of corticosteroids if they are at 33+6 weeks gestational age or less and are expected to deliver within 7 days (ie if the infant is expected to be born at a gestational age of 34+6 weeks or less). Outside of this time frame, maternal corticosteroids should be considered on a case-by-case basis when delivery is anticipated between 35+0 and 36+6 weeks gestational age.

Magnesium sulphate:
Some literature suggests that magnesium sulphate decreases the risk of infant death and the development of cerebral palsy. At a cellular level, magnesium inhibits calcium influx into cells and has anti-inflammatory effects. Currently, both the Canadian Paediatric Society as well as the Society of Obstetricians and Gynaecologists of Canada suggest that intrapartum magnesium sulphate be considered for all mothers at or less than 33+6 weeks gestation who are expected to give birth within 24 hours. If a woman does not deliver after receiving the first dose of magnesium sulphate, at this time, there is not enough evidence to support giving a repeated course of antenatal magnesium sulphate for fetal neuroprotection.

Preterm premature rupture of membranes and risk of chorioamnionitis:
Chorioamnionitis increases the likelihood of preterm labour and delivery. Higher rates of chorioamnionitis also occur at earlier gestational ages. There is conflicting evidence as to whether chorioamnionitis is associated with brain injury such as intraventricular hemorrhage, periventricular leukomalacia, as well as cerebral palsy. Regardless, current guidelines from the Society of Obstetricians and Gynaecologists of Canada and the Canadian Paediatric Society indicate that antibiotics should be promptly given to mothers with preterm premature rupture of membranes (PPROM) expected to deliver at or before 32+6 weeks gestational age. Penicillin and a macrolide should be administered. If a mother has a penicillin allergy, then a macrolide should be used as a single agent. Not only does antimicrobial therapy reduce the risk of chorioamnionitis and possibly have tocolytic effects, it also provides coverage against group B streptococcus.

Case:
Now let's return to our case.

After doing a bit of reading, you feel prepared to see Ms. Browne. During your discussion, you reassure her that the obstetrical team is doing everything they can to promote the best neonatal outcomes, and specifically point out some of the things with neuroprotective benefit. You note that she already completed a course of corticosteroids 48 hours prior, and that the obstetrical team has appropriately decided to give her magnesium sulphate as they expect delivery is imminent in the next 24 hours. She is also receiving penicillin and erythromycin for her PPROM. You reassure Ms. Browne that the NICU team will continue to follow her and her baby, and be present when delivery occurs.

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Perinatal strategies:

We will move on to talking about factors around the time of delivery that can affect the likelihood of neonatal brain injury. Important considerations include the location, timing, and mode of delivery, as well as timing of umbilical cord clamping and prevention of hypothermia.

Location of delivery:

Studies have demonstrated an increased rate of acute brain injury in preterm infants born outside of tertiary care facilities. There is conflicting evidence on whether transferring preterm infants at or less than 32+6 weeks gestational age is a risk factor for brain injury. Some suggest that noise, vibration, and acceleration during transit could predispose them to this. However, the increased rate of brain injury in these premature infants may be due to other factors including whether antenatal corticosteroids are given, as well as the training and expertise that resuscitating teams have in managing such preterm neonates.

The CPS advises that when possible, mothers at risk of preterm delivery should be transferred to a tertiary care facility. If this is felt to be unsafe, then a tertiary care team should be consulted to discuss the administration of maternal corticosteroids and magnesium sulphate.

Mode and timing of delivery:

There is no demonstrated advantage of routine caesarean section over vaginal delivery for reducing neonatal mortality or acute brain injury, unless the fetus is in breech position. The decision about vaginal delivery versus C-section is up to the mother and her obstetrical team. However, a caesarean section should be considered if the infant is very preterm and has malpresentation such as breech position.

When considering the ideal timing of delivery of a preterm infant with suspected compromise, evidence is lacking. Expectant management may allow for more fetal maturation and for antenatal corticosteroids to take effect. However, there is no proven difference in incidence of infant brain injury between immediate and deferred delivery. Overall, there is no clear evidence for immediate delivery unless other indications are present.

Timing of umbilical cord clamping:

Delayed clamping of the umbilical cord allows increased placental blood flow to the neonate in the moments after delivery. This increases perfusion to their organs while the lung vascular bed opens up with first few breaths. Strategies to promote placental transfusion and optimize neonatal blood volume after delivery include delayed cord clamping and umbilical cord milking where blood is squeezed towards the baby. Delayed cord clamping for up to 3 minutes (180 seconds) in preterm infants has been shown to decrease the overall incidence of acute brain injury and improve motor outcomes later in life. Umbilical cord milking may provide the similar benefit and allow for faster neonatal resuscitation than delayed cord clamping. However, there is more potential for variation in techniques and fewer studies on this.

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Taking all of this into consideration, the CPS advises that all preterm infants who do not require immediate resuscitation receive delayed cord clamping of 30 to 120 seconds. If this is not possible, cord milking may be considered.

Temperature control:
Preterm infants are at a higher risk of hypothermia, which can negatively impact resuscitation efforts. Rapid heat loss is associated with adverse outcomes such as increased risk of acute brain injury and death. Given this, care should be taken to maintain normothermia in all neonates born at or less than 31+6 weeks gestational age. Strategies include applying a polyethylene bag or wrapping as well as a hat, using a thermal mattress and pre-heated and servo controlled radiant warmer, and maintaining an ambient delivery room temperature of 25-26 degrees Celsius.

Case:
You are on the call the next day and are paged by the labour and delivery nurses. Ms. Browne is about to have her baby! As you rush into the room you receive a quick update from the obstetrical team. She is now at 26+1 weeks gestational age. Aside from this, labour has progressed as expected. You go to the warmer to check your equipment, and everything seems to be in order. Then you hear someone exclaim, “it’s a boy” followed by a weak cry. Cord clamping is delayed for 60 seconds, and then the infant is brought to the warmer. He is placed in a polyethylene wrap and you begin your assessment. You decide to start CPAP for respiratory distress as per Neonatal Resuscitation Program guidelines, before transferring him to the NICU for ongoing care.

Postnatal strategies:
Finally, we will discuss what can be done after birth to confer neuroprotection. This includes empiric antibiotic treatment when indicated, cautiously using inotropes, maintaining normocapnia, and ensuring neutral head positioning and a nurturing care environment. Let’s talk about each of these in more detail.

Empiric antibiotic treatment:
Infants born at 32+6 or fewer weeks gestational age should have blood cultures drawn and empiric antibiotic treatment for any of the following indications: premature rupture of membranes, concern for chorioamnionitis, or unexplained non-reassuring fetal status. This is due to the increased risk of early onset sepsis in these situations. Prolonged rupture of membranes for more than 72 hours is also a risk factor for brain hemorrhage. It is important to keep in mind that infants with early onset sepsis may initially appear asymptomatic. Antibiotics can be stopped if blood cultures are negative at 36 to 48 hours.

Management of hypotension:
Currently there is variation in how hypotension has been defined and managed in preterm infants. Different cutoffs exist for the diagnosis of hypotension, including a mean arterial pressure less than a neonate’s gestational age in weeks or less than 30mmHg on two consecutive readings. Strategies to provide circulatory support can include volume expansion, inotropes, and corticosteroids. We will discuss the evidence surrounding volume expansion and inotropes in very preterm infants in more detail.

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At present, there is no evidence to support routine early use of volume expanders such as IV fluids, blood or colloids in hemodynamically stable neonates. In infants with cardiovascular compromise, the benefit of early volume expansion and type of expander that should be use are both unclear.

The use of vasopressors and inotropes in preterm babies has been associated with morbidity and mortality. Multiple studies link vasopressor use to increased risk of acute brain injury. Similarly, inotropes have been identified as a risk factor for acute brain injury and mortality, as well as adverse outcomes for future motor development. Given the potential for harm, inotropes should used be judiciously in preterm infants, and should not be administered for isolated hypotension. However, they can be considered when there is a constellation of signs associated with hemodynamic instability including decreased urine output, prolonged capillary refill time or elevated lactate. Clinicians should also consider assessing for iatrogenic causes of hypotension including excessive water loss and lung hyperinflation. Lung hyperinflation due to assisted ventilation can impair blood return to the heart, which can lower systemic blood pressures. A chest x-ray can assess for hyperinflation and guide changes in ventilation strategies. It may also be reasonable to give a slow fluid bolus prior to starting inotropes.

Ventilation:
Volume targeted ventilation should be the first mode of ventilation for preterm infants within 72 hours of delivery. It has been associated with lower chance of intraventricular hemorrhage compared to pressure-limited ventilation, and lower risk of intraventricular hemorrhage than early high-frequency oscillatory ventilation.

PaCO2 should be closely monitored in the first 72 hours of life in infants born at or less than 32+6 weeks gestational age. Target PaCO2 should be between 45 mmHg and 55mmHg, to a maximum of 60mmHg. There is increased risk of periventricular leukomalacia when PaCO2 is below 35mmHg, and of intraventricular hemorrhage when PaCO2 is above 60mmHg. The adverse effects of hypercapnea appear to be dose dependent in extremely low birth weight infants. Attention should be paid to metabolic acidosis along with hypercapnia.

Prophylactic indomethacin and ibuprofen:
A patent ductus arteriosus (PDA) is common in premature infants born at less than 32 weeks gestational age. The majority of these will spontaneously close by 3 days of life. Therefore the decision to treat with a cyclooxygenase inhibitor such as indomethacin and ibuprofen requires careful consideration of possible risks and benefits. While there is an increased risk of acute brain injury in premature neonates with hemodynamically significant PDAs, treatment is not benign. There is strong evidence that prophylactic indomethacin reduces the likelihood of intraventricular hemorrhage, however, it can increase the risk of retinopathy of prematurity and/or spontaneous bowel perforation. Moreover, there is no evidence that shows that prophylactic indomethacin improves long-term neurodevelopmental outcomes. Additionally, ibuprofen has not been shown to decrease the rate of acute brain injury or mortality.

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Given this, the CPS advises that prophylactic treatment with indomethacin or ibuprofen should target high-risk extremely preterm infants. An example of a high-risk infant could be a neonate born outside of a tertiary care centre at 24 weeks, who received only one dose of antenatal corticosteroids 6 hours before vaginal delivery. In this high-risk case, you could consider doing prophylactic treatment with indomethacin or ibuprofen to close a PDA. Clinicians should also consider other risk factors for acute brain injury when deciding whether to treat with pharmacotherapy.

Head positioning:
The position of an infant's head can affect cerebral perfusion. While the evidence surrounding this is limited, a neutral midline head position may help protect against brain injury by minimizing venous congestion, jugular venous obstruction, and raised intracranial pressure. CPS guidelines state that a preterm infant's head should be kept midline with the head of the bed elevated 30 degrees during the first 72 hours of life.

Nurturing environment:
When possible, developmentally supportive care should be provided to infants to optimize neurodevelopmental outcomes. This includes minimal handling, minimization of painful stimuli, encouraging skin-to-skin contact and maternal voice exposure, minimizing noise, and cycling lights. It is also important to promote growth in premature infants using nutritional strategies such as early parenteral nutrition and early initiation of feeding, especially with maternal fresh milk. Their brain is their most metabolically active organ, and poor growth has been linked to adverse cognitive outcomes.

Case:
You are back in the NICU and caring for Baby boy Browne again. He is now 24 hours old. He remains on empiric antibiotics that you ordered shortly after birth for PPROM. You expect blood cultures will be back tomorrow and he still requires CPAP. Today the baby develops hypotension with a mean arterial pressure of 24 mmHg. He does not have any signs concerning for compromised end organ perfusion, and has good perfusion on exam and a normal serum lactate. Remembering what you read about the risk of brain injury with inotropes, you hold off on starting inotropes for now. You consider some of the iatrogenic causes for hypotension, and order a chest x-ray to assess for hyperinflation. The baby has lost some weight and is tachycardic so you deliver a slow fluid bolus for the possibility of excessive water loss. You are happy to see that his head is in an ideal position within the isolette - it is midline and the head of the bed is elevated to 30 degrees. You plan to frequently reassess him, provide his parents with an update on his status

Summary:
Before we leave, let's review a few key points:

1. Infants born ≤ 32+6 weeks gestation are at increased risk of acute brain injury due to fragile blood vessels and immature autoregulatory systems. Injury can be parenchymal or intraventricular due to ischemia/reperfusion.
2. The first 72 hours after birth are the highest risk time for brain injury to occur.
3. Neuroprotection strategies in the antenatal period include administering maternal corticosteroids for delivery expected ≤ 34+6 weeks gestational age, magnesium

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sulphate for imminent delivery ≤ 33+6 weeks, and antibiotics for preterm premature rupture of membranes and expected delivery ≤ 32+6 weeks.

4. Perinatal factors with neuroprotective benefit include delivery at a tertiary care centre when safe, delayed cord clamping, and prevention of hypothermia.
5. Postnatal strategies should include empiric antibiotic treatment for risk of early onset sepsis, cautious use of inotropes for hypotension, and targeted use of prophylactic indomethacin. If ventilatory support is being provided, volume targeted ventilation is the mode of choice. It is also important to ensure neutral head position and provide developmentally appropriate care.

That concludes this podcast reviewing the Canadian Paediatric Society position statement on “Neuroprotection from acute brain injury in preterm infants.” Thank you very much for listening!

References

Ryan M, Lacaze-Masmonteil T, Mohammad K. Canadian Paediatric Society, Fetus and Newborn Committee. Neuroprotection from acute brain injury in preterm infants. June 17, 2019.

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