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Position Statement

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Neuroprotection from acute brain injury in preterm infants

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Abstract

Infants born at ≤32^{+6} weeks gestation are at higher risk for intracranial ischemic and hemorrhagic injuries, which often occur in the first 72 hours postbirth. Antenatal strategies to reduce the incidence of acute brain injuries include administering maternal corticosteroids and prompt antibiotic treatment for chorioamnionitis. Perinatal strategies include delivery within a tertiary centre, delayed cord clamping, and preventing hypothermia. Postnatal strategies include empiric treatment with antibiotics when chorioamnionitis is suspected, the cautious use of inotropes, the avoidance of blood PCO2 fluctuation, and neutral head positioning. Clinicians should be aware of the policies and procedures that, especially when combined, can provide neuroprotection for preterm infants.

Keywords: *Acute brain injury; Infant; Intraventricular hemorrhage; Neuroprotection; Neuroprotective strategies; Premature*

Acute brain injury, which can occur in the form of infarction caused by ischemia and/or hemorrhage caused by reperfusion within the cerebral ventricles or parenchyma, is a common and serious morbidity associated with prematurity. The pathophysiology of injury involves the premature infant's fragile cerebral vasculature and immature autoregulatory system, with rapid changes in perfusion causing ischemia or intraventricular hemorrhage (IVH) into the brain. In Canada, approximately 21% of preterm infants born at ≤32^{+6} weeks gestational age (GA) show an abnormal brain image (IVH or parenchymal lesions) on cranial ultrasound (1). While another variant of white matter brain injury, cystic periventricular leukomalacia (cPVL), is in decline (2), the noncystic form of PVL is becoming increasingly recognized due to magnetic resonance imaging (MRI) (3). Abnormal brain images in the neonatal period are strongly associated with neurodevelopmental impairment in the long term (4).

The first 72 hours postbirth ('the critical window') is the highest risk period for acute preterm brain injury (5,6), and 95% of IVH or parenchymal lesion cases are detected by day 5 (7). Approaches to preventing IVH and PVL in this critical period vary considerably among perinatal centres and neonatal intensive care units (NICUs) (8). The purpose of this statement is to summarize and evaluate evidence-based strategies for neuroprotection, with the aim of reducing incidence of brain injury in preterm infants. Generally, these strategies target infants born at ≤32^{+6} weeks GA, and where they may also apply to infants born closer to term, it will be clearly noted.

Methods

A comprehensive literature search was performed using MEDLINE, including in process and other non-indexed citations (1946 to February 1, 2018). The population of interest included very low birth weight infants (<1,500 g at birth), and infants born at ≤32^{+6} weeks GA. A total of 5,010 references were retrieved, of which 195 articles and 12 Cochrane reviews were reviewed. The hierarchy of evidence from the Centre for

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Evidence-Based Medicine (Oxford CEBM-March 2009) (9) was applied to these publications, and recommendations are based on the format by Shekelle et al. (10).

Chorioamnionitis and preterm premature rupture of membranes (PPROM)

Chorioamnionitis is a primary risk factor for preterm labour and delivery, with higher incidence with decreasing gestational ages (1,11). One systematic review concluded that chorioamnionitis increases risk for both cerebral palsy (CP) and cPVL (12). However, subsequent systematic reviews and large-scale retrospective studies have found no or only weak associations between chorioamnionitis and IVH, PVL, or CP (13–15). Conflicting findings may relate to whether PPROM has occurred (16) and whether prompt treatment with antibiotics was initiated. The Society of Obstetricians and Gynaecologists of Canada (SOGC) recommends administering penicillin and a macrolide (or a macrolide alone if a patient is allergic to penicillin) to any mother presenting with PPROM and expected to deliver at ≤32^{+6} weeks GA (17). This empiric regimen also offers coverage against Group B streptococcus and may help prolong pregnancy and reduce morbidity for both mother and newborn (17) (level of evidence 1a).

Neonates born at ≤32^{+6} weeks GA to mothers with suspected or confirmed chorioamnionitis, PPROM, preterm labour, or an unexplained onset of nonreassuring fetal status, should be carefully evaluated, have a blood culture drawn, and be started on empiric antibiotics. All such infants are at higher risk for early onset sepsis and may be asymptomatic initially (18,19). Duration of rupture of membranes for longer than 72 hours is also an independent risk factor for IVH or intraparenchymal hemorrhage (odds ratio [OR] 2.33, 95% confidence interval [CI] 1.420 to 3.827) (20). Antibiotics should be discontinued after 36 to 48 hours if blood cultures are negative.

Antenatal corticosteroids

Corticosteroids accelerate organ system maturity in animal models (21). Vasoconstriction is apparent in the fetal brain when antenatal corticosteroids are used, which may protect against injury. One Cochrane meta-analysis (22) has demonstrated that treatment with antenatal corticosteroids is associated with reducing neonatal morbidities and mortality, including IVH (average relative risk [RR] 0.55, 95% CI 0.38 to 0.91). The timing of the last dose of corticosteroid before delivery also influences risk for brain injury, with significantly reduced risk observed when the interval since the last dose is greater than 48 hours, compared with less than 24 hours (23). Routinely administering antenatal corticosteroids within 7 days to all mothers expected to deliver a premature infant ≤34^{+6} weeks GA (and between 35^{+0} and 36^{+6} weeks GA in select clinical situations) is recommended, with the optimal interval being greater than 48 hours between the last dose administered and birth (24) (level of evidence: 1a).

Magnesium sulphate

Magnesium has several intracellular actions, including anti-inflammatory effects and inhibiting the influx of calcium into cells (25,26). One Cochrane review (27) and a meta-analysis of five randomized control trials (RCTs) (28) demonstrated that magnesium sulphate effectively decreases risk for CP (RR 0.69, 95% CI 0.55 to 0.88) and for the composite outcomes of death or cerebral palsy (RR 0.86, 95% CI 0.75 to 0.99). There is insufficient evidence that a repeated course of antenatal magnesium sulphate should be administered for fetal neuroprotection (25). The current recommendation is to consider magnesium sulphate for all women experiencing imminent preterm delivery (≤ 33^{+6} weeks GA), which is consistent with SOGC guidelines (level of evidence: 1a).

Mode of delivery

Expectant management can provide more time for antenatal corticosteroids to take effect and for the fetus to mature. One Cochrane review (29) comparing women randomized to deliver immediately versus expectant management care showed the latter group gave birth an average 4 days later, with no differences in neonatal brain injury.

There is no evidence that routine caesarean section confers protective benefit over vaginal delivery for preterm infants at risk for mortality or IVH, including intraparenchymal lesions (30), except when they are in breech position (31,32). It is possible that urgency of delivery entails higher risk for brain injury than mode of delivery (33).

There is insufficient evidence of the benefits or harms of immediate versus deferred delivery to recommend optimal delivery timing. However, there appears to be no benefit to immediate delivery without other, clear indications. There is also insufficient evidence to recommend routine caesarean section for women in preterm labour, unless the fetus is malpresenting. Although the ultimate decision on mode of delivery lies with the labouring mother and her obstetrical team, the discussion should be multidisciplinary (level of evidence: 2b).

Timing of umbilical cord clamping

Cord clamping at delivery terminates placental transfusion and decreases perfusion to a newborn's organs. In Canada, 42% of preterm infant deliveries documented delayed cord clamping in 2017 (1). One systematic review (34) found that delaying cord clamping for up to 180 seconds was associated with less acute brain injury overall (RR 0.59, 95% CI 0.41 to 0.85), but not with reducing intraparenchymal lesions or severe IVH specifically. Delayed cord clamping also appears to protect against motor disabilities later in life (35,36).

Other systematic reviews have found that delayed cord clamping or cord milking, when compared with immediate cord clamping, reduces overall risk for acute brain injury (RR 0.62, 95% CI 0.43 to 0.91) (37). Umbilical cord milking allows faster infant resuscitation while potentially providing the same benefits as delayed cord clamping. Meta-analyses comparing immediate cord clamping with cord milking found that infants whose cords were milked had a lower incidence of acute brain injury overall (37). No adverse effects were observed in any of the reviewed studies. One recent, large RCT showed no difference between immediate and delayed cord clamping. However, the study combined death with an array of morbidities for its primary outcome, rather than focusing on death and severe brain injury, and 21% of neonates in the 'delayed' group were clamped at <30 seconds (38).

All infants who do not need immediate resuscitation should receive delayed cord clamping of 30 to 120 seconds (level of evidence: 1a). Delayed cord clamping is preferred over umbilical cord milking because the studies assessing impacts of cord milking are few, techniques vary, and there have been no follow-up studies. Cord milking may be considered when delayed cord clamping cannot occur (level of evidence: 2).

Hypothermia

Preterm infants are at high risk for rapid heat loss (39). Cold stress can accelerate oxygen consumption and impair resuscitation (40). Hypothermia has been associated with increased risk for acute brain injury and death (40,41). One systematic review (42) demonstrated that preterm infants experienced less hypothermia upon admission to the NICU when resuscitation or stabilization included using polyethylene wrapping or a bag to keep them warm. Other recommended measures to prevent hypothermia include regulating the temperature in the delivery room at 25°C to 26°C, using a preheated servo-controlled radiant warmer with a temperature sensor (43), providing a thermal mattress, putting a hat on the infant, and providing a preheated transport incubator (level of evidence: 1a).

Inotropes and hypotension

No consistent definition of hypotension or standardized approach to managing this condition in preterm infants presently exists (44). Common definitions of hypotension include a mean arterial blood pressure less than the infant's GA or <30 mmHg for two consecutive measurements. However, multiple studies have associated the use of vasopressors to treat hypotension in preterm infants with developing IVH and other brain injuries (45–47). The use of inotropes has been clearly associated with mortality and brain injury in this at-risk group (45,48), with potential lasting effects on motor development when assessed at 20 months corrected age (49,50). Despite the apparent benefits of improving blood pressure and perfusion to organs, Lightburn et al. (51) found no difference in cerebral blood flow velocities among extremely low birth weight (ELBW) infants with and without documented hypotension. A Cochrane review found no evidence for the routine use of volume expansion in preterm infants without cardiovascular compromise and insufficient evidence that infants with cardiovascular compromise benefit from volume expansion when outcomes such as severe disability, cerebral palsy or mortality were reviewed (52).

Because the use of inotropes is a significant risk factor for acute brain injury, the care provider should be cautious when treating hypotension in premature infants. Indications to consider inotropes should include, along with low blood pressure, a combination of prolonged capillary refill, decreased urine output, elevated lactate or echocardiography findings. Potential iatrogenic reasons for hypotension, such as hyperinflation or dehydration, should also be ruled out. Therefore, a chest x-ray and a slowly infused fluid bolus before initiating inotropes should be considered (level of evidence: 5).

Prophylactic indomethacin and ibuprofen

In Canada, in 2017, 28% of preterm infants <32 weeks GA were documented as having a patent ductus arteriosus (PDA), and just under one-half of these infants underwent treatment (1). When left untreated, an estimated 58% of infants close their PDA spontaneously by day 3 (53). Preterm infants with a hemodynamically significant PDA have an increased risk for acute brain injury (54), but treatment with a cyclo-oxygenase inhibitor can have significant side effects, particularly on the renal system. One Cochrane review assessing the effects of prophylactic indomethacin in preterm infants found a significant reduction in IVH (RR 0.88, 95% CI 0.80 to 0.98), including severe IVH with ventriculomegaly, and in intraparenchymal lesions (RR 0.66, 95% CI 0.53 to 0.82) (55). However, there were no long-term neurodevelopment benefits observed at 18 months of age (56), and follow-up study results did not support use of indomethacin as a treatment that improved long-term infant outcomes (57). One 2011 Cochrane review assessed the prophylactic use of ibuprofen, which is thought to have a better side effect profile than indomethacin, but this study found no difference in IVH or mortality (53). Because many PDAs often close spontaneously and the potential for side effects from cyclo-oxygenase inhibitors are significant, the prophylactic use of indomethacin or ibuprofen should be targeted based on combined risk factors including GA, exposure to antenatal steroids, and birth site (58) (level of evidence: 1a).

Hypercapnia/ hypocapnia and ventilation mode

Hypercapnia, defined as PCO2 blood levels >60 mmHg, is a risk factor for acute brain injury in ELBW infants that may impair cerebral autoregulation and cause vasodilatation (59). Rising PCO2

levels also appear to be a dose-dependent predictor for IVH risk (60). However, permissive hypercapnia (defined as allowing PCO2 levels of 45 mmHg to 55 mmHg) is a common strategy to minimize risk for lung injury and bronchopulmonary dysplasia in preterm infants. Various RCTs have evaluated infants managed with permissive hypercapnia PCO2 or with PCO2 levels above the typical hypercapnia range (PCO2 55 mmHg to 65 mmHg), compared with normocapnia (PCO2 35 mmHg to 45 mmHg). Authors found no difference in the incidence of severe IVH with ventriculomegaly, intraparenchymal lesions or long-term neurodevelopmental outcomes (61,62). However, median PCO2 levels higher than 72 mmHg or lower than 32 mmHg were both independently associated with acute brain injury (63). Both extreme hypercapnia (PCO2>60 mmHg) and hypocapnia (PCO2 <35 mmHg) appear to cause brain injury and should be avoided (64,65). Monitoring PCO2 via blood gases or transcutaneous or end-tidal CO2 is recommended for infants born at ≤32^{+6} weeks GA, with a goal of achieving PCO2 levels of 45 mmHg to 55 mmHg in the first 72 hours postdelivery (level of evidence: 1b).

Volume-targeted ventilation has been associated with lower odds of severe IVH (OR 0.53, 95% CI 0.37 to 0.77) compared with pressure-limited ventilation (66). Early use of rescue high-frequency oscillatory ventilation may increase the risk of IVH (RR 1.77, 95% CI 1.06 to 2.96) (67). Whenever possible, volume-targeted ventilation should be used in premature infants in the first 72 hours postdelivery (level of evidence: 1a).

Head positioning

Routine care of the preterm infant in the first 72 hours postdelivery can affect cerebral blood flow (68). Maintaining a neutral head position may avoid jugular venous obstruction, reduce ipsilateral venous congestion, and potentially lower risk for IVH (68). Few clinical trials have been conducted to address this issue and most relevant studies have used a nonrandomized, convenience sample design (69). In general, these studies documented changes in cerebral blood flow based on infant head positioning, noting either an increase in cerebral blood volume (69) or a decrease in jugular blood flow (70) when an infant's head was turned 90 degrees. A few studies have also found decreased intracranial pressure when the head was midline and elevated (71–73), although one Cochrane review found no significant difference in IVH rates for head position at 0 versus 90 degrees (74). Based on infant physiology and the relative ease of implementing this practice, and because fluctuations in intracranial pressure may increase risk for acute brain injury, consideration should be given to keeping the infant's head midline or neutral with the torso and the head of the bed elevated at 30 degrees (level of evidence: 5).

Transport

Transporting a preterm infant (≤32^{+6} weeks GA) between facilities is believed to be an independent risk factor for acute brain injury. Possible causes for this include noise, vibration and acceleration during travel (75). Several studies, however, found no worse outcomes for infants transferred between neonatal centres (76,77), and at least one suggested the act of transport was not an independent risk factor for acute brain injury (78). The increased rate of acute brain injury in preterm infants born outside tertiary centres may relate to the decreased likelihood of receiving antenatal corticosteroids (79) and resuscitation (78) by teams who may lack specific training and expertise for preterm infant care. Transport to a tertiary care centre should occur when appropriate. When it is deemed unsafe to move a mother before delivery, antenatal corticosteroids should be administered and neuroprotective measures taken throughout stabilization and transport, in consultation with a tertiary care team (level of evidence: 5).

Nurturing environment

Neurodevelopmental delay is common among infants born extremely preterm, even when their MRIs appear relatively normal (80,81). Fostering a care environment that encourages skin-to-skin contact, maternal voice exposure and interaction, light cycling, and a low general noise level, is crucial for optimal brain growth (82,83). Developmental care strategies can mitigate painful procedures (84) and decrease opioid use (85), which are both associated with adverse neurodevelopmental outcomes (86–88). Finally, because substandard growth has been associated with brain injury and neurodevelopmental delay (89), early parenteral nutrition to optimize growth is also essential (90).

RECOMMENDATIONS

Based on summaries of best evidence, the following recommendations for practice are offered to guide clinical care and minimize risk for brain injury in extremely preterm infants:

- Mothers experiencing preterm premature rupture of membranes (PPROM) and expecting to deliver an infant ≤32^{+6} weeks gestational age (GA) should be treated with antibiotics: penicillin and a macrolide or a macrolide alone if she is allergic to penicillin (Grade A recommendation).
- Infants ≤32^{+6} weeks GA born to mothers with chorioamnionitis or PPROM should be treated empirically with antibiotics for 36 to 48 hours, pending a negative blood culture (Grade D recommendation).
- Mothers at ≤34^{+6} weeks gestation with risk of delivery in the next 7 days should be routinely offered a course of antenatal corticosteroids (Grade A recommendation).
- Consider intrapartum magnesium sulphate for mothers at risk for imminent delivery of an infant ≤33^{+6} weeks GA in the next 24 hours (Grade A recommendation).
- Consider delivery via caesarean section when an infant is very preterm and malpresenting. The ultimate decision

regarding mode of delivery lies with the obstetrical team and the mother (Grade B recommendation).

- Delayed cord clamping should be offered for all preterm infants not in need of immediate resuscitation (Grade A recommendation). Cord milking can be considered when delayed cord clamping is not feasible (Grade B recommendation).
- To help prevent hypothermia, routine use of a polyethylene bag or wrapping, a thermal mattress, a preheated radiant warmer with servo-control, a hat, and other precautions, such as maintaining the temperature of the delivery room at 25°C to 26°C, should be used for all infants ≤31^{+6} weeks GA (Grade A recommendation).
- Avoid inotropes to treat hypotension unless a combination of other clinical signs are present, such as elevated lactate, prolonged capillary refill time, decreased urine output or low cardiac output. Care should also be taken to avoid iatrogenic causes of hypotension, such as lung hyperinflation or dehydration (Grade B recommendation).
- Prophylactic indomethacin should be targeted to high-risk, extremely preterm infants, and the decision to treat should be based on combined risk factors (Grade A recommendation).
- To help prevent periventricular leukomalacia (PCO2 below 35 mmHg) and intraventricular hemorrhage (PCO2 above 60 mmHg), a PCO2 of 45 mmHg to 55 mmHg, to a maximum of 60 mmHg, should be targeted (Grade B recommendation).
- Volume-targeted ventilation is the mode of first choice for all preterm infants in the first 72 hours postdelivery (Grade A recommendation).
- In the first 72 hours postdelivery, a preterm infant's head should be in a neutral, midline position, with the head of the bed elevated 30 degrees (Grade D recommendation).
- When appropriate, at-risk mothers should be transported to a tertiary care centre to deliver (Grade A recommendation). When transport is deemed unsafe, routine corticosteroids and magnesium sulphate should be considered through telephone/telehealth consultation with a tertiary care team (Grade A recommendation).

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