**V. Neurologic and Seizure Management**

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**I. What medications should be used for analgesia during hypothermia?**

Though optimal therapy for sedation in neonates is a highly debated topic, neonates being cooled do demonstrate agitation and irritability in response to cooling. Studies of animal models of global hypoxic insults demonstrate that unsedated piglets subjected to hypothermia post hypoxic injury do not benefit from total body cooling and have grossly elevated cortisol levels, shivering, and generally increased motor activity that is postulated to diminish and even counteract the neuroprotective benefits of total body hypothermia. Due to known suppression of the cytochrome P450 pathway due to cooling as well as the risk for polypharmacy and drug interactions in acutely ill neonates, care must be taken in choosing a medication for analgesia.

*Recommendations:*

1. Begin an opiate *or* dexmedetomidine infusion upon initiation of cooling. The recommended starting doses are: Fentanyl 0.5 mcg/k/hour and dexmedetomidine 0.3 mcg/k/hour [1].
2. May consider titrating continuous infusions based on the neurologic exam and NPASS score (range: -10 to 10).
   1. NPASS scores should be assessed every 3 hours. Goal is score less than 3.
   2. If any NPASS score is below 0, wean the sedation.
   3. If the NPASS score is 0 for 3 consecutive assessments, wean the sedation.
   4. If The NPASS score is consistently between 0-3, consider weaning.
   5. If the score is 3 or higher, increase the dose to achieve target scores.
3. Stop unnecessary analgesia and sedation after warming has occurred.
4. If opiate or dexmedetomidine at low dosages does not provide adequate analgesia, the dose can be gradually increased or alternate infusion may be added (see above). The goal should be continuous and adequate analgesia and anxiolysis to prevent excessive irritability/agitation and not an attempt to maintain the infant on mechanical ventilation, unless clinically indicated. For intermittent agitation, may consider a small bolus of either agent as needed for NPASS scores exceeding 3.
5. The clinician may consider obtaining a serum cortisol to assess the degree of stress. The cortisol along with the heart rate may aid the clinician with the management of sedation.

*Level of Evidence:* V Expert opinion based on current review of the literature and animal models.

**II. When and how should infants be monitored for seizures?**

Multiple studies have shown the benefit of continuous EEG monitoring of neonates with HIE. Besides being a very useful early predictor of neurologic outcomes [2, 3], studies have shown that aggressive treatment of seizures decreases neurologic sequlae [4]. Due to the large amount of resources consumed by continuous EEG monitoring, amplitude integrated EEG has been used extensively for neonates with HIE for monitoring. The ease of application and interpretation of aEEG makes it especially useful in continuous monitoring.

*Recommendations:*

1. Upon admission to the NICU, neonates suspected of having HIE should have an aEEG placed (see #3).
2. Monitoring duration via aEEG should optimally occur during the entire systemic hypothermia process, including warming.
3. If video EEG is used for continuous monitoring instead of aEEG, someone at the bedside of the patient should be trained in interpretation of the EEG or the aEEG feature on the video EEG should be monitored by the bedside personnel.
4. If aEEG demonstrates seizure activity and/or an abnormal background pattern, it is recommended to obtain formal EEG evaluation and continuously monitor for electrographic seizures until warming has occurred and seizures are under control (2).

*Level of Evidence:*  IIC based on outcome data and case control studies

**III. How should seizures be managed in neonates with HIE?**

HIE is the number one cause of neonatal seizures. Despite the high incidence of seizures in this population of neonates, a Cochrane review did not find benefit in morbidity and mortality with routine use of prophylactic anti-epileptic medications [5].

Though there is no evidence to support routine prophylaxis, studies have shown a definite benefit to aggressive therapy of seizures: clinical or electrographic. FDA approved management for seizures in neonates is limited to Phenobarbital and Fosphenytoin. Studies have not demonstrated a benefit of Phenobarbital over Fosphenytoin [6]. Recent randomized control studies have demonstrated that Keppra is a safe and effective therapy in neonatal seizures with vastly better pharmacokinetics and side effect profile than Phenobarbital and Fosphenytoin [7-9]. Some studies have also demonstrated a potential neuroprotective benefit of Keppra and neurotoxic side effects associated with Phenobarbital and Fosphenytoin [10].

*Recommendations:*

1. Any electrographic or clinical evidence of seizures should be aggressively treated with appropriate anti-epileptic therapy and close monitoring for recurrence as over 50% of seizures from HIE will require more than one medication for treatment.
2. Initial treatment may be with either an intravenous benzodiazepine or IV Phenobarbital at 20 mg/kg.
3. Maintenance treatment may be started if neonates continue to have seizure activity. If maintenance is started, recheck in one week to reassess if AED can be discontinued.

**VI. What is the optimal time for neuroimaging in neonates with HIE?**

Appropriate neuroimaging is an important part of evaluating the etiology of HIE and predicting long term neurodevelopemental outcomes. Magnetic Resonance Imaging with diffusion weighted images and spectroscopy of the basal ganglia is the imaging study of choice [11]. Elevated lactate peaks and low N-acetylaspartate levels in the basal ganglia are associated with poor neurodevelopemental outcomes [11, 12]. Deep gray matter injuries including basal ganglia injuries and thalamic injury can indicate acute injury while injuries in the watershed areas can indicate prolonged partial hypoxia [6].

*Recommendations:*

1. Head ultrasound should be acquired on admission.
2. MRI with diffusion weighted images and spectroscopy of the basal ganglia is the preferred study.
3. Suggested MRI imaging can be performed at 4-5 days of life and again at 7-12 days. If only one MRI can be performed, it should occur during the 7-12 day period. These recommendations may need to be adjusted in critically ill neonates who will be compromised in obtaining the MRI.

*Level of Evidence:* IA randomized control trials.

**V. References**

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