

## Use of Opioids in Asphyxiated Term Neonates: Effect on Brain Metabolites and Outcomes

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**Introduction:** Perinatal asphyxia is a common cause of neonatal encephalopathy, a type of brain injury known to result in cerebral palsy. A cascade of biochemical events takes place following asphyxia resulting in changes in brain metabolites that can be monitored non-invasively using proton magnetic resonance spectroscopy (MRS). We recently reported that asphyxiated term neonates treated with opioids during the first week of life had significantly less brain injury in the basal ganglia and watershed regions as assessed by magnetic resonance imaging (MRI) scores as well as better long-term neurologic outcomes (1). In asphyxiated infants, use of opioids may attenuate inefficient ATP utilization by preventing neuronal depolarization due to calcium influx and glutamate excitotoxicity. To examine the hypothesis that opioids alter brain energy metabolism in asphyxiated term neonates, we analyzed and compared brain metabolite data in control, opioid treated and non-opioid treated neonates using MRS. The number of tissue-damaging procedures in the first 4 days of life was correlated to brain metabolite data to examine the hypothesis that exposure to untreated pain and stress alters brain biochemistry by altering brain metabolite levels. We also correlated brain metabolite data with MRI findings. Finally, we correlated brain metabolite data with neurologic outcome to determine if acute changes in brain metabolites are predictive of neurological development in the first year of life.

**Methods:** With Institutional Review Board approval, medical, radiological and research records of newborns with brain injury were reviewed. Inclusion criteria included an MRI/MRS study in the first month of life and at least one of the following criteria: (a) 5 minute APGAR of  $\leq 5$  (b) Cord umbilical arterial pH  $\leq 7.10$ , (c) Cord Base Excess  $\geq -10$  and (d) clinical post-asphyxial syndrome (encephalopathy, seizure, IVH). Control patients were full-term NICU patients with no history of asphyxia with questionable seizures of unknown etiology who did not receive opioids and who had a normal MRI/MRS and neurologic outcome. The frequency of tissue damaging procedures (defined as those that are known to result in pain, stress or discomfort) were recorded. Using a 1.5T MR scanner, MRI/MRS was acquired within 10 days after birth. MRI was scored using a validated scoring system (2). Short echo time single voxel (STEAM; TR/TE/TM=3000/20/13 ms) MRS (SVS) from occipital gray matter (OGM) and intermediate echo time multi-voxel MR spectroscopic imaging (MRSI) (PRESS; TR/TE=3000/144 ms) from a 10 mm thick slab through the level of the basal ganglia (BG) and thalami (TH) (1cc/voxel) were acquired. Metabolite levels for NAA, creatine (Cr), Cho, myo-Inositol (Ins), Glx and lactate (Lac) and ratios for SVS in each patient were quantitatively measured using LCModel (3). For MRSI data, peak areas for NAA, Cr, Cho and Lac, if present, were measured using Luise (Siemens Medical Solutions). Long-term neurologic outcome (1 year) was assessed by a pediatric neurologist using the Pediatric Cerebral Performance Category Scale (PCPCS).

**Results:** In the first 4 days of life (DOL), opioid and non-opioid treated neonates were exposed to  $34 \pm 4$  and  $32 \pm 2$  tissue-damaging procedures, respectively (P = NS). However, we found that opioid-treated neonates had significantly higher NAA/Cr in OGM ( $1.3 \pm 0.09$  vs.  $1.1 \pm 0.07$ ) and significantly higher NAA/Cho ratios in OGM, BG and TH (see Figure; \* p < 0.05 Kruskal Wallis) than non-opioid-treated infants. Lactate was not present in any opioid treated neonates compared to 39% of non-opioid treated patients (p = 0.04). We found significant positive correlations between Cho and Glx ratios (OGM, BG) and tissue damaging procedures. Lastly, we also found statistically significant negative correlations between NAA ratios from OGM, BG and TH with long-term outcome and significant positive correlations with Cho/Cr ratios from OGM, BG, and TH with long-term outcome

**Conclusion:** Our findings suggest that tissue-damaging procedures may increase the amount of neonatal pain and stress, that this hyperexcitability may augment neonatal brain injury associated with hypoxia-ischemia, and that opioids may serve an acute neuroprotective role that could affect long term outcome.

### References:

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