

Perinatal Asphyxia and Hypoxic Ischemic Encephalopathy – The Current Situation

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INTRODUCTION

Complications during delivery can lead to poor neonatal outcomes in otherwise normal fetuses. Perinatal asphyxia (PA) is an important cause of death and disability related to events during birth and results from compromised placental or pulmonary gas exchange. This can lead to hypoxia and hypercarbia resulting in anaerobic glycolysis and acidosis causing severe metabolic challenges, even when the insult doesn't lead to fatal outcome¹. Following PA, systemic hypoxia-ischemia results in multi-organ dysfunction, but the most significant long lasting effects are evident in cerebral function of affected infants. The resulting condition caused by the hypoxic ischemic insult to the brain is termed Hypoxic Ischaemic Encephalopathy (HIE). Cerebral hypoxia-ischemia remains a major cause of acute perinatal brain injury, leading to severe neurodevelopmental impairments. Despite improvements in perinatal care PA still occurs^{2,3} with the incidence of 2–6/1000 term births in developed countries⁴, reaching higher rates in developing countries^{5,6}. Though some cases of asphyxia are preventable, the ability to predict those fetuses at risk remains poor⁷.

CAUSES AND RISK FACTORS

Intrapartum events, such as placental abruption, umbilical cord prolapse and uterine rupture, accounts for majority of cases (56–80%)^{8,9}. Intrapartum

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disturbance usually in association with an antenatal risk factor, such as diabetes mellitus, preeclampsia, or intrauterine growth restriction (IUGR) occurs in 10 to 35% of cases of PA⁷. Placental insufficiency will contribute to 10% of cases of PA. Intra-amniotic infection and prolonged or difficult deliveries also associated with an increased risk of PA¹⁰, encephalopathy and cerebral palsy^{11,12}. Postnatal insult occurs only in 10% of cases of PA, due to prematurity severe cardiopulmonary abnormalities such as congenital heart disease, persistent pulmonary hypertension of the newborn or severe circulatory insufficiency¹³. These catastrophic events are usually not preventable and sometimes may not be predictable¹⁴.

However, the timing of injury often is difficult to establish for an individual infant, in part because antepartum and intrapartum events may not lead to signs that are detectable in the fetus. In addition, a fetus who has suffered an antepartum insult may be at increased risk of incurring further intrapartum injury¹⁵.

ANTEPARTUM SCREENING AND DIAGNOSIS

Fetal movement counting

Even though, fetal movements decreases in response to hypoxemia, making formalized maternal assessment of fetal movements a potentially simple method of monitoring fetal oxygenation and well-being, a recent systematic review concluded that there is insufficient evidence to recommend routine fetal movement to reduce PA¹⁶. CST, NST, biophysical properties (BPP) and modified BPP

The contraction stress test (CST) is based on the promise that uterine contractions transiently restrict oxygen delivery to the fetus and that a hypoxic fetus will demonstrate recurrent late decelerations. Drawbacks to the CST include the

need to stimulate contractions and the fact that inducing contractions is contraindicated in a number of conditions (e.g., placenta previa)¹⁷. CST is replaced by a less intensive method, the non stress test (NST), combined with real-time ultrasonography. When normal, these tests are highly reassuring with a low false-negative rate.

The biophysical profile (BPP) combines the ultra sonographic estimation of Amniotic Fluid Volume (AFV) with the NST is felt to assess indicators of both acute (NST, breathing, body movement) and chronic (AFV) hypoxia, and the BPP score is linearly correlated with fetal pH¹⁸.

Recent evidence suggests that Doppler evaluation of fetal veins combined with arterial assessments is useful for predicting PA in growth-restricted fetuses¹⁹.

INTRAPARTUM MONITORING

Although, there is insufficient scientific evidence to demonstrate, that any form of intrapartum fetal monitoring including cardiotocography, fetal blood sampling, fetal PH monitoring lactate measurement, fetal pulse oximeter and ST waveform analysis improves clinical outcome, several centres have reported a reductions in HIE and intrapartum death rates^{20,21}.

DIAGNOSIS OF PA IN THE NEONATE

The American Academy of Paediatrics (AAP) and the American College of Obstetrics and Gynaecologist (ACOG) have the following essential criteria to diagnose PA²²:

- I. profound metabolic or mixed acidemia (pH <7.0 in an umbilical arterial blood at birth)
- II. persistence of an Apgar score of 0–3 for longer than 5 min



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- III. neonatal neurologic sequelae (e.g. seizures, coma, hypotonia),
- IV. multiple organ involvement (e.g. kidney, lungs, liver, heart, intestines)

A widely used clinical classification of HIE devised by Sarnat & Sarnat (1976) classifies HIE into 3 stages, according to the conscious level, neurological and autonomic parameters and collates these with electroencephalographic (EEG) findings in the baby²³;

1. Mild (stage I)- characterized by hyper alertness, uninhibited Moro and stretch reflexes, sympathetic effects, and a normal EEG
2. Moderate (stage II)- infant has obtundation, hypotonia, strong distal flexion, and multifocal seizures. The EEG shows a periodic pattern sometimes preceded by continuous delta activity.
3. Severe- stage 3 – infant is stuporous and flaccid, with suppressed brain stem and autonomic functions. The EEG is iso-potential or has infrequent periodic discharges.

HIE is known to cause a wide spectrum of long-term neurological and psychiatric outcomes. Severe HIE causes cerebral palsy, mental retardation and epilepsy²⁴. Mild to moderate asphyxia has been associated with cognitive and behavioral disorders such as low IQ, hyperactivity, autism and attention deficits in children and adolescents. There has also been an increased incidence of schizophrenia and psychotic disorders in adulthood in affected infants²⁴.

MARKERS OF PA

Since early intervention minimizes or prevents long-term adverse neurological outcome, much effort has been directed towards identifying early markers of PA. There is no single serological marker predictive of HIE. The number of Nucleated RBC (NRBC) count and NRBC count per 100 white blood cells (NRBC/100WBCs) have been found to be higher in patients developing HIE grade III²⁵. Serum lactate dehydrogenase [LDH] was also found to be a good predictor of HIE during the first 12 hours after birth^{26,27}. These results offer potential inexpensive prognostic markers in newborn infants with perinatal asphyxia.

Other markers include serum levels of creatine kinase – Brain Band (CK-BB) and Interleukin-6 and which show a correlation with the severity of HIE and its long-term outcome. Elevated levels of CK-BB show an early positive correlation (as early as 2 hours after birth), with the severity of asphyxia²⁵. However these markers are not routinely available in resource-restricted settings, where PA is more prevalent.

EEG MONITORING

EEG is a simple bedside investigation which usefully correlates with the broad outcome of HIE. While a normal EEG denotes normal outcome, and EEG with burst suppression indicates death or a pathological outcome in affected infants²⁵. Amplified integrated EEG (a EEG) – a continuous bedside monitoring of single channel EEG - recorded during the first 72 hours after birth, also had a strong predictive value in infants with HIE²⁸.

IMAGING STUDIES

Cranial ultrasound is a simple, freely available investigation which can be used to identify changes of HIE, but it is not very useful in the early stages. Magnetic Resonance Imaging (MRI) is the most useful since it shows specific changes as early as 4th day of HIE, and hence could be used as an early prognostic tool²⁵.

Changes in MRI performed during the second week of life can be used as a prognostic indicator for long-term outcome in affected neonates²⁹.

TREATMENT MODALITIES

Therapeutic hypothermia (TH) is a process of controlled cooling of head and/or body, used as a method of neuroprotection in conditions of severe insults to the brain. During the last decade, TH has become established as the standard treatment method for infants with moderate or severe HIE born after 35 weeks of gestation.

Current treatment protocols for TH consist of slow controlled head or body cooling. TH is essentially commenced within the first 6 hours of life, with cooling to either $34.5 \pm 0.5^\circ\text{C}$ (for head cooling) or $33.5 \pm 0.5^\circ\text{C}$ (for whole-body cooling) and continued for 48–72 hours³⁰.

Meta analyses from RTC shows a definite beneficial effect of TH for infants with

moderate and severe HIE, specially when treatment is commenced within the first six hours of life³¹. However, its efficacy and safety in infants less than 35 weeks of gestation is yet to be established³⁴. Adverse effects observed with TH were infrequent in the target temperature ranges and time limits used – 33.5°C to 34.5°C , up to 72 hours³¹. The most common were sinus bradycardia and prolongation of the QT interval on ECG - both physiological responses to hypothermia. Rare effects included reddening or hardening of the skin (in systemic hypothermia) and of the scalp (in head cooling), and subcutaneous fat necrosis. Significant thrombocytopenia (platelet count $<150\,000/\text{mm}^3$) occurred in some patients³¹.

COMBINED THERAPY

Improved neuro protection has been reported when TH was combined with anticonvulsant or anti-excitatory drugs including phenobarbital^{32,33}, topiramate and levetiracetam^{34,35}. A phase III clinical trial on the adjuvant effect of Magnesium sulphate on TH (which has been recently concluded) is also showing important evidence to this effect, while erythropoietin, and Stem Cell transplants show promising results in a few ongoing clinical trials^{25,36}.

CONCLUSION

Perinatal asphyxia will result in neonatal hypoxia and tissue/organ injury. A variety of maternal, obstetric, and neonatal conditions predispose the fetus and newborn to asphyxia, which can occur before, during or after birth. One of the most effective ways to reduce the risk is to be vigilance of at-risk pregnancies and appropriate timely intervention. It is important to develop intra partum fetal monitoring techniques and to assure that health-care professionals have an easier access even though many of these techniques is controversial and the ability to detect fetal compromise is often unknown.

In the last decade, significant progress has been made in the treatment of infants affected with HIE. Therapeutic Hypothermia has emerged as the most useful treatment option in the last decade and more extensive research needs to be done to fine tune its therapeutic option and their applicability in pre term infants.

Early clinical trials with other adjuvant therapies such as anticonvulsants, antioxidants and anti-inflammatory drugs have also proven to be of use. Other interventions such as brain Stem cell transplantation, and the use of Insulin like GF and erythropoietin are also showing promising results in ongoing trials.

Although PA is hypothetically preventable, as clinicians we realize that this is not so in real life situations. Therefore, it is heartening to know that successful therapeutic options are available for affected infants. However, the main treatment options are still at a relatively early stage and further urgent research is needed to maximize benefits of these options.

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