

RECENT ADVANCES IN THE MANAGEMENT OF HYPOXIC ISCHEMIC ENCEPHALOPATHY

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Abstract : Perinatal asphyxia is an important cause of both neonatal deaths and devastating sequelae amongst survivors. Conventional neuroprotection treatments have not been very useful in improving outcomes. There have been newer strategies such as hypothermia, phenobarbitone, magnesium sulphate and allopurinol which seem to hold some promise for improving outcomes of neonates with hypoxic ischemic encephalopathy.

Perinatal asphyxia accounts for about 20% of neonatal deaths. Hypoxic ischemic encephalopathy (HIE) is an important cause of morbidity and mortality in term neonates. It is also an important cause of cerebral palsy and mental retardation. The pathogenesis of HIE is a result of cascade of multiple biochemical processes. Our current understanding of the cellular mechanisms of HIE indicate neuronal damage is consequent to several mechanisms that occur in response to hypoxia and ischemia to the neuronal cell. These include release of oxygen free radicals, calcium influx into the cell and presence of glutamate, which facilitates calcium influx into the cell consequent to cell energy failure¹. The result of these responses is either cell necrosis due to primary energy cell failure or delayed neuronal death due to secondary energy cell failure and apoptosis. The interval between the primary and secondary energy failure phases offers a 'therapeutic window' during which time treatments can be applied to reduce brain injury. The exact duration of this therapeutic window is not known, but animal experiments suggest that it could be about 6 hours².

CURRENT STANDARD MANAGEMENT

In asphyxiated neonates it is important that effective resuscitation is carried out to establish oxygenation and circulation. There is sufficient evidence to indicate that room air is as effective as 100% oxygen in neonatal resuscitation and results in lower mortality and potentially generate less oxygen free radicals. Standard management practices include maintaining ventilation, perfusion, fluid and electrolyte balance and normal acid-base status. The conventional practices for neuroprotection in neonates with HIE aimed at reducing cerebral edema - hyperventilation or use of decongestive agents, and seizure control have not resulted in improved outcome of neonates with HIE. Investigators were prompted to use oxygen radical scavengers, calcium channel blockers and glutamate antagonists to ameliorate the damage due to primary energy cell failure and necrosis. However, in animal experiments their benefit has been demonstrated when animals were pre-treated with these agents before the hypoxic insult. However, these modalities are not of great benefit in the clinical situation. Promising interventions have been hypothermia, phenobarbital and drugs such as allopurinol.

Phenobarbital.

Phenobarbital has been a subject of investigation in perinatal asphyxia

for several years. Hall et al conducted a randomized controlled study to study the effect of 40mg/kg phenobarbital given within few hours of birth in babies with severe asphyxia. The phenobarbital group had a 27% lower incidence of seizures and improved neurodevelopmental outcome at 3 years⁴. In a more recent study Singh et al⁵ conducted an RCT in neonates > 34 weeks with HIE in the first six hours of life to study the effect of phenobarbital 20 mg/kg IV on death or abnormal neurologic examination at discharge. There was a significant reduction in seizures in the phenobarbital group (8%) compared to the controls (40%). There was no significant difference in mortality or neurologic abnormality at discharge. However, it is still not clear who are the neonates who should get phenobarbitone, when and at what dosage?

Hypothermia.

Hypothermia during experimental ischemia has been shown to have long lasting neuroprotection. The exact mechanism for its beneficial effects is not known, but it is believed that cooling affects all pathways that leads to cell death. Reduction of cerebral metabolic rate by cooling of the head has demonstrated substantial neuronal cell recovery. Both experimental and clinical trials have demonstrated recovery of cellular energy functions after head cooling and consequently better long term outcomes in animals or infants treated by head cooling. Hypothermia also decreases permeability of the blood-brain barrier and recovery of electrophysiologic function after cerebral ischemia. A meta-analysis by Schulzke et al⁶ reviews all randomized clinical trials that have used either head or whole body cooling in asphyxiated neonates. They identified 5 clinical trials that enrolled 552 neonates. These trials considered infants as asphyxiated if one of the following were present: 10 minute apgar was ≤ 5 , pH ≤ 7.1 within one hour of life or ongoing resuscitation at 10 minutes of life. One of the studies used selective head cooling while the remaining 4 used total body cooling. The target cooling ranged from 32.5-35.5°C. The analysis revealed a relative risk (RR) of 0.78 (95%CI 0.66-0.92) for death or disability in favor of hypothermia on pooling data from 3 trials. When mortality was assessed, pooled data from all 5 trials showed a benefit in favor of therapeutic cooling (RR 0.75; 95% CI 0.59,0.96). When neuro-developmental abnormality at >18 months was assessed, a significant benefit was seen in favor of cooling (RR 0.72; 95% CI 0.52, 0.98). There was no benefit with respect to visual or hearing disabilities. Significant adverse events reported included sinus

bradycardia and thrombocytopenia. In addition to the trials reviewed, there are atleast three more trials^{7,8,9} that have just been completed and would add about another 600 neonates to the number treated with this modality of treatment.

There are, however, several unanswered questions – who are the target subjects to be included for cooling?, what is the optimal age to initiate cooling, to what extent and how long should cooling be done? What is the most effective and safe way of cooling?

MAGNESIUM SULPHATE

Magnesium is a NMDA receptor antagonist that blocks the influx of Ca^{++} into the neuronal cell. Experimental studies in newborn animals have demonstrated a neuroprotective effect of magnesium. A retrospective study indicates that preterm neonates whose mothers received $MgSO_4$ as tocolysis, had decreased cerebral palsy compared to gestation matched infants whose mothers had not been exposed to $MgSO_4$ (10). While these suggest some promising effects, there are at present no randomized controlled clinical trials in asphyxiated neonates which have shown its benefit. One would have to wait for results from RCTs before it can be recommended in clinical practice.

Allopurinol. It is an inhibitor of xanthine oxidase enzyme, resulting in the blocking of conversion of hypoxanthine to xanthine and thus avoiding the formation of free oxygen radicals. In experimental animal models pre-treatment with allopurinol before inducing hypoxia and ischemia results in protective effect by preserving cerebral energy metabolism. In the clinical setting, administration of 40mg/kg of allopurinol within 4 hrs of birth to 22 asphyxiated newborns resulted in improved survival in the allopurinol group compared to the controls as also decreased free oxygen radical formation¹¹.

FUTURE THERAPIES

Some of the newer therapies which could impact the outcome of HIE in the future include gene therapy and intracellular calcium buffering. Bcl-2 is a proto-onco gene which is known to be an inhibitor of pathways leading to cell death. It is postulated that HIE induced apoptosis could be modified by gene therapy.

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