NEUROPROTECTION IN NEONATAL HYPOXIC ISCHEMIC ENCEPHALOPATHY: THERAPEUTIC HYPOTHERMIA AND BEYOND

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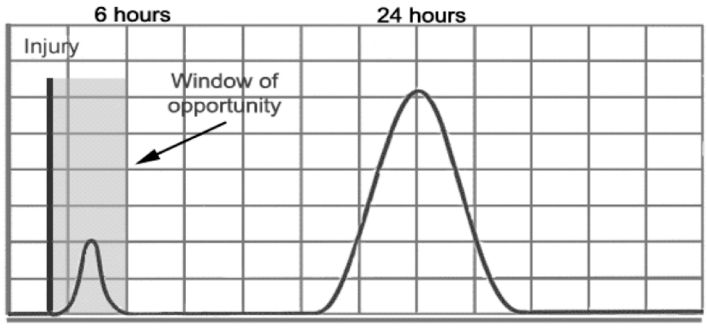
Perinatal Asphyxia continues to be a major cause of neonatal mortality and morbidity even in the most technologically advanced and prosperous countries of the world. The incidence remains unchanged; 1-2% of live births in developed world countries[1] and much higher in developing world countries[2]. The Indian National Neonatal Perinatal Database reported an incidence of 5% among studies conducted in sixteen medical institutes[2]. Perinatal Asphyxia is a multisystem disorder. Neonatal brain is the most important organ affected by Asphyxic insult because the resulting neuronal damage is permanent. Hypoxic Ischemic Encephalopathy (HIE), the pathognomonic clinical syndrome of asphyxic neuronal insult, occurs in 50-60% of babies with Perinatal Asphyxia[3]. Moderate and severe HIE causes significant neonatal mortality and morbidity[4]. Among patients with moderate HIE, 10-20% die and 30-40% develop neurological deficit, whereas 50% of patients with severe HIE die and almost all survivors develop neurological deficits[5]. Hence the toll on the society continues to be very high in spite of dramatic improvements in neonatal intact survival, particularly in developed world countries.

Until recent years, the management of HIE was limited to supportive intensive care only because there was no specific treatment available to rescue neurons during HIE. However, over the last decade, therapeutic Hypothermia, has emerged as a promising new therapy in reducing neonatal mortality and morbidity due to HIE[6]. This is due to improved understanding of the physiology of neuronal damage during asphyxia insult[7]. Hypoxic Ischemic Encephalopathy (HIE) is a dynamic process which evolves over a period of seventy two hours starting from the time of insult (Fig 1). Two distinct episodes of neuronal damage occur during this time. The immediate (primary) hypoxic insult is followed by a latent period of recovery which lasts for almost six hours. This is followed by a much longer and profound period of secondary neuronal damage due to the release of chemical mediators. Therapeutic modalities which can potentially reduce the release of these chemical mediators will provide neuronal rescue. Moderate controlled hypothermia (33.5-34.5 ^{0}C) offered during the first 72 hours after the asphyxic insult is one such therapeutic modality which has been the subject of animal studies as well as extensive multicenter trails in human infants over the last two decades[8-12].

Figure 1: Physiology of neuronal damage during Hypoxic Ischemic Encephalopathy secondary to Perinatal Asphyxia



The studies on animal models have not only confirmed the safety of moderate therapeutic hypothermia; they have also shown a dramatic neuronal rescue in experimental HIE model of lambs subjected to prolonged therapeutic hypothermia immediately after birth[8]. This was followed by pilot RCT's in human infants; the outcomes of which were very encouraging[9]. However a universal change of practice required large well designed multicenter trails and Meta analyses. Three recently published large multicenter RCT's and two meta analyses have provided sufficient evidence of the safety and neuroprotective efficacy of moderate therapeutic (33.5-34.5 ^{0}C) administered to human infants during the first 72 hours of life[10-12]. Among the NICU's in the developed world, therapeutic hypothermia has now become a standard of care for asphyxiated term neonates[13].

The large multicenter Total Body Hypothermia (TOBY) Trial from UK has confirmed that therapeutic hypothermia improves the combined outcome of death and severe disability with increased rate of survival without neurologic abnormality and reduced risks of cerebral palsy at 18 months of age[10]. The neo.nEURO.network therapeutic hypothermia trial, conducted in 24 European centers, has shown a strong neuroprotective effect of systemic hypothermia at 18 to 21 months of age in babies with HIE due to Perinatal Asphyxia[11]. The study also documented two new additional conclusions: one that therapeutic hypothermia is also neuroprotective in severe HIE and second that the combination of therapeutic hypothermia and morphine as a co treatment had a statistically significant neuroprotective effect as compared to therapeutic hypothermia and fentanyl[11]. The second finding has opened a new era of designing hypothermia plus therapies which may have a potential additive neuroprotective effect. Wen-hao Zhou and colleagues have recently (2010) published the results of a large hypothermia trial from China[12]. Their study has shown that selective head cooling combined with mild systemic hypothermia for 72 hours may significantly decrease the combined outcome of severe disability and death, as well as severe disability alone[12].

The Cochrane meta-analysis of 2007 had shown the effectiveness of hypothermia for improving the combined outcome of death and neurodevelopment disability after hypoxic ischemic injury[14]. A most recent large meta analysis of ten studied including three large RCT's has shown that prolonged moderate hypothermia improves survival and reduces the rate of disability at 18 months of age in infants who survive hypoxic ischemic encephalopathy[15]. Although the six year follow up data from the major trials is still awaited, the beneficial effects of therapeutic hypothermia are likely to persist because large Magnetic Resonance Imaging (MRI) data sets have shown significantly less structural brain damage in cooled infants[16].

After having established therapeutic hypothermia as a safe and effective modality for neuroprotection in HIE, the neonatologists are facing a new question. Can we enhance the neuroprotective effect of therapeutic hypothermia by adding other potential neuroprotective agents[13,17]? These potential therapeutic agents include Xenon, Erythropoetin, Magnisium Sulphate, Allopurinol, Opoids, Topiramate, Inhaled Nitric Oxide (iNO), N-Acetylcystine, Minocycline and Melatonin[13,17]. Due to their different mechanisms of action, it is likely that these neuroprotective therapies may add incrementally to the proven beneficial effects of hypothermia. Indeed hypothermia may buy additional time for these neuroprotective agents to act within an expanded 'therapeutic window'[13]. These Hypothermia plus therapies are going to be the subject of many new RCT's worldwide over the next few years.

Magnesium Sulphate, a potential neuroprotective agent, acts by reducing neuronal excitotocity[17]. MgSO4 has long been used in Obstertrics as a tocolytic agent and has a proven neuroprotective effect in preterm babies born to mothers tocolyzed with MgSO4[18]. A recently conducted RCT in human neonates has compared postnatal magnesium sulfate with placebo in the management of Neonatal HIE[19]. This study, which did not use hypothermia therapy due to lack of facilities, has shown that treatment with MgSO4 improves neurologic outcomes at discharge in term neonates with severe perinatal asphyxia[19]. The animal studies done by Knuckley's group has compared a combination of therapeutic hypothermia and MgSO4 with therapeutic hypothermia alone. In their rat model MgSO4 alone had a minimal beneficial effect. However, MgSO4 plus hypothermia had a significant beneficial effect in reducing the size of the post asphyxia infact[20]. This animal focal stroke model provides an intriguing suggestion that hypothermia plus MgSO4 provides an additive neuroprotection. No human studies have been done so far to test the difference between therapeutic hypothermia alone and therapeutic hypothermia plus MgSO4. Meg Cool Study (Hypothermia plus MgSO4 Vs Hypothermia plus placebo), a multicenter randomized controlled trial, is one such study to test this hypothesis in near future.

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