Editorial

Therapeutic Hypothermia for Neonatal Hypoxic-Ischaemic Encephalopathy

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Hypoxic-ischaemic encephalopathy (HIE) is an important cause of death and later neurological disability in full-term neonates worldwide. Perinatal asphyxia causes about 19% of the over 5 million neonatal deaths worldwide annually.[1] Despite advances in antepartum and intrapartum monitoring, and neonatal resuscitation, the incidence of HIE varies between 1.8 and 6 per 1000 term infants in developed nations, whereas in developing countries it appears to be more common.[2,3] At KK Women's and Children's Hospital, Singapore the incidence of HIE during the year 1992-1995 was 0.9 per 1000 births, and in 2003-2004 this has been reduced to 0.3 per 1000 births.

Types of Brain Injury

Neonatal HIE is a progressive and evolving process, and multiple biochemical cascades contribute to its pathogenesis.[4] The brain injury begins with the initial hypoxic-ischaemic event (primary phase of energy failure). After resuscitation from the initial insult, there is a latent stage characterised by restoration of the cerebral oxidative metabolism. However, 6 to 24 hours later, there may be a further deterioration resulting in a secondary phase of energy failure. The severity of this delayed energy failure closely correlates with survival and neurodevelopmental sequelae.[5] The interval between the primary and the secondary energy failure corresponds to the therapeutic window, and during this time treatment may be applied to reduce brain injury. The exact duration of this therapeutic window is not known but in fetal sheep it is up to 5.5 hours after the ischaemic insult.[6] Some specific neuroprotective strategies have emerged in the past decade. Mild-to-moderate cerebral hypothermia begun before the secondary deterioration seems to offer neuroprotection in experimental animals, adult patients and newborn infants. The neuroprotective effect diminishes and disappears if cooling is delayed beyond 6 hours.

Current Management

The cornerstone of management after hypoxic-ischaemia is still supportive care. It is essential to establish adequate oxygenation and restore circulation by appropriate, rapid and effective resuscitation. Air is as effective as 100% oxygen in resuscitation, and may cause less potentially harmful cerebral vasoconstriction and lesser generation of excess free radicals.[7] It is vital to maintain adequate ventilation, systemic blood pressure, tissue perfusion, and normoglycaemia; to control seizures; and to correct electrolyte and acid-base disorders. Hyperthermia should be avoided and normothermia (core temperature 36°C to 37°C, skin temperature 36.0°C to 36.3°C) needs to be maintained. However, follow-up results of infants with HIE who were managed by the above standard intensive regimen has not been encouraging. The adverse outcome (death or disability) for infants with severe HIE varies between 75% and 100%, and for those with moderate HIE between 25% and 50% (468).[8,9] There is clear evidence that brain injury is more severe when fever is superimposed on a hypoxic-ischaemic insult.[10] Intrapartum fever has been reported to be associated with an increased risk of unexplained early-onset neonatal seizures and cerebral palsy in term infants.[11] It may be prudent not to keep near-term and term infants who have sustained perinatal asphyxia, under a radiant warmer after resuscitation, because of the risk of inadvertent hyperthermia, which may aggravate brain injury. Severe hyperoxia and hypocapnia have also been associated with adverse outcome in infants with HIE and, therefore, during the first hours of life, oxygen supplementation and ventilation should be rigorously controlled.[12]

Animal Studies

Hypothermia has been extensively studied as a neuroprotective strategy in newborn and adult animal models after ischaemia and hypoxia-ischaemia. The documented benefits include the amelioration of delayed energy failure, attenuation of extracellular excitotoxcity, reduced nitric oxide production, blockade of caspase-3 activation and the inhibition of apoptosis.[13] Thus, brain cooling interferes favourably with the multiple pathways contributing to brain injury and has been shown to improve neuropathological, cerebral energetic, electrophysiological and neurobehavioural outcomes.[13-15] A reduction in both

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the severity and the extent of brain injury has been demonstrated in experiments in perinatal animals (sheep, rats and piglets) even when a reduction in brain temperature of 2°C to 5°C is initiated up to 5.5 hours after the brain insult.[6]

Brain Cooling Methods

Brain hypothermia can be achieved by cooling the body, cooling the head selectively, or by cooling the head and body together. Whole body cooling provides homogeneous cooling to all brain structures, including the peripheral and central brain regions, whereas selective head cooling provides greater cooling to the periphery of the brain than to the deeper brain structures.[16] The combination of head and body cooling minimises the temperature gradients across the brain and also facilitates the cooling of the deeper regions

Several cooling systems have been used in the newborn infants to induce moderate hypothermia. In a study by Gunn et al,[17] selective head cooling was accomplished by circulating water at 10°C through a coil of tubing wrapped around the head (CoolCap). A servo-controlled overhead heater was used to maintain rectal temperature at 34°C to 35°C. Simbruner et al[18] in their study on asphyxiated newborn infants induced hypothermia by placing a cap, formed from cooled packs around the head at a temperature of 10°C, to maintain a nasopharyngeal temperature of 34°C to 35°C for 3 days. The other method of brain cooling was by means of systemic hypothermia, accomplished by placing infants on a water blanket pre-cooled to 5°C and the blanket temperature was servo-controlled to maintain an oesophageal temperature of 33.5°C for 72 hours.[19] A commercially available cooling system (Blanketrol II Hyperthermia-Hypothermia System) was used to control brain temperature during whole body hypothermia. The use of a second cooling blanket has been recommended to minimise the variability in oesophageal temperature, which reflects the core temperature of the brain. Azzopardi and coworkers[20] had examined the feasibility of inducing whole-body hypothermia by blowing cool air through a translucent perforated paper blanket that was placed over the infant.

Safety

A wide range of adverse effects from mild to modest hypothermia have been described.[17] They include decreased cardiac output, hypotension, hypertension, arrhythmias, hyperviscosity, increased vascular resistance, platelet dysfunction, excessive fibrinolytic activity, diuresis due to suppression of antidiuretic hormones, pulmonary hypertension, impaired leukocyte mobility and phagocytosis, metabolic acidosis, hyperglycaemia and hypokalaemia. Two randomised controlled trials have established the safety of mild hypothermia (rectal temperature 34°C to 35°C) with selective head cooling.[17,21] The reported side effects were scalp oedema, relative bradycardia, and mild transient hyperglycaemia in infants assigned to head cooling. A randomised pilot trial of moderate systemic hypothermia (33°C) versus normothermia (37°C) for 48 hours reported a significantly higher incidence of bradycardia, haematuria, longer dependence on vasopressors, prolonged prothrombin times, and thrombocytopaenia requiring platelets transfusions, in the hypothermia arm.[22] However, the side effects were manageable with minor interventions. On the contrary, a larger study on whole-body hyperthermia did not find any difference in the incidence of serious adverse events between the hypothermia and controlled groups.[19] Four (4%) of the infants in the hypothermia group had skin changes (erythermia, sclerema, cyanosis and subcutaneous fat-necrosis), which resolved spontaneously.

Efficacy

Recently, 3 multicentre randomised controlled trials[19,21,22] of induced hypothermia in near-term and term infants with HIE have been published. The CoolingCap Study by Gluckman et al[21] included clinical, biochemical and amplitude integrated electroencephalography (aEEG) criteria for enrolment in the trial. Selective head cooling with mild systemic hypothermia was used in the intervention arm. The results showed no significant difference in death or severe disability at 18 months between the hypothermia and controlled groups, 59/108 (55%) vs 73/110 (66%), with odds ratio of 0.61; 95% CI, 0.34-1.09, $P = 0.1$. Predefined subgroup analysis suggested that head cooling had no effect in infants with severe aEEG abnormalities 79% vs 68%, $P = 0.51$, but was beneficial in infants with moderate aEEG changes 48% vs 66%, $P = 0.02$, odds ratio 0.42; 95% CI, 0.22-0.80, $P = 0.009$. The number needed to treat was 6 infants (95% CI, 3-27).

The two other studies used whole-body hypothermia as a rescue strategy and the eligibility criteria were clinical signs of moderate/severe HIE and presence of severe acidosis. Eicher et al[22] showed a significant reduction in the combined outcome of death and severe motor scores at 12 months in the hypothermia group, 14/27 (52%); 95% CI, 0.43-0.6, compared with 21/25 (84%); 95% CI, 0.77-0.91 in the control group ($P = 0.019$). The number needed to treat was 3. A large randomised study of whole-body hypothermia by Shankaran et al[19] demonstrated protection among all infants (irrespective of severity of HIE) studied at 18 to 22 months. Death or moderate or severe disability occurred in 45/102 (44%) in the hypothermia group versus 64/103 (62%) in the control group (risk ratio 0.72; 95% CI, 0.54-0.95, $P = 0.01$), and the number needed to treat was 6 infants. The rate of cerebral palsy was not significantly lower in the hypothermia group, 19% vs 30% (risk ratio 0.68; 95% CI, 0.38-1.22, $P = 0.20$).

The results of the brain cooling studies in newborn infants with HIE appear favourable, but they do not provide the necessary evidence of efficacy. The randomised and feasibility studies support the safety of mild-to-moderate hypothermia with minimal adverse events in the infants studied. One of the major concerns with any new therapy in neonatal medicine is the possibility that the new intervention would increase number of surviving infants with major disabilities who would have succumbed otherwise.

However, the published studies allay this concern. The reasons for the poor neuroprotective effect of hypothermia in some infants studied are not clear, and they may include:- delay in the initiation of therapeutic hypothermia; occurrence of irreversible brain damage in some infants with severe encephalopathy; hypoxic-injury may not be the aetiology of encephalopathy even in the presence of depressed Apgar scores and cord blood acidaemia and the neuroprotective role of moderate hypothermia has not been established for conditions other than HIE. There is also insufficient information to determine whether one method of cooling is more effective than the other.

Currently, a number of well-designed trials of therapeutic hypothermia for HIE are under way, using different cooling strategies in the USA, Europe and Australia. We await with optimism the results of those studies, as well as their synthesis into systematic reviews and useful meta-analysis. Until then, the widespread application of therapeutic hypothermia in the care of newborn infants with HIE cannot be recommended; brain cooling can be initiated only as part of a randomised trial in tertiary care neonatal units. Neonatal centres, which do not participate in such trials, should be encouraged to do so to expedite the completion of the studies. Each country should have a centralised registry for neonatal encephalopathy and the prospectively collected data should include treatment modalities including brain cooling and neurodevelopmental follow-up.

Until more data are available, centres which do not take part in brain cooling studies may continue to manage infants with HIE with the current standard supportive care as described above. However, care should be taken to avoid hyperthermia, hyperoxia and hypocapnia, which may further aggravate brain injury.

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