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Review

PERINATAL ASPHYXIA AND TREATMENT WITH HYPOTHERMIA

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Hypoxia-ischaemia in the perinatal period is a major cause of neonatal death and long-term disability. There are advances in research of cellular processes and molecular mechanisms underlying hypoxic-ischaemic encephalopathy (HIE) over the last decades. In recent multicenter clinical trials, hypothermia initiated within the first 6 postnatal hours has emerged as the only effective treatment in reducing the risk of death and impairment. As hypothermia is a time-critical emergency treatment after perinatal asphyxia, optimal collaboration among local hospitals, transport team, and cooling centers is essential. National cooling protocols are needed in order to ensure safe cooling, appropriate monitoring, imaging, and follow-up assessment. A national registry is important to collect data on diagnosis, treatment, adverse events, and outcome.

Descriptors: HYPOTHERMIA, HIE, HYPOXIC-ISCHAEMIC ENCEPHALOPATHY, NEONATE, PERINATAL ASPHYXIA

Abbreviations:

aEEG - amplitude-integrated electroencephalography; CI - confidence interval; HIE - hypoxic ischaemic encephalopathy; MRI - magnetic resonance imaging; MRS - magnetic resonance spectroscopy; NCT - National Clinical Trial (http://clinicaltrials.gov); NICHD - National Institute of Child Health and Human Development; OR - odds ratio; RCT - randomized controlled trial; RR - relative risk

INTRODUCTION

The clinical term "asphyxia" is widely used but there is little consensus as to what is meant by it. The expression "hypoxic-ischaemic insult" better describes the pathophysiology of intrapartum ischaemia and stresses the two major factors that contribute to the injury of the infant: inadequate blood flow (ischaemia) and oxygen delivery (hypoxia) to the brain. Asphyxia as a pathophysiological and clinical concept is also quite loosely defined due to the lack of reliable diagnostic criteria. In practice a number of different methods and concepts have been used, therefore caution is advisable when comparing incidence and outcome results. In the past, depression of the Apgar score has been widely used, and often misused, as a method for determining asphyxia and predicting outcome. A score of 5 or less at 10 minutes after birth was used as the most sensitive of different Apgar ratings in the prediction of adverse outcome and was also highly specific (1). In the last decade, biochemical parameters such as pH, base deficit, lactate, and circulating biochemical markers specific for brain damage (such as vasoactive agents and nervous tissue peptides) determined by fetal, cord and arterial blood sampling before, at or shortly after birth became increasingly important (2, 3). To attribute hypoxic ischaemic encephalopathy (HIE) to perinatal asphyxia presence of a combination of parameters at birth or in the first hours after birth is required, such as metabolic acidosis with a cord blood pH <7.0 or a base deficit ≥12 mmol/L, early onset of clinical signs for encephalopathy, several organ dysfunction; and exclusion of other etiology such as trauma, coagulation disorders, metabolic disorders, and genetic causes (4). However, these criteria have been derived through consensus, not through evaluation of collated summaries of evidence (5).

INCIDENCE OF PERINATAL ASPHYXIA

In developed countries, peripartum asphyxia affects 3-5 per 1000 live births with subsequent moderate to severe HIE in 1.5 (95% CI: 1.3 to 1.7) per 1000 live full-term births (6). In resource-poor countries, its incidence is probably ten times more common (7). Of affected newborns, approximately 15-20% will die in the first postnatal months. At least 25% of survivors will sustain devastating long-term neurologic disabilities, including mental retardation, visual motor or perceptive dysfunction, increased hyperactivity, and seizure disorders (8). Specific types of cerebral palsy can be connected to perinatal hypoxic-ischaemic injury in 15% (9).

PATHOPHYSIOLOGY OF HYPOXIC - ISCHAEMIC (HI) INSULT

The development of brain injury after HI insult is an evolving process which is initiated during acute insult and extends into a reperfusion phase. Primary energy failure, which is a prerequisite for all subsequent deleterious events, is characterized by reductions in cerebral blood flow and consequently delivery of oxygen and substrates to brain tissue (10). High-energy phosphorylated compounds such as ATP and phosphocreatine are reduced, which causes a switch to anaerobic metabolism with accumulation of lactate and H+. Primary energy failure is associated with acute intracellular derangements, such as loss of membrane ionic homeostasis with increase of intracellular calcium, sodium and water, release and blocked uptake of excitatory neurotransmitters (particularly glutamate) which cause over activation of the receptors, defective osmotic regulation, and inhibition of protein synthesis (11). Increased intracellular calcium activates lipases, proteases and endonucleases and thus triggers destructive pathways resulting in acute cell death.

After resolution of HI insult cerebral metabolism may recover within time interval which is influenced by maturation, preconditioning events, simultaneous diseases, substrate availability, body temperature, and possibly individual genetic variations. However, after any significant HI insult secondary energy failure occurs in which decline of high-energy phosphorylated compounds is not accompanied by brain acidosis (10). The appearance of this phase varies according to species and to the nature of the insult with the onset at 8-16 hours and a nadir at 24-48 hours (12). It involves multiple pathophysiologic processes, including further accumulation of excitatory transmitters and hyperactivity of glutaminergic receptors, oxidative injury with free radical production, secondary inflammatory reaction, altered synthesis of proteins and growth factors, and ultimately initiation of accelerated apoptosis in brain cells or apoptosis of cells in the regions of brain where it is unintended. In contrast to the cell membrane disruption in primary energy failure that leads to necrosis, such programmed cell death is a nuclear phenomenon with DNA fragmentation and condensation (13). The interval between primary and secondary energy failure represents a latent phase that corresponds to an optimal available therapeutic window, possibly through alteration or avoidance of secondary energy failure.

PATHOLOGY

Advanced methods of neuroimaging have been used to identify changes after perinatal ischaemic insult to the immature brain. These patterns depend on the severity of the insult and the age at which it occurs (14). In the immature newborn and mature adult brain, the order of cellular elements vulnerable to asphyxia is neuron>oligodendroglia>astrocyte>microglia. Serial neuroimaging studies have shown that particular cells within central nervous system have selective susceptibility to injury with respect to maturational stage (15). In term newborns with HIE, three major regional patterns of neuronal necrosis are described: diffuse disease, cerebral-deep nuclear disease with prominent involvement of cerebral neo-cortex, hippocampus and basal ganglia-thalamus, and deep-nuclear-brain stem disease. Due to presence of vascular end- and border-zones in the white matter and impairment of cerebrovascular auto regulation, the principal form of HI brain injury in the immature brain involves cerebral white matter, causing periventricular leukomalacia (16).

CLINICAL FEATURES AND INVESTIGATIONS IN INFANTS WITH HIE

The presence of an abnormal neurologic examination in the first days of life remains the most useful indicator that a brain insult has occurred. For more than 40 years, clinicians evaluate term or late preterm infants after perinatal asphyxia in terms of Sarnat scores, or slightly modified variants of these scores (17). Newborns with mild HIE (Sarnat I) do not have an increased risk of motor or cognitive deficits. Those with moderate HIE (Sarnat II) may have significant memory impairment, visual dysfunction, increased hyperactivity, and delayed school readiness. Neonates with persistent severe encephalopathy (Sarnat III) have a high risk of death, and a risk of cerebral palsy and mental retardation among survivors that approaches 100%. Neuromonitoring with conventional EEG and a bedside amplitude-integrated EEG (aEEG) can provide additional information regarding current status and can be helpful in predicting long term outcome (18, 19). Cerebral oxymetry records regional saturation of the brain using Near Infrared Spectroscopy (NIRS) and provides a non-invasive method to continuously monitor brain oxygen imbalance. Serial magnetic resonance neuroimaging (MRI), including diffusion-weighted (DW) imaging, which measures the diffusion of water in tissues (less diffusion is proportional to more injury) is used to demonstrate evolving pathology in the first postnatal weeks (20). Magnetic resonance spectroscopy (MRS) of neonatal brain can detect metabolites such as lactate, N-acetyl aspartate, choline, and creatine that provide functional data regarding metabolic integrity of the brain (21). Although availability of MRI-DW may be limited in many clinical settings, the combination of all these methods (serial clinical assessment, EEG/aEEG, patterns of injury on MRI/MRS, and NIRS) is likely to be most useful for the prognosis in infants after perinatal asphyxia.

MANAGEMENT

As perinatal asphyxia creates a major burden for the individual, family and society, there is an urgent need to improve outcomes in affected infants. For decades, the treatment has been limited to supportive intensive care only. The latter includes correction of hemodynamic and pulmonary disturbances (such as hypotension, metabolic acidosis, hyper- or hypocapnia), maintenance of glucose, calcium, magnesium, and other serum electrolytes homeostasis, treatment of seizures if present (with phenobarbital as the preferred drug), and monitoring for other organ dysfunctions (such as acute renal failure) (22).

The insight into the biochemical and cellular mechanisms of neuronal injury in HIE helps to provide interventions to interrupt deleterious cascades, particularly during the short latency period between primary and secondary energy failure. At present, therapeutic mild hypothermia (3-5ºC below the normal level) seems to be the only effective intervention for HIE in term and late preterm infants for reducing the risk of death or

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neurological disability. The beneficial effects of hypothermia occur at multiple sites (23). A decrease in brain temperature from normothermic values reduced cerebral metabolic rate by approximately 5% for every 1ºC cooled (24). This lowered energy utilization could contribute to neuroprotection by enhancing the maintenance of high-energy ATP stores during and after hypoxic-ischaemic insult. Cerebral hypothermia during the latency and the secondary energy failure periods include normalization of protein synthesis, reduction in toxic nitric oxide and free radicals production, decreased release and increased uptake of excitatory amino acids (glutamate, dopamine), and modulation of activation of microglia and cytokine production (11, 12). Importantly, hypothermia influences apoptotic mechanisms within cells: caspase 3 activity is lessened and cytochrome c translocation is diminished, resulting in reduction in apoptotic neurons. Review of experimental studies of focal cerebral ischaemia indicates that mild hypothermia is associated with an approximately 50% reduction in infarct size. Following global hypoxic-ischaemic insult, hypothermia reduces damage in the cortex, thalamus, and hippocampus (25).

On the other hand, cooling may also be associated with harmful physiological changes in cardiovascular parameters (arrhythmia, decreased heart rate, elevated blood pressure), altered clotting, immunologic defects, pulmonary compromise, metabolic adverse effects, and hematologic effects (26).

The first RCT of hypothermia after perinatal asphyxia was reported by Gluckman et al in 2005 (*CoolCap trial*, 27). A total of 234 term infants with moderate to severe encephalopathy and an abnormal aEEG were randomized in the first 6 postnatal hours to either selective head cooling with mild systemic cooling (to a rectal temperature of 34-35ºC) for 72 hours or to conventional care in normothermia range. A protective effect of hypothermia with respect to combined outcome measure (death or severe disability at 18 months) was suggested (OR 0.57, 95% CI: 0.32-1.01), particularly in the group of infants with less severe aEEG changes (OR 0.42, 95% CI: 0.22-0.80). No clinically important complications associated to cooling were reported. Secondary analyses of data from CoolCap trial were published in 2007 and 2008 with the aim to examine a range of possible clinical factors that might influence outcomes (28, 29).

In a study similarly sized employing whole body cooling to 33.5ºC for 72 hours infants were selected by biochemical and medical history parameters, and a baseline neurological examination (National Institute of Child Health and Human Development, *NICHD trial*, 30). Prior a-EEG was not included in the enrollment criteria. As in the CoolCap trial, the relative risk for adverse outcome of death or moderate to severe disability at 18 months of age was reduced in cooled infants when compared to controls (RR 0.73, 95% CI: 0.56-0.95) and the number needed to treat to avoid one death or moderate/severe disability was 6 (27).

In 2009, the results of the Total Body Hypothermia for Neonatal Encephalopathy *(TOBY) trial* were reported; 325 infants were enrolled in the study before 6 hours of age (31). The infants were eligible for the study if they were at least 36 weeks of gestational age, plus, at 10 minutes of age, had either an Apgar score of 5 or less or a continued need for resuscitation, or within 60 minutes after birth, metabolic acidosis (umbilical cord, arterial or capillary pH of <7.0 or a base deficit of 16 mmol/L or more). They also had to show signs of moderate to severe encephalopathy and have at least 30 minutes of abnormal aEEG tracings (abnormal background activity or seizures).

Cooled infants received 72 hours of hypothermia to 33.5ºC with slow rewarming (rise of 0.5ºC per hour). The authors' conclusions were that the induction of moderate hypothermia for 3 days in infants after perinatal asphyxia did not significantly reduce the composite rate of death and severe disability (RR 0.86; 95% CI: 0.68-1.07, p=0.17), but resulted in increased rate of survival without neurologic disability (RR 1.57; 95% CI: 1.16-2.12, p=0.003). As in previous studies, serious adverse effects were rare and were not associated with cooling.

In the *ICE* (Infant Cooling Evaluation) *trial*, infants were recruited from wide geographic areas in Australia, and were cooled on transport using HotCold gel packs cooled to 10ºC (32). The cooled group core rectal temperature goal was 33-34ºC for 72 hours. The study enrolled 221 infants with gestational age of 35 weeks or more and evidence of intrapartum asphyxia plus moderate to severe encephalopathy. Enrollment ended in July 2007 because investigators had lost equipoise following publication of the studies by Gluckman and Shankaran and several meta-analyses of these and other smaller studies demonstrating a consistent benefit (27-30).

The European *neo.nEuro.network* trial of whole body cooling for 72 hours to 34.5ºC was terminated earlier than planned as well because of ethical concerns as current evidence of benefits of hypothermia did not justify further randomization of subjects to the control group (33). The authors reported significantly lower risk for death or severe disability at 18 months of age (OR 0.21, 95% CI: 0.09-0.54, p=0.001) than those in previously reported trials (27-32). They explained this difference by a stronger effect of hypothermia administered according to their protocol, which included an opioid analgesic (morphine 0.1 mg/kg every 4 hours or an equivalent dose of fentanyl) as a cotreatment.

In spite of different methods used to achieve hypothermia, different inclusion criteria, different target temperatures, and cotreatments in the RCTs, several independent *meta-analyses* of these trials have consistently concluded that hypothermia significantly reduces both death and disability after perinatal encephalopathy; is safe; produces outcomes that are homogeneous both within and between trials (1-3, 34-37). Assessments of secondary outcomes, including mortality separately, and disability separately, also demonstrated benefit. This is important because there were concerns that if mortality was averted by cooling, more survivors would be handicapped.

According to ILCOR 2010 guidelines, therapeutic hypothermia (33.5º to 34.5ºC) implemented within 6 hours

Table 1
Slovene inclusion and exclusion criteria for systemic hypothermia in infants with HIE (2011)

Tablica 1.
Kriteriji uključenja i isključenja za sistemsku hipotermiju u novorođenčadi s HIE u Sloveniji (2011)

Inclusion criteria
≥1 of criteria A (birth asphyxia)
- Apgar score of <5 at 10 minutes after birth
- Continued need for resuscitation (including endotracheal intubation or mask ventilation) at 10 minutes after birth
- Acidosis: pH <7.0 or base deficit of >16 mmol/L in umbilical cord, arterial or venous blood within 60 minutes after birth
AND
Criteria B (encephalopathy) with lethargy, stupor, or coma and ≥1 of the following:
- Hypotonia
- Abnormal reflexes, including oculomotor or pupillary abnormalities
- Absent or weak suck
- Clinical seizures
AND
Criteria C (abnormal aEEG recording)
- Abnormal background activity of at least 30 minutes duration on aEEG or
- Seizures on aEEG.
Exclusion criteria
- Infants expected to be ≥6 hours of age at time for beginning of hypothermia
- Infants with major congenital malformations (chromosomal abnormalities, brain malformations)

of birth is recommended as a standard practice for term or late preterm infants with moderate to severe HIE (38). A specific protocol and follow-up coordinated through a regional perinatal system is advocated.

In spite of numerous trials, currently there is either limited or no direct evidence that the use of additional drugs such as calcium channel blockers (nicardipine), free radical scavengers (allopurinol, deferoxamine, 3-iminobiotin), corticosteroids, inotropes (dopamine), mannitol, magnesium sulphate, prophylactic anticonvulsants, opiate antagonists (naloxone), or interventions such as hyperventilation, fluid restriction, and hyperbaric oxygen treatment, would be effective and safe in reducing mortality and adverse neurological outcomes in infants after perinatal asphyxia (39, 40).

Cautious optimism is warranted regarding the use of high-dose growth factors, such as recombinant human erythropoietin (rHuEPO) or brain-derived neurotrophic factor, as experimental evidence demonstrates decrease in oxidative injury, inflammation and apoptosis, and enhanced repair due to increased vasculogenesis and neurogenesis throughout or even late in the injury process (41, 42). Xenon (Xe), a rare, expensive (45 USD per L) monoatomic inert anesthetic gas with no documented adverse effects, possesses neuroprotective properties by inhibiting N-methyl-D-aspartate (NMDA) receptors and other subtypes of glutamate receptors, and by reducing apoptosis (43). Research in animals and preliminary results in infants have shown that inhaling 30-50% Xe for up to 18 hours in addition to cooling doubles neuroprotection; the protective effect is additive, and not synergistic (44, 45).

FUTURE

With 40% or more of cooled infants still dying or suffering moderate or severe long-term impairment, more work to discover additional neuroprotective strategies is required. The hypothermia trials excluded many infants, including those of age >6 hours and those with prematurity of <36 weeks, abnormal coagulation, persistent pulmonary hypertension, and congenital malformations. Given current knowledge and evidence these exclusion criteria should be reconsidered in future studies (46). Longer cooling duration (120 versus 72 hours), deeper cooling temperature (32º versus 33.5ºC) and their effects on the outcomes are currently being studied in NICHD study (47). A multicentric study of systemic hypothermia initiated after 6 hours of age ("late" cooling) has been initiated recently in the USA (48).

Hypothermia is also likely to be tested for its ability to provide neuroprotection for infants with heart disease requiring by-pass surgery and neonates on extracorporeal membrane oxygenation (ECMO; "NEST" trial, 49). A speculation has been raised regarding neuroprotective benefit of hypothermia for premature infants with HIE or necrotizing enterocolitis (50).

CONCLUSIONS

As hypothermia is a time-critical emergency treatment after perinatal asphyxia, optimal collaboration among obstetricians and neonatologists in local hospitals, transport team, and cooling centers is essential. National cooling protocols are needed in order to ensure safe cooling, appropriate monitoring, imaging, and follow-up assessment. A national registry is substantial to collect data on diagnosis, treatment, adverse events, and outcome. Local and national results should be reported to large databases where effectiveness and possible hazards of hypothermia can be analyzed in detail.

CURRENT STATUS OF THERAPEUTIC HYPOTHERMIA FOR NEONATAL HIE IN SLOVENIA

As the efficacy and safety of hypothermia has been demonstrated in multiple clinical trials, cooling of severely asphyxiated newborn has gained enthusiasm in all three Slovene intensive care units that provide tertiary level of care

for critically ill newborns. At first, controlled selective head cooling was applied at one center only (PICU of Pediatric Surgery and Intensive Care Department in University Medical Centre Ljubljana, 51). Passive systemic cooling with relatively simple techniques (ColdHot packs and turning the power of the heater above the baby off) was applied in the NICU of Maternity Hospital Ljubljana.

With increasing awareness of need for national guidelines with uniform cooling protocols and follow-up assessments, an advisory group for therapeutic hypothermia in newborns with HIE has been constituted in 2010. The aim was to offer systemic hypothermia to all term and near-term infants at highest risk for brain injury in consistency with protocols used in previous RCTs (31).

Slovene inclusion and exclusion criteria for therapeutic hypothermia are presented in Table 1. They are based on stepwise evaluation of evidence of birth asphyxia, clinical evidence of encephalopathy, and electrophysiological findings of HIE with aEEG (1-3). Cooling should be initiated within 6 hours of birth (exceptionally within 12 hours, due to the late admission to cooling center after transfer from local maternity hospital) and continued for 72 hours. Phase of rewarming should last at least 6 hours.

Hypothermia is induced within 60 minutes after the start of cooling and maintained with a servo-adjusted, water perfused cooling wrapping (CritiCool™, MTRE Advanced Technologies, Israel) for 72 hours. Skin temperature and rectal temperature (target 33º-34ºC, measured with thermistor probe 6 cm within the rectum) are monitored continuously. Uniform guidance on ventilatory and circulatory care, management of seizures, sedation (morphine 10 µg/kg/h, fentanyl and midazolame exceptionally), and fluid, electrolyte and glucose requirements is provided. Cranial ultrasonography should be performed daily for the first 4 days after birth, and MRI within 4 to 7 days after birth.

Follow-up evaluations consist of serial neurologic evaluations on the basis of Amiel-Tison neurological assessment to the age of 18 months, standard EEG recordings (at 2 weeks and 3 months of age), brain stem acoustic evoked potentials (at 3 months of age), ophthalmologic evaluation (at 1 year), and final neurodevelopmental assessment in the age of 18 months (Bayley Screening Test, BSID III, 53) (52). A national registry is planned to collect data on diagnosis, treatment, adverse events, and outcome from all Slovene cooling centers.

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Sažetak

ASFIKSIJA NOVOROĐENČETA I TERAPIJSKA HIPOTERMIJA

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Hipoksija i ishemija u perinatalnom razdoblju su najvažniji uzroci neonatalnog mortaliteta i oštećenja. Tijekom proteklog desetljeća veliki napredak je postignut u istraživanjima podloge hipoksično-ishemične encefalopatije (HIE) na razini staničnih i molekularnih mehanizama. U posljednjim multicentričnim kliničkim studijama utvrđeno je da hipotermija primijenjena u prvih 6 sati života novorođenčeta zapravo jedina smanjuje rizik oštećenja ili smrtnog ishoda. Kako je najvažnije započeti hipotermiju u prvih nekoliko sati vrlo je važna međusobna suradnja lokalnih bolnica, transportnog tima i centara koji rade hipotermiju. Važne je i postojanje smjernice na razine države da bi se osiguralo izvođenje hipotermije na siguran način, prikladno monitoriranje i naknadno praćenje. Također je potreban i registar na razini države radi skupljanja podataka o dijagnozi, liječenju i ishodima djece koja su tretirana hipotermijom.

Deskriptori: HIPOTERMIJA, HIE, HIPOKSIČNO-ISHEMIČNA ENCEFALOPATIJA, NOVOROĐENČE, PERINATALNA ASFIKSIJA