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CURRENT INSIGHTS IN BRAIN PROTECTION FOR THE SICK NEWBORN INFANT

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Abstract. This paper presents an overview of the modern antenatal and postnatal strategies in brain protection for both preterm and term born infants. It is known, that the two most common causes of neonatal brain injury are prematurity and hypoxic-ischemic encephalopathy (HIE) in the term born infant. Approximately one in nine babies is born before term. Nowadays these preterm born infants more often survive the neonatal period due to developments in treatment options in the last decades. They are however at a high risk for developing brain damage and neurodevelopmental impairment later in life. Approximately 40 % of survivors develop long-term intellectual or physical impairment, including cerebral palsy (CP). Term born infants born after perinatal asphyxia may also survive with a variety of neurocognitive disorders due to brain damage as a result from the hypoxic ischemic encephalopathy (HIE). Untreated, the sequelae of moderate to severe HIE includes a 60 to 65 % risk of mental retardation, CP, hydrocephalus, seizures, or death. The main goal in neonatal care for these surviving but vulnerable infants is to preserve brain function and prevent further brain damage, in order to improve neurocognitive outcome and the subsequent quality of life. In preterm brain protection antenatal strategies besides educating and supporting pregnant women regarding life style and healthy food intake, centralization of care for extreme preterm born infants, fetal monitoring in high risk pregnancies, administration of antenatal steroids for lung maturity, the use of intravenous magnesium sulfate administration to mothers just before preterm delivery are of great importance. In the postnatal strategies setting optimal oxygen saturation, the avoidance of prolonged artificial mechanical ventilation, hypoglycemia, hypocapnia electrolytic imbalances, hyperbilirubinemia, blood pressure shifts, stress and pain, inflammation, necrotizing enterocolitis as well as adequate feeding strongly predict neurocognitive outcome. In the term asphyxiated infants the brain experiences a cascade of problems occurring after energy failure which in fact are the basis of neuroprotective strategies. These strategies consist of anti-oxidative, anti-inflammatory, anti-excitatoxic and anti-apoptotic agents, and in the future possibly neurogenetic approaches, including stem cell therapy. In antenatal strategies prevention of asphyxia starts at promoting a healthy pregnancy and of an early recognition of fetal, placental or perinatal risk factors for hypoxia. Recent experimental trials have shown a possible beneficial effect of antenatal administration of the anti-oxidative agent allopurinol in a HIE. In postnatal strategies two methods to achieve therapeutic hypothermia were evaluated in newborn infants with HIE: whole body cooling and selective head cooling with mild systemic hypothermia with the conclusion: hypothermia should be instituted in term infants with moderate-to-severe hypoxic ischemic encephalopathy if identified before six hours of age. Monitoring of brain activity by means of amplitude integrated electroencephalography to identify infants with HIE is promising. Potential agents with either anti-oxidative, anti-inflammatory, anti-excitatoxic or anti-apoptotic capacities are currently being investigated in various phases of research.

Ключевые слова: newborn; hypoxic-ischemic encephalopathy; preterm born infants; antenatal prophylaxis and therapies; postnatal prophylaxis and therapies.

СОВРЕМЕННЫЕ ПОДХОДЫ К ЗАЩИТЕ МОЗГА БОЛЬНЫХ НОВОРОЖДЕННЫХ ДЕТЕЙ

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Резюме. Статья представляет собой обзор современных стратегий анте- и постнатальной защиты головного мозга доношенных и недоношенных детей. Известно, что основными причинами поражения мозга в неонатальном периоде являются недоношенность и гипоксически-ишемическая энцефалопатия (ГИЭ). Приблизительно каждый девятый ребенок рождается недоношенным. В настоящее время благодаря успехам в терапии, достигнутым в последние десятилетия, недоношенные дети чаще благополучно переживают неонатальный период. Тем не менее риск поражения головного мозга у них велик, и вероятность развития нарушений его развития в последующие годы остается высокой. Приблизительно у 40 % переживших неонатальнй период недоношенных детей развиваются длительные интеллектуальные или физические нарушения, в том числе церебральный паралич (ЦП). В постнеонатальном периоде у доношенных детей, родившихся в перинатальной асфиксии, из-за поражения мозга вследствие ГИЭ тоже могут оставаться нейрокогнитивные нарушения. При отсутствии лечения тяжелая и средней тяжести ГИЭ с 60–65 % вероятностью приводит к задержке умственного развития, ЦП, гидроцефалии, судорогам или смерти. Основной целью лечения в неонатальном периоде этих жизнеспособных, но очень ранимых детей, является сохранение функций головного мозга, предотвращение дальнейшего его поражения, улучшение прогноза по сохранности нейрокогнитивных функций и повышение качества последующей жизни. В стратегии антенатальной защиты головного мозга недоношенных, кроме обучения и поддержки беременных женщин в части здорового образа жизни и правильного питания, важно

предусмотреть централизацию помощи недоношенным с экстремально низкой массой тела, мониторинг плода в случае беременности высокого риска, антенатальное назначение стероидов для обеспечения созревания легких, внутривенное введение сульфата магния женщине перед преждевременными родами. В стратегии постнатальной защиты обеспечение оптимального насыщения кислородом, отказ от длительного искусственного дыхания, исключение гипогликемии, гипокапнии, электролитного дисбаланса, гипербилирубинемии, скачков артериального давления, стресса и боли, воспаления, некротизирующего энтероколита, обеспечение адекватного питания в значительной мере определяют прогноз сохранения нейрокогнитивных функций. Головной мозг доношенных новорожденных, переживших асфиксию нуждается в относительно большом количестве энергии. Это лежит в основе стратегии его защиты. Она включает в себя назначение антиоксидантов, противовоспалительных, антиэксайтотоксичных, антиапоптических препаратов и, возможно, в дальнейшем использование нейрогенетических подходов, включая использование стволовых клеток. Стратегия антенатального предупреждения асфиксии имеет своей отправной точкой обеспечение нормального протекания беременности и раннего выявления факторов риска гипоксии, обусловленных состоянием плода, плаценты или особенностями протекания перинатального периода. Последние экспериментальные исследования доказали высокую вероятность эффективности антенатального назначения антиоксиданта аллопуринола при ГИЭ. В части разработки стратегии постнатальной защиты результаты оценки эффективности применения 2 методов лечебной гипотермии новорожденных с ГИЭ — тотальной гипотермии и селективной гипотермии головы с легкой гипотермией тела — позволили сформулировать рекомендации: гипотермию целесообразно использовать у доношенных детей с тяжелой и средней тяжести ГИЭ при ее выявлении в течение первых шести часов жизни. Многообещающими являются попытки мониторирования активности головного мозга с использованием амплитудно-интегрированной энцефалографии для выявления детей с ГИЭ. В настоящее время на разной стадии оценки эффективности находится ряд препаратов с антиоксидантным, противовоспалительным, антиэксайтотоксичным, антиапоптическим действием.

Ключевые слова: новорожденные; гипоксически-ишемическая энцефалопатия; недоношенные; антенатальная профилактика и терапия; постанатальная профилактика и терапия.

The two most common causes of neonatal brain injury are prematurity and hypoxic-ischemic encephalopathy (HIE) in the term born infant.

Approximately one in nine babies is born before term. Nowadays these preterm born infants more often survive the neonatal period due to developments in treatment options in the last decades [5, 30]. They are however at a high risk for developing brain damage and neurodevelopmental impairment later in life [13]; approximately 40 % of survivors develop long-term intellectual or physical impairment, including cerebral palsy (CP). The rapidly growing brain is very vulnerable to hypoxia-ischemia, inflammation and poor nutrition. Especially white matter is extremely susceptible to injury when normal development is interrupted from premature birth [34]. Furthermore, intracranial hemorrhage, periventricular leukomalacia, and inflammation are risk factors for poor outcomes.

Term born infants born after perinatal asphyxia may also survive with a variety of neurocognitive disorders due to brain damage as a result from HIE. HIE is estimated to contribute significantly to all neonatal deaths that occur annually. Untreated, the sequelae of moderate to severe HIE includes a 60 % to 65 % risk of mental retardation, CP, hydrocephalus, seizures, or death.

The main goal in neonatal care for these surviving but vulnerable infants is to preserve brain function and prevent further brain damage, in order to improve neurocognitive outcome and the subsequent quality of life.

In the past decade new preventive and therapeutic strategies have emerged and are currently being applied or being researched in perinatal medicine.

The following overview is a short presentation of a selection of these strategies for both preterm and term born infants.

PRETERM BRAIN PROTECTION

Antenatal strategies

Possibly the most important way to prevent mortality and morbidity in newborn infants is the need for adequate prenatal care, in order to prevent prematurity. This can partly be achieved, by educating and supporting pregnant women regarding life style, such as healthy food intake, avoidance of substance use including smoking and alcohol, and frequent checkups by their well trained midwifes to promptly recognize signs of fetal distress such as intrauterine growth retardation, or maternal hypertension.

Centralization of care for extreme preterm born infants (<32 weeks of gestation) [21, 23], the administration of antenatal steroids [24] and improved knowledge on ventilation, surfactant administration and peri- and postpartum monitoring has probably led to the increased survival rate for preterm infants the last decades. Fetal monitoring of heart rate in high risk pregnancies and subsequent performing cesarean section to terminate pregnancy may not have resulted in less intrauterine fetal demise, but possibly in preservation of brain function for those infants that were at risk of brain damage due to underperfusion by placental dysfunction or of inflammation due to transcending infection; a meta analyses of using cardiotocography during labour and subsequent actions showed a reduction in seizures in the newborn in-

fants [1]. Also centralization of the treatment of extreme preterm born infants without the need for transport [20, 32] by timely referring pregnant women to specialized centers, contributes to optimal care for preterm infants [23]. The administration of antenatal steroids for lung maturity seems to also have neurological benefits with mainly a lower incidence of IVH and cerebral palsy [35] possibly partly explained by reducing the need for prolonged intubation and artificial ventilation.

Recently, the use of intravenous magnesium sulfate administration to mothers just before preterm delivery (below 32 weeks of gestational age) has become standard care in large parts of Europe. When birth is imminent (preferably 4 hours before), 4 grams of MgSO4 is administered iv followed by 1 gram per hour, until birth.

A meta analyses of 5 randomized controlled trials concluded that fetal exposure to magnesium sulfate in women at risk of preterm delivery significantly reduces the risk of cerebral palsy without increasing the risk of death. The number needed to treat to prevent one case of cerebral palsy among those who survive until age 18–24 months is 46 in infants exposed to magnesium sulfate in utero before 30 weeks, and 56 in infants exposed to magnesium sulfate in utero before 32 to 34 weeks [4].

Some concerns have risen regarding a possible increase for the need for mechanical ventilation when these infants may be breathing insufficiently from hypotonia after birth.

Postnatal strategies

One should avoid oxidative stress by limiting oxygen administration by setting oxygen saturation limits, both during transition and after admittance to the neonatal intensive care unit. Aiming for arterial oxygen saturation target values after birth and limiting oxygen administration to 30% (as opposed to >60%) tends to decrease mortality [27].

Until recently we were unaware of the optimal arterial oxygen saturation levels after admission to the neonatal ward. Hyperoxia was increasingly being avoided, to prevent oxidative stress related organ damage, such as retinopathy of the premature. Hypoxia and/or ischemia on the other hand is associated with white matter damage in preterm infants. Several trials have therefore been performed in which infants were randomly assigned into either a low (85–89%) or a high (90–95%) oxygen saturation target range. It became clear that for the very low birth weight infants, mortality was significantly higher in the infants assigned to the low target range. A meta analysis of these studies showed relative risks (RR; 95% CIs) comparing a low versus a high oxygen saturation target to be 1.41 (1.14–1.74) for mortality at discharge or at follow-up, 0.74 (0.59–0.92) for severe retinopathy of prematurity, 0.95 (0.86–1.04) for physiologic bronchopulmonary dysplasia, 1.25 (1.05–1.49) for necrotizing enterocolitis, 1.02 (0.88–1.19) for brain injury, and 1.01 (0.95–1.08) for patent ductus arteriosus (RR > 1.0 favors a high oxygen saturation) [27].

Of course the avoidance of (prolonged) artificial mechanical ventilation, hypoglycemia, hypocapnia and other electrolytic imbalances as well as hyperbilirubinemia also helps in preserving brain tissue. The same probably holds true for avoiding blood pressure shifts, avoiding stress and pain [8], prevent inflammation, sepsis and necrotizing enterocolitis [10, 25]. Whether the administration of caffeine for apnea of prematurity really improves neurocoginitve outcome for these infants remains to be seen [9, 22].

Last but not least: adequate feeding, enough proteins and other nutrients for brain growth from day one after birth, strongly predicts head growth and neurocognitive outcome [2].

BRAIN PROTECTION FOR THE TERM ASPHYXIATED NEWBORN INFANT

Hypoxic ischemic neuronal damage is caused by a lack of oxygen and therefore energy failure. The brain needs a relative large amount of energy, which is provided by hydrolysis of ATP in the presence of oxygen. The effect of energy depletion during a hypoxic event is first a depolarization of the neuronal membrane and loss of synaptic function and conductivity. This depolarization causes neurons to release high amounts of the excitatory neurotransmitter glutamate into the synaptic cleft. Subsequent activation of channels causes a passive influx of Cl- (and Na+) into cells causing osmotic (cytotoxic) edema and rapid cell death. Additional structural damage develops hours or days later as a result of Ca^{++} influx into neurons. Activation of NMDA and AMPA receptors by excess of glutamate causes massive influx of Ca^{++} into neurons. Ca^{++} activates catabolic enzymes, and it also activates NO synthase, resulting in formation of the free radical NO. Additional free radicals result from the impairment of oxidative phosphorylation. Free radicals and activated catabolic enzymes destroy structural proteins, membrane lipids, nucleic acids, and other cellular contents, causing neuronal necrosis. DNA damage from endonucleases and mitochondrial injury from free radicals trigger apoptosis. After 6–12 hours a second episode after reperfusion occurs, probably by an increase of inflammatory cytokines inducing this ‘secondary energy failure’. A large part of the actual brain damage occurs during this second phase, and allows for a short window of time after birth for intervention. HIE is the immediate result, permanent brain damage may follow. Similar pathways, albeit more localized, probably occurs in case of neonatal cerebral (thrombotic) stroke.

Counteracting these events is the basis of neuroprotective strategies that are part of current practice or at an experimental stage. These strategies consist of anti-oxidative, anti-inflammatory, anti-excitatoxic and anti-apoptotic agents, and in the future possibly neurogenetic approaches, including stem cell therapy [16].

Antenatal strategies

Prevention of asphyxia starts at promoting a healthy pregnancy and of an early recognition of fetal, placental or neonatal risk factors for hypoxia before, during or after birth. Also for term pregnancies, the primary care midwife plays a pivotal role in this early detection of at risk pregnancies. Intra uterine growth retardation, oligohydramnios, macrosomia, maternal diabetes, high blood pressure etc. all warrant further examination and treatment via an obstetric specialized centre. Women with these high risk pregnancies also should be giving birth at the hospital with skilful team of dedicated doctors and nurses present, to evaluate the infant after birth and give proper treatment, to prevent further brain damage.

Recent trials have shown a possible beneficial effect of antenatal administration of the anti-oxidative agent allopurinol in a HIE induced ovine animal model [19]. Allopurinol reduces free radicals and crosses the placenta readily. So far, this effect has not been successfully shown in humans and the agent is not routinely being prescribed, but trials are currently being conducted [18]. Allopurinol administration after birth has not shown to be beneficial [3].

Postnatal strategies

Therapeutic hypothermia

The most promising and effective method to decrease brain damage after HIE is therapeutic hypothermia. Since several large trials have shown the beneficial effect on neurodevelopmental outcome, this strategy has widely been accepted and implemented. A meta analysis of the 1505 infants investigated in these trials concluded that therapeutic hypothermia is beneficial in term (and late preterm) newborns with hypoxic ischaemic encephalopathy [15]. Inclusion criteria were: newborn infants with evidence of peripartum asphyxia, with each enrolled infant satisfying at least one of the following criteria:

a) apgar score of 5 or less at 10 minutes;
b) mechanical ventilation or resuscitation at 10 minutes;
c) cord pH < 7.1, or an arterial pH < 7.1 or base deficit of 12 or more within 60 minutes, of birth AND evidence of encephalopathy according to Sarnat staging [26]:
   a) stage 1 (Mild): hyperalertness, hyper-reflexia, dilated pupils, tachycardia, absence of seizures;
   b) stage 2 (Moderate): lethargy, hyper-reflexia, miosis, bradycardia, seizures, hypotonia with weak suck and Moro;
   c) stage 3 (severe): coma, flaccid muscle tone, apnea.

Many neonatal intensive care units currently use the Thompson score (table 1) to identify which infant may benefit from hypothermia. Term infants without large congenital or syndromal abnormalities with a Thomson scores ≥ 8 one to three hours after birth are eligible for therapeutic hypothermia.

Two methods to achieve hypothermia were being evaluated in newborn infants with HIE: whole body cooling and selective head cooling with mild systemic hypothermia. Various devices with continuous feedback loop for maintaining a constant core temperature are now on the market. Infants in all studies were randomized within six hours of age. Five studies used head cooling devices in conjunction with mild systemic hypothermia while the other six used whole body cooling. The duration of hypothermia was 72 hours in all but one study that cooled infants for 48 hours and one that cooled from 48 hours to 72 hours depending on neurological recovery. Figure 1 is a forest plot from the meta analysis showing a risk reduction of 33–38 % on major neurodevelopmental disability.

Therapeutic hypothermia also resulted in a statistically significant and clinically important reduction in the combined outcome of mortality or major neurodevelopmental disability to 18 months of age (relative risk of

Table 1

HIE score according to Thompson [31]. LOC: level of consciousness, IPPV: intermitted positive pressure ventilation

Sign	Score			
	0	1	2	3
Tone	Normal	Hyper	Hypo	Flaccid
LOC	Normal	Hyper alert stare	Lethargic	Comatose
Fits	None	Infreq < 3/day	Frequent > 2/day	
Posture	Normal	Fisting, cycling	Strong distal flexion	Decerebrate
Moro	Normal	Partial	Absent	
Grasp	Normal	Poor	Absent	
Suck	Normal	Poor	Absent + bites	
Respiration	Normal	Hyperventilation	Brief apnea	IPPV (apnea)
Fontanel	Normal	Full, not tense	Tense	

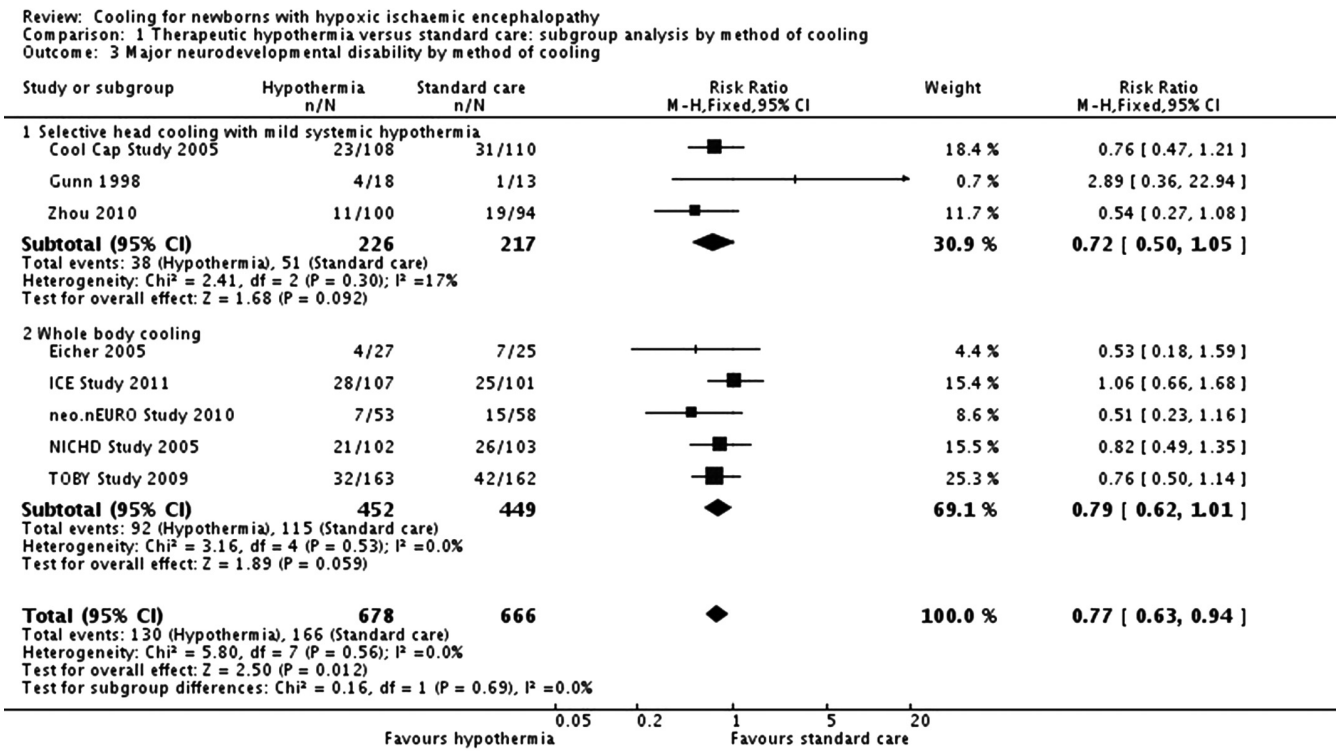

Fig. 1. Relative strength of treatment effects in multiple quantitative scientific studies (from [15])

0.75 (95% confident interval: 0.68 to 0.83). The number needed to treat for an additional beneficial outcome was 7 (95% confident interval: 5 to 10). This meta analysis also showed that cooling reduces mortality without increasing major disability in survivors. The conclusion therefore was that hypothermia should be instituted in term infants with moderate-to-severe hypoxic ischemic encephalopathy if identified before six hours of age.

Other strategies

aEEG

Continuous awareness of brain activity and occurrence of seizures by means of amplitude integrated electroencephalography (aEEG, fig. 2) may be helpful indentifying infants with HIE. Abnormal low activity can be another criterion to decide to start hypothermic therapy [28]. Especially in sedated infants, the assessment of presence of encephalopathy can be impossible using Sarnat or Thompson scores. Furthermore, in these infants at risk of seizures, aEEG is a very usefull tool in detecting subclinical seizures and differentiating actual seizures from other forms of muscle contractions such as myoclonic jerks [29].

Proper treatment of actual seizures is an important part of brain protection in these infants [12].

Promising agents [17]

Other potential agents with either anti-oxidative, anti-inflammatory, anti-excitatoxic or anti-apoptotic capacities are currently being investigated in various phases of research.

A promising agent is melatonin, an anti-oxidant. The first beneficial effects of administrating five daily enteral doses of melatonin 10 mg per kg, in combination with hypothermia, have recently been published. In a relative small group of post asphyxia infants with HIE, the administration of melatonin led to fewer seizures, less MRI abnormalities, and an improved survival without neurological abnormalities, compared to hypothermia alone. This seems to be a promising additive to the hypothermia treatment, and will with accumulation of evidence possibly be implemented in clinical protocols.

A potential but expensive anti-excitotoxic agent is Xenon, a noble gas used as an anesthetic agent. It counteracts the NMDA receptor and has been shown

Fig. 2. aEEG

to be an effective agent against hypoxic-ischemic insult both to cortical neurons in vitro and in several in vivo models [6]. The first feasibility study in human neonates has been conducted and showed no adverse respiratory or cardiovascular effects. Furthermore, 7 of 11 survivors had mental and physical developmental index scores ≥ 70 at follow-up at 18 months [7].

One of the agents with neurotrophic capacities is erythropoietin (Epo). Epo and its receptor are essential in brain development [36]. The anti-inflammatory, anti-excitotoxic, anti-oxidant and anti-apoptotic effects on neurons and oligodendrocytes probably account for its positive effects in brain injury. Some evidence now shows that Epo has neuroprotective qualities: it reduces learning impairment after brain injury, and improves behavioral outcome [14, 33]. When combining hypothermia with Epo, a small study in rats showed a borderline additive effect of Epo [11].

CONCLUSION

The most susceptible newborn infants for brain damage are preterm infants and (near)term infants born after perinatal asphyxia. Preterm infants whose brain development is interrupted from preterm birth benefit the most from centralization of care, avoiding postnatal transportation, avoiding hypoxia and hyperoxia, mechanical ventilation, stress, blood pressure shifts, and imbalances in metabolic processes. Adequate nutrition and prevention of inflammatory events furthermore support optimal brain development.

Preventing neurodevelopment impairment in post asphyxia infants with HIE is still being under thorough investigation. The most promising medical development in the last decade is providing these infants with therapeutic hypothermia, in order to reduce mortality and improve neurodevelopmental outcome. Many agents counteracting the processes occurring during hypoxic-ischemic events and the reperfusion phase are currently being investigated. Allopurinal, melatonin, and Epo may be promising future additives to hypothermia in the treatment of infants with HIE.

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