·专家讲座·

# Hypothermic neuroprotection in neonates – cooler head prevails

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The occurrence of hypoxic-ischemic encephalopathy (HIE) in the newborn period carries significant importance as a predictor of later neurologic disability. It occurs about 1-6 per 1 000 live term births. About 15% - 20% of the affected infants with HIE die during the acute phase and an additional 25% develop permanent neurological deficits. In Asia birth rate varies significantly from state to state and there is limited data on the incidence and severity of HIE.

The identified antenatal risk factors for neonatal encephalopathy include maternal hypotension, chorioamnionitis, diabetes, thyroid disorders, treatment for infertility and premature birth. Occasionally, some factors during the intrapartum period result in HIE such as forceps delivery, breech extraction, abruption and compression or cord prolapse. Postnatal severe respiratory distress syndrome, sepsis and shock may also contribute to HIE, however this occurs in fewer than 10% of term infants with HIE.

The severity of HIE depends on the timing and duration of the insult maturity of brain and secondary insult. Complications of HIE may include neonatal seizures, stroke, intracranial haemorrhage, coagulopathy, electrolyte disturbances, syndrome of inappropriate antidiuretic hormone secretion, severe neurologic deficits and death. HIE is often seen with associated harmful conditions such as lactic acidosis, accumulation of excitatory aminoacids, impaired auto regulation and reperfusion injuries.

The medical approach to the newborn with HIE is evolving. There has been significant progress over the last few years from a scientific and clinical perspective and we continue to accumulate new information. In the past, therapy for HIE generally focused on supportive measures and symptomatic therapy but there is some promising evidence regarding the utilization of hypothermia to minimize the cascade of damaging events that follow the primary insult related to HIE. The latest updates in understanding and managing neonatal HIE will be explored ahead.

## 1 Overview of the pathogeneses of HIE

Brain injury after a hypoxic-ischemic insult is a process with internal biochemical and molecular changes leading to evolution of the insult followed by repair. This has been demonstrated in various animal models under many different conditions.

With HIE there is a primary insult followed by reperfusion when the brain metabolism will often recover partially or completely. This phase is refereed to as "latent phase". Very often a secondary phase occurs that involves a cascade of events leading to deterioration of neuronal cell function. This is known as "delayed phase of injury", where neurons and oligodendroglia continue to die for longer periods. This process of cell injury and death appears to be predictable. It involves cellular depravation of oxygen and nutrients leading to anaerobic glycolysis, depletion of high energy phosphate reserves, loss of cell membrane functions, accumulation of lactic acid, and neuro toxic excitatory neuro transmitters such as glutamate. This leads to deterioration of the cell function. If it is not interrupted this cascade ultimately leads to cell death. Hypothermia protective strategies appear to ameliorate this process. There are also other promising treatment strategies, which are still under scientific investigation.

Interestingly in addition the biochemical processes mentioned above, a series of inter- related mechanisms further perpetuate the initial injury. These may include cytosolic accumulation of the calcium, exposure to free

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radicals such as nitric oxide (NO) and hydroxyl radicals. Furthermore, the accumulation of iron and release of inflammatory mediators induces mitochondrial dysfunction leading to neuronal death. This and other processes trigger apoptotic pathways leading to additional oligodendroglial and neuronal death.

The secondary phases, following the primary insult with HIE, are amenable to certain interventions. Induced hypothermia is one important example. The benefit of this strategy depends on magnitude and pattern of repetition of the initial insult and the maturity of the brain. The insult to the preterm brain is not the subject of this report. This report deals with HIE in the term and near-term infants. The maintenance of regional and global cerebral blood flow is essential for this process to work.

HIE animal models have revealed that when body temperatures are reduced to 33-34 degrees there is improvement in histologic and neurobehavioral outcomes. The reason for this is not clearly understood but there are various hypotheses. Suppression of glutamate and free radicals as well as conservation of high energy phosphates and retardation of apoptotic processes have all been theorized

## 2 Clinical human trials

To date there have been four randomized clinical trials and eight nonrandomized trials. In addition several pilot, safety, efficacy and feasibility trials have been published. The overall conclusion from the existing literature is that induced hypothermia is beneficial with regard to long-term neurological outcome in infants with HIE and doesn´t have significant associated adverse effects.

Gluckman et al published a randomized trial in the *Lancet* in 2005 ('Cool Cap'). They randomized infants with HIE to be normothermic or to have mild hypothermia (head cooling). They utilized EEG to identify the severity of injury. The patients were followed for 18 months looking at death and major disability as the primary outcome. Their results, although having borderline significance, showed a protective effect of hypothermia (odds ratio 0.57) for the primary outcome. Despite not providing a definitive answer about the efficacy of hypothermia in HIE it did help with regard to design methods in future trials. For example severity of insult needed to be stratified in order to reveal a significant difference.

The second major randomized control trial was by Shankaran et al who randomized 208 patients to either normothermia or whole body hypothermia for newborns with HIE. Their primary outcome was death or moderate or severe disability. Death or severe disability occurred in 44% of the hypothermia patients and 62% of the control group ($P = 0.01$). They concluded that whole body hypothermia indeed reduced the risk of death or disability in infants with moderate or severe HIE. Besides the two studies there were studies from GUNN 1998, Eicher 2005, Coolcap and Tobi trials in recent years. If one places the results of all the studies published on a relative risk ratio (*RR*) grid the mean *RR* showed less than one, meaning the over all effect ($Z = 2.15$, $P = 0.03$) favouring hypothermia.

The bottom line of those published results suggest hypothermia in mild to moderate HIE appears to be beneficial. These studies enrolled infants from a wide geographic region using simplified protocols with future plans to identify even later outcomes (5 years).

## 3 Major deficiencies in knowledge

There are several unresolved issues in the randomized control trials and pilot studies.

The real world cooling (i. e. using ice bags, cold water bottles, ect) needs to be further defined and efficacy and safety of such treatment need to be explored further before instituting in local hospitals.

Long-term safety and efficacy data for the application of hypothermia on patients with HIE is not fully established based on the current trials.

There is a need for standardisation of the electro diagnostic and neurophysiologic tests that should be used for determination of severity of injury.

The latest postnatal age for initiation of the therapeutic hypothermia still needs to be determined. The effectiveness of hypothermia appears to rely on the timing of introduction. The question of "How late is not too late?" is real and relevant.

Cooling and re-warming issues, i. e. when and how fast needs further clarification.

The optimal mode of cooling, i. e. whole body versus selective head is still unknown, although both modalities appear to be effective.

The role of the MRI in predicting long-term outcomes needs to be studied.

The duration of the follow up and appropriate tests to assess outcome should be standardised so that the outcome under different protocols can be compared and the clinical effect evaluated. Long-term follow ups are necessary and all studies should strive to report long-term outcomes. The rapidly accumulating short-term

clinical and laboratory data related to hypothermia has given us avenues for safe treatment. However, completed studies provide data only up to 18 months of age. We need follow-up data for longer duration i. e. 5 to 10 years of age. Therefore, the long-term impact of hypothermia for HIE remains unknown.

## 4 Conclusions

Only a proportion of neonatal encephalopathy is caused by hypoxia and ischemia. The group of infants with encephalopathy secondary to hypoxia and ischemia are those who likely benefit from hypothermia. Perinatal HIE is not a single disease from a single cause and one should appreciate the fact that there is a great diversity in the timing and magnitude of the brain injury. Therefore, it seems appropriate that any single intervention may not provide a uniformly favourable outcome. The current literature recommends diagnosing HIE clinically and by EEG in one study. Therefore caution must be taken prior to utilizing whole body or selective head cooling in routine clinical practice until more specific guidelines are established with regard to diagnosis and management algorithms. These infants require vigilant staff with experience inducing and discontinuing hypothermia. Based on the available evidence there continues to be a need for longer term data on the safety and efficacy of therapeutic hypothermia. If hypothermia is offered, it likely should be done under published protocols with plans for longer term follow up. Additional brain imaging techniques such as MRI, and neurophysiologic and electrodiagnostic studies are ongoing waiting for additional evaluation.

"Toby" trial has been completed and was published in the *New England Journal of Medicine* and "ICE", need to be completed and reported. This will undoubtedly enhance our understanding of the role of hypothermia in perinatal asphyxia. Institutions and physicians offering hypothermia should recognize the knowledge gaps and ensure that those deficiencies are resolved by keeping a registry and ensuring follow up. In neonatology, history has taught us in more than one instance, that a hasty and premature introduction of therapeutic interventions may come back to haunt us. Those units and physicians want to use hypothermia as treatment may only be used with appropriate monitoring and must be similar to the methods that have been proven to be safe.

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# Hypothermic neuroprotection in neonates – cooler head prevails（摘译）
# 亚低温对新生儿脑损伤的神经保护作用 – 盛行的头部亚低温治疗

Koravangattu SANKARAN 著，刘玲 译

新生儿缺氧缺血性脑病（HIE）是导致小儿神经系统后遗症的主要疾病，发生率约为活产儿的1‰～6‰，其中15%～20%的重症患儿在急性期死亡，存活者中约25%可留下永久的神经系统后遗症。由于亚洲各国之间的出生率不一致，至今尚无各国HIE的发生率和严重度的确切数据。已经证实的导致新生儿脑病的产前高危因素包括母孕期高血压，绒毛膜羊膜炎，糖尿病，甲状腺疾病，不孕症的治疗和早产等。有时，分娩时的一些因素也可导致HIE，如产钳术，臀位产，脐带断裂、受压和脱垂；严重的呼吸窘迫综合征、败血症及休克同样也会导致HIE，然而这些因素所致的HIE在足月儿中不超过10%。

HIE的程度取决于新生儿脑的成熟度、缺氧缺血的持续时间及缺血再灌注损伤等。HIE的并发症包括惊厥、脑梗塞、颅内出血、凝血功能障碍、电解质紊乱、抗利尿激素的异常分泌以及严重的神经系统后遗症和死亡等。HIE患儿的体内同时存在乳酸性酸中毒、兴奋性氨基酸积聚、脑血流自动调节功能的受损及再灌注损伤。

在过去的几年里关于HIE的治疗从科研到临床虽取得一定的进展，但主要还是集中在支持及对症处理。目前有乐观的证据表明亚低温能减轻脑缺氧缺血后神经细胞凋亡的级联反应。本文将目前关于新生儿HIE的最新进展及管理作一简介。

## 1 HIE的发病机制概述

许多的动物实验已经证实缺氧缺血可引发脑组织神经细胞发生一系列内在的生化及分子结构的变化。HIE的损伤包括脑组织的缺氧缺血和再灌注损伤，之后脑组织的代谢可部分或完全恢复，这个时间段称为“潜伏期”。随之进入第二个阶段，缺血再灌注导致凋亡级联反应的启动致神经细胞形态和功能的损伤，又称之为“延迟损伤期”，神经元及少突神经胶质细胞在这个时期会持续很长时间的死亡。但这个过程中细胞的损伤和死亡是可预知的，这个过程包括细胞氧及营养物质的被剥夺而导致无氧酵解、ATP耗竭、细胞膜功能受损、乳酸堆积、兴奋性氨基酸如谷氨酸释放后的神经毒性作用，这些都导致细胞功能的恶化，如果不阻断这个级联反应，最终将会导致神经细胞的死亡。亚低温的保护机制就是针对这一过程。当然还有其他有前景的治疗方法，然而目前仍处于研究阶段。除以上所提及的细胞生化变化外，其他一系列的相关事件进一步加重了脑损伤，包括自由基如NO和羟自由基的产生引起的细胞内$Ca^{2+}$内流。此外，铁的积聚和炎症介质的释放又使线粒体功能障碍而导致神经元死亡。这些事件与其他触发凋亡的程序最终导致少突胶质细胞和神经元的死亡 。在HIE的继发性损伤阶段采取一定的干预措施可减轻神经细胞的损伤，亚低温就是一个非常重要的治疗手段。但亚低温治疗的保护作用取决于脑的成熟度、缺氧缺血的程度以及治疗开始的时间。本文谈到的亚低温治疗只包括足月儿和近足月儿，不包括早产儿。亚低温治疗过程中维持大脑区域或全脑的血流灌注是最根本的。动物实验结果发现当体温降至33～34℃时，神经细胞的组织学和神经行为方面有改善，个中原因尚不清楚，但有很多假说，包括谷氨酸及氧自由基释放的抑制、能量代谢的恢复及细胞凋亡过程的受抑等。

## 2 人体临床试验

以前已经发表的关于亚低温治疗的文献包括4个随机和8个非随机的临床试验研究以及一些预试验及亚低温安全性、有效性和可行性研究。现有文献所得出的关于亚低温治疗HIE的结论都有利于改善HIE患儿的预后且没有明显的副作用。Gluckman等2005年在*Lancet*上发表了一个关于亚低温治疗HIE的随机对照试验（‘冰帽’）。他们将HIE的患儿随机分为正常体温组和轻度亚低温组（头部亚低温），脑电图了解脑损伤的严重度，随访患儿到18个月，了解其死亡率和伤残率。其结果显示亚低温对HIE有保护作用（$OR = 0.57$）。尽管该研究没有对亚低温治疗HIE提供明确的答案，但对设计今后的研究提供了帮助。例如在以后的研究中需要对

HIE 的损伤严重度进行分层减少研究的混杂因素，从而得到更客观的结果。第 2 个重要的随机对照试验是 Shankaran 等进行的研究，他们将 208 名 HIE 患儿随机分为常温组及全身亚低温组，主要观察这些患儿的死亡率或中重度残疾的发生率。研究结果发现亚低温组死亡或重度残疾的发生率为 44%，而对照组为 62%（$P=0.01$）。他们的研究结论表明全身亚低温确实可降低中重度 HIE 患儿的死亡及残疾发生率。除上述两个研究外，GUNN 1998，Eicher 2005 也进行了头部亚低温和全身亚低温治疗 HIE 的研究。上述所有的研究均证实亚低温对轻～中度 HIE 的保护作用，$RR<1$（$Z=2.15$，$P=0.03$）。

## 3 主要不足

在一些随机对照及预试验研究中仍有一些尚未解决的问题。对一些医院利用如冰袋、冷水瓶等实施亚低温治疗前这些方法的安全性和效果需要进行明确的界定。现有文献资料对实施亚低温治疗 HIE 患儿的长期疗效及安全性尚未确定。对于确定损伤严重度的脑电图及神经生理测试的诊断应当标化。对患儿出生后开始亚低温治疗的最迟时间也应进一步确定。亚低温的临床疗效取决于治疗开始时间。“多晚开始治疗不算晚”仍然是一个悬而未决的问题。降温和复温的问题？什么时候降温和复温及速度等都需要进一步明确。尽管头部低温或全身降温两者研究表明均有效，但哪一种最好尚未明确。对 MRI 判断 HIE 患儿的远期预后仍需要进一步研究。随访的时间及判断患儿预后的一些测试方法需要标化以便不同地区和医院的治疗效果和患儿预后能进行比较。长期随访是非常必要的，并且所有的单位都要力求报道长期随访患儿的远期预后。大量的短期临床及实验研究数据表明了亚低温治疗是安全的。但目前较为完整的研究只随访患儿到 18 个月。最好能长期随访患儿到 5～10 岁。因此，亚低温治疗 HIE 的远期疗效目前仍不十分清楚。

## 4 小结

由于只有一部分新生儿脑病是由于缺氧缺血所致，因此亚低温治疗只对这些因缺氧缺血导致脑损伤的患儿有效。围产期的 HIE 并不是一个单因素所致的单一的疾病，研究人员应认识到导致脑损伤的原因是多种多样的，且脑损伤的时间及程度也是不一样的。因此，任何单一的干预措施都不可能得到一致的疗效。目前有文献推荐 HIE 的诊断需依靠临床和 EEG。因此，在日常的临床工作中应该谨慎地选择是全身亚低温还是头部选择性亚低温，直到更多关于诊断及管理的具体的指导方针的确立。因此开始亚低温治疗诱导及停止时均需要医务人员多观察。根据现有的文献资料，关于亚低温使用的安全性及有效性的问题仍有待进一步的研究。如果需要进行亚低温治疗，应当按公认的治疗方案进行并对患儿进行长期的随访，和脑影像学如 MRI、神经生理和脑电图检查等。全身亚低温临床研究已经完成并发表在《新英格兰医学杂志》和“ICE”，但还需要进一步完善和报道。这些研究毫无疑问将提高我们对亚低温治疗新生儿窒息的认识。开展亚低温治疗的临床医生和医院应当认识到对亚低温疗效、安全性等的了解还不够，但可通过对患儿长期严密的随访提高我们的认识。在新生儿学科的发展史上，历史给了我们很多经验教训，如果仓促地引入一个未成熟的治疗手段可能会使我们倒退许多。对于一些想开展亚低温治疗的医院和医师必须密切监护患儿病情并采用已经证实为安全的一些方法。

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