

# New frontiers in hypothermia

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## Proceedings

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### Abstract

Therapeutic hypothermia has currently become a standard of care for asphyctic newborns with moderate-severe hypoxic-ischemic encephalopathy (HIE). Strict criteria are required to include these newborns in the hypothermic treatment. On some occasions, in the clinical practice, some discrepancies were found among the 3 inclusion criteria. In such circumstances the knowledge of the accuracy of each criterion, the knowledge of the evolution of clinical and neurophysiologic parameters in the few hours following birth, and the knowledge of the pathogenesis of the asphyxia can help to take the right decision on who to treat with hypothermia. The usefulness of hypothermia in newborns of gestational age lower than 36 weeks or when started beyond the 6th hour of life remains unclear. Perinatal stroke, as HIE, is an evolving process and if early diagnosed could benefit from hypothermia. In addition, infants may experience hypoxic-ischemic episodes that are not related to the birth such as early apparent life-threatening events (ALTEs) or near miss events. Also in these cases hypothermia can be theoretically efficacious in preventing the progression of brain damage.

The above issues will be discussed in the present paper.

### Keywords

Hypoxic-ischemic encephalopathy, therapeutic hypothermia, perinatal stroke, apparent life-threatening events, inclusion criteria, new frontiers.

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## Introduction

Induced therapeutic hypothermia has become a standard of care for mild-severe hypoxic-ischemic encephalopathy (HIE) in order to prevent mortality (number needed to treat [NNT] between 11 and 17) and neurological deficits in survivors (NNT between 6 and 8) [1-3].

The most recent recommendations on neonatal resuscitation state that term or near term neonates with moderate to severe HIE should be offered therapeutic hypothermia [4]. The treatment should be implemented according to the studied protocols, which currently include commencement within 6 hours following birth, continuation for 72 hours, and slow rewarming over at least 4 hours in newborns of GA > 35 weeks. Therapeutic hypothermia should be administered under clearly defined protocols similar to those used in published clinical trials and in facilities with the capabilities for multidisciplinary care and longitudinal follow-up. A task force of the Study Group of Neonatal Neurology, that belongs to the Italian Society of Neonatology, has drawn up national recommendations on the criteria for inclusion to the hypothermic treatment [5]. These criteria include: indicators for intrapartum asphyxia (10 minutes Apgar Score lower than 5 or need for respiratory support at 10 minutes or pH lower than 7.0 or base excess equal or greater than 16 mmol/l); signs of moderate to severe HIE on neurological examination; amplitude integrated electroencephalogram (aEEG)/electroencephalogram (EEG) abnormalities.

However, in the clinical setting, discrepancies can exist among the three above criteria with risk of over- or under-treatment. In addition, the newborn/infant can be exposed to hypoxic-ischemic insults that not occur during birth: may hypothermia still be useful in these cases?

The following lists some special situations where therapeutic hypothermia can be taken into consideration.

1. Pathological neurological examination in the absence of criteria of peripartum asphyxia
2. Pathological neurological examination in the absence of aEEG abnormalities
3. Uncertainty in the classification of HIE severity: mild-moderate HIE

4. Early apparent life-threatening events (ALTEs)/near miss events
5. Perinatal stroke
6. Postnatal age greater than 6 hours
7. Preterm newborn (gestational age [GA] lower than 36 weeks).

## Pathological neurological examination in the absence of criteria of peripartum asphyxia

In this situation errors in cord blood sampling or prolonged/partial asphyxia with metabolic compensation at time of birth need to be considered.

Sampling errors have been reported in 18-39% of cases [6-8] and are primarily the result of inadvertent collection of mixed arterial and venous blood or inadvertent collection of blood from the vein instead of the artery. For this reason professional societies [9,10] strongly advocate obtaining and analyzing samples from both the umbilical artery and vein (paired blood gas analysis) to ensure the biological validity of the blood gas values obtained: arteriovenous differences in pH (greater or equal 0.01 pH units) and pCO<sub>2</sub> (greater or equal 0.2 mmHg) are used to confirm two-vessel sampling [11].

Prolonged partial asphyxia may be suggested by the following characteristics [12]:

- usually there is not an acute sentinel event;
- cardiotocographic anomalies may be present during labor;
- watershed cerebral lesions are more frequent than basal ganglia lesions;
- there could be a partial recovery before birth with a less severe depression and less severe acidosis.

In these cases, the assessment of the EEG/aEEG pattern can help to decide whether or not to start the hypothermic treatment, i.e.:

- if EEG/aEEG is pathological start hypothermia;
- if EEG/aEEG is normal re-evaluate the neurological examination; if it is still abnormal consider other possible causes of alteration of the neurological examination.

## Abnormal neurological examination in the absence of aEEG abnormalities

Consider the presence of artifacts; artifacts have been reported in up to 12% of the early traces [13],

especially muscles artifact and especially if the baby is in 'overcooling'. If there is a suspicion of hypoxic ischemic encephalopathy it would be useful:

- extend the aEEG recording over 30 minutes,
- integrate with EEG/Video EEG,
- refer to a III Level center in the rare case in which the assessment was made in a peripheral center, re-evaluate after administration of drugs (such as midazolam, muscle relaxants).

If alterations in neurological examination persist, in the presence of criteria of perinatal asphyxia, even in the absence of aEEG/EEG abnormalities start hypothermia given that possible lifelong benefits would outweigh the small risks. In these cases informed consent would not be required as four RCT [14-17] enrolled newborns without the neurophysiologic criterion.

#### **Uncertainty in the classification of HIE severity: mild-moderate HIE**

It can occur up to 26% of cases [18], mainly in case of early neurological examination. In these cases it is useful to evaluate EEG/aEEG as it has been shown that the combination of the neurological examination and aEEG increases the predictive value: in the presence of aEEG/EEG anomalies start hypothermia otherwise re-evaluate neurological status: in most of the cases with normal EEG the neurological examination will rapidly improve.

#### **Early apparent life-threatening events (ALTEs) and near miss events**

The estimated incidence is 0.032-0.034 per 1,000 births. Mortality rate is 0.017 per 1,000 births. Three potential risk factors have been identified for this condition: skin-to-skin contact, primiparous mother, mother and baby left alone in the delivery room. Airway obstruction is a likely cause for some cases of ALTEs [19,20]. Foran et al. [21] reported patterns of brain injury and outcome in 12 term neonates presenting with postnatal collapse within 72 hours from birth: in 7 cases who became severely encephalopathic magnetic resonance showed acute severe hypoxic-ischemic injury very similar to that reported in newborns with perinatal asphyxia. There are no randomized clinical trials on the efficacy and safety of therapeutic hypothermia in these cases; in any case, evaluated the hypoxic-ischemic nature of the events, it is reasonable to propose the

hypothermic treatment after collection of informed consent.

*Case report:* female newborn, born from uncomplicated pregnancy, vaginal delivery, GA 37 weeks, birth weight 2,765 g, Apgar score at 1 and 5 minutes: 9 and 10, respectively. At 1 hour and 15 minutes after birth, during kangaroo-care in the delivery room, there was a cardiorespiratory arrest. Blood gas analysis showed severe acidosis (pH 6.7). After cardiopulmonary resuscitation the newborn showed a severe HIE; aEEG showed a burst suppression background pattern. Selective hypothermia was initiated at 2.5 hours of life and was continued for 72 hours. Parental consent to the treatment was obtained. Her neurological examination recovered slowly: at 5 days of life she was still hypotonic, hyporeactive, with absent Moro. The neurological status improved starting from the 6<sup>o</sup> day of life. No concomitant pathologies were diagnosed. Psychomotor development was evaluated at 1 year of age with the Griffith's scale and showed a developmental quotient of 102.

#### **Perinatal stroke (PS)**

Incidence of PS is 1/2,800 to 1/5,000 live-births. Stroke is an evolving process: peri-infarct depolarizations (a form of spreading depression) propagate from the infarct core, causing depolarization within the penumbra, and increase the ischemic tissue volume. Animal models have demonstrated that this increase occurs within the first 24 hours [22]. A systematic review and meta-analysis on hypothermia in animal models of acute ischaemic stroke [23] concluded that hypothermia improves outcome especially when animals were cooled to lower temperatures, where treatment was started before or at the onset of ischaemia and in temporary rather than permanent ischaemia models. However, a substantial reduction in infarct volume was also observed with cooling to 35 °C and with initiation of treatment between 90 and 180 min. In human infants it has been reported that stroke is present in 4-5% of cases of HIE [24]. In that study hypothermia was associated with the absence of seizures in neonates presenting with encephalopathy and a focal infarct on neuroimaging. This association was not observed in the group of non-stroke controls that were matched for degree of encephalopathy, even though a similar proportion of the control group received hypothermia. This is the first human study to suggest associations between therapeutic

hypothermia and improved seizures after perinatal stroke. Unfortunately, diagnosis of PS is often delayed until after seizure onset, owing to the subtle nature of associated signs: indeed, about 40% of the children do not have specific symptoms in the neonatal period, and are only recognized later with the emergence of motor impairment, developmental delay, specific cognitive deficiency or seizures. In those who present with early symptoms, mostly recurrent focal seizures, the time interval between insult and occurrence of seizures is longer than in hypoxic-ischaemic encephalopathy with a mean seizure onset interval of 27.8 hours [25], may be too late to start a neuroprotective treatment. Walsh et al. [26] suggested that EEG features described in neonatal stroke are present in the early neonatal period before the onset of seizures, and that they progress and become more evident over the first days of life. These authors showed occasional focal sharp waves over the affected region on the EEG from 3 hours after delivery. One can speculate that that early EEG monitoring in newborns at risk of PS may help to diagnose perinatal stroke before seizures. All the following have been shown to be risk factors for PS: infertility, pre-eclampsia, chorioamnionitis, prolonged rupture of membranes, primiparity, oligohydramnios, decreased fetal movement, prolonged second stage of labor, fetal heart rate abnormalities: when 3 or more risk factors are present, the probability of delivering a child with PS is as high as 1 in 200 [27]. EEG monitoring in these cases could help to early identify cases with perinatal stroke. Beyond these speculations, presently, there are no randomized trials of cooling in cases of neonatal arterial ischaemic stroke and so definite evidence of benefit is lacking. However, for an infant cooled because of suspected HIE where an early revised diagnosis of neonatal arterial ischaemic stroke is made, it is reasonable to persevere with cooling for a full 72 h period.

### Postnatal age greater than 6 hours

The studied protocols commenced hypothermia within 6 hours following birth. A currently recruiting study [28] has been designed in order to evaluate whether induced whole-body hypothermia initiated between 6-24 hours of age and continued for 96 hours in infants  $\geq$  36 weeks gestational age with hypoxic-ischemic encephalopathy will reduce the incidence of death or disability at 18-24 months of age. Waiting for these results, in cases of inadvertent delay, especially when a passive cooling has been

instituted, it is still reasonable to commence cooling in infants aged between 6 and 12 h postnatal, given that possible lifelong benefits would outweigh the small risks (informed consent should be collected).

### GA lower than 36 weeks

Two RCTs on the safety and efficacy of therapeutic hypothermia included newborns of 35 weeks gestational age [14, 17]. For this reason the Italian Recommendations [5] indicate as a criterion for inclusion to the hypothermic treatment a gestational age of 35 instead of 36 weeks. It has been reported the occurrence of HIE after peripartum asphyxia also in the more premature infant. Salhab and Perlman [29] described a group of preterm newborns (31 to 36 weeks gestation) with severe fetal acidemia who developed encephalopathy with or without seizures or neuroimaging abnormalities. Another study [30] reported that screening criteria for HIE that use biochemical and neurological assessments as performed in term newborns can be applied to preterm infants of 33 to 35 weeks' gestation. A pilot study [31] on head cooling in preterm infants (GA lower than 36 weeks but greater than 32 0/7 weeks) with hypoxic ischemic encephalopathy was aimed at investigating the hypothesis that premature infants' can have enough cooling applied to cool their brain to decrease CNS injury without cooling their body. Currently, the recruitment status of this study is unknown. Pending clinical trials on safety and efficacy of hypothermia in preterm newborns is advisable to perform this treatment in infants with a gestational age of at least 35 weeks.

### Declaration of interest

The Author declares that there is no conflict of interest.

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