EDITORIAL

Therapeutic hypothermia for hypoxic–ischemic encephalopathy: challenges during transfer and global perspectives

Hipotermia terapêutica para encefalopatia hipóxico-isquêmica: desafios durante a transferência e perspectivas globais

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Perinatal asphyxia resulting in hypoxic–ischemic encephalopathy (HIE) occurs in 1–2/1000 live births in high income countries, and 10–20/1000 in low- and middle-income countries (LMICs). Worldwide, HIE affects around 2.7 million newborn infants, of whom 690,000 die. Over half of survivors go on to develop cerebral palsy, epilepsy, and other forms of lifelong neurological disability. The adoption of therapeutic hypothermia (TH) in high-income countries has been one of the most significant advances in neonatal care over the past 20 years, and follows rigorous basic science and clinical research. The meta-analysis of the clinical trials showed a remarkable consistency toward the benefit of TH in both mortality and neurodisability. It may surprise, however, given the global burden of HIE and relative simplicity of the treatment, that TH has not been universally adopted outside high income countries. The reasons for this are complex and multifactorial.

The idea of cooling an infant following perinatal asphyxia is not new. A quick survey of the literature will bring up the work of James Miller from New Orleans and Bjorn Westin from Stockholm, who in the 1950s described the use of hypothermia in infants with ‘asphyxia neonatorum’. Their original study, on 10 infants who had failed to respond to conventional resuscitation and were subsequently placed in a cold-water bath and cooled to between 23 °C and 30 °C, showed remarkable outcomes: at follow up at 10 years, nine infants had survived with normal neurology. However, the importance of keeping all newborn infants warm overshadowed development in this field, until the work of Reynolds et al. in the 1980s, who, using the recently developed technique of magnetic resonance spectroscopy (MRS), showed a latency in cell death following perinatal asphyxia, which could be ameliorated by mild hypothermia. Research in this field gained traction and moved from experimental models to large, randomized clinical trials.

One of the reasons that cooling may be so effective in newborns, where it appears to lack efficacy in older children and adults following cardiac arrest, could be that hypothermia is a physiological response in the newborn, which has evolved precisely to prevent potential brain injury.
following hypoxia–ischemia at birth. Born naked, wet, and
devoid of fur, with a large head, the newborn infant will
lose heat rapidly without intervention. Around the same
period that Miller and Westin published their work on cool-
ing infants, Burnard & Cross published a study showing that
infants with asphyxia get colder and take longer to estab-
lish normothermia. Indeed, the fact that babies get cold
after birth forms the basis of the ‘World Health Organiza-
tion warm chain,’ as outside the controlled setting of neo-

tal intensive care, the morbidity and mortality associated
with hypothermia is significant and preventable. Whether
natural hypothermia following perinatal asphyxia is a phys-

iological or pathophysiological phenomenon is difficult to
prove; however, in the era of TH, it does highlight the impor-
tance good thermal control of infants with HIE, particularly
during transfer.

Most infants who suffer perinatal asphyxia are born out-
side tertiary-level units who have the necessary equipment
and expertise not only to cool infants for 72 h, but also to
provide the neurophysiological, radiological, and other
services necessary for diagnostic and prognostic purposes.
However, both experimental and clinical evidence suggests
that the sooner cooling is initiated, the more efficacious
the therapy. It is now standard practice in most deliv-
ery settings to begin cooling as soon as possible after birth,
and maintain this until arrival at the cooling center. A num-
ber of studies have been published, including this latest one
from Carreras et al., describing cooling during transfer. The
majority of the publications describe passive cooling.
In the study by Carreras et al., it is interesting to note that
the majority of infants were transferred without the need
for external heating sources; however, 22% of infants were
not at target temperature at arrival at the cooling center
and 16% were below target temperature. Interestingly,
the risk of overcooling was associated with severity of HIE and
acidosis at birth, confirming the findings of Burnard & Cross
almost 60 years ago.

Only two studies have been published comparing active
vs. passive cooling on transport. One, by Chaudhary et al.
for the Acute Neonatal Transfer Service, based in the East of
England, UK, was a retrospective observational study com-
paring 64 passively cooled infants and 70 infants cooled
using a servo-controlled cooling mattress. In the passively
cooled group 27% of infants did not reach the target tem-
perature, and 34% of infants were overcooled (more than
double in the study of Carreras et al.). In the active cool-
ing group, all infants were at target temperature on arrival
at the cooling center; perhaps more significantly, the sta-
bilization time was significantly reduced, perhaps reflecting
the reduced need for thermal management by the transfer
team, facilitating the transfer process. The second study by
Akula et al., from a consortium in California, was a ran-
domized controlled trial of mode of cooling on transfer;
49 infants were transferred with passive cooling, whereas
51 infants were actively cooled using a servo-controlled
system. The actively controlled group achieved better
thermal control than the passive group, although in this
study stabilization time was not improved. The limited evi-
dence available would therefore suggest that there are
advantages to active cooling on transfer; however, in the
study by Akula et al., operational errors occurred in nine
newborns receiving active cooling and centers with higher
enrolment had fewer device usage errors; this highlights
that with any equipment, there is both a learning curve
and critical usage activity required. Perhaps the most impor-
tant message from all the studies published to date is the im-
portance of core (rectal) temperature monitoring, especially
to prevent overcooling.

The decision as to who to cool is, at first sight, relatively
straightforward. All the clinical trials used a combination
of (A) evidence of fetal compromise (reduced pH, high lac-
tate, low Apgar score, prolong resuscitation, etc.) and
(B) evidence of on-going encephalopathy and/or seizures,
with some trials including an abnormal amplitude integrated
electroencephalography (aEEG) recording, with all infants
being enrolled before 6 h of age. In clinical practice, with
the desire to start cooling as early as possible, criterion A can
be identified relatively easily; however, criterion (b) is an evolv-
ing picture, which can be harder to objectively assess in the
first hour of life. Similarly, application of the aEEG during
the initial stabilization phase may not be appropriate; moreover,
access to both equipment and expertise to read the aEEG
may not be available, particularly in more remote deliv-
ery settings. The practice described by Carreras et al. is to
transfer all infants with encephalopathy and then formally
assess them at the cooling center, before commencing active
cooling. This ensures that there is consistency in assess-
ment of the infants, and delayed presentation of infants
with moderate-to-severe HIE, who were initially thought to
be mild, is prevented. However, this approach may not be
applicable in all settings, as it is both resource intensive
for the transfer team and cooling centers, and also takes babies
away from their mothers – sometimes to considerable dis-
tances – when not always necessary. The importance of early
and regular neurological assessment in such infants cannot
be underestimated. Horn et al. have shown that early clin-
ical signs in neonates with HIE can predict abnormal aEEG
at 6 h of life. With improved telemedicine facilities, it is
also possible to link aEEG recordings to regional centers for
assessment. How to manage the infant who meets criteria A
but where criteria B is unclear or evolving remains contro-
versial; it may be that specific guidelines should be drawn
up, depending on the local resources available.

There is no doubt that TH has had a major impact in the
survival and neurological outcome of many infants in high-
income countries. The impact in low- and middle-income
countries, where most of these infants are born, is less
clear. A number of small studies have been undertaken in
LMICs; none have been adequately powered to examine
clinically important outcomes. A recent meta-analysis of
therapeutic hypothermia in LMICs has shown a reduction in
neonatal mortality based upon seven RCT’s enrolling a total
of 567 infants, although the reduction was not statistically
significant. However, the data is difficult to interpret due
to inconsistent inclusion and exclusion criteria, as well as
poor follow up. The studies are heavily biased toward India,
with only one RCT in Africa and none in Central and South
America. There is an urgent need to develop better evidence
base for different resource settings across the globe, not
only for the efficacy of cooling in specific populations, but
also regarding the best way of stabilizing and transferring
such infants to specialist centers. Clearly, establishing TH
early is important and maintaining it during transfer is fea-
bile, but as first described in 1958, careful core temperature
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monitoring is essential to prevent overcooling, particularly in infants with severe HIE.

**Conflicts of interest**

The author declares no conflicts of interest.

**References**