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Review

Cooling in a low-resource environment: Lost in translation

Paolo Montaldo [a], Shreela S. Pauliah [a], Peter J. Lally [a], Linus Olson [b], Sudhin Thayyil [a, *]

[a] Centre for Perinatal Neuroscience, Imperial College London, Hammersmith Hospital, London, UK
[b] Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

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SUMMARY

Although cooling therapy has been the standard of care for neonatal encephalopathy (NE) in high-income countries for more than half a decade, it is still not widely used in low- and middle-income countries (LMIC), which bear 99% of the encephalopathy burden; neither is it listed as a priority research area in global health. Here we explore the major roadblocks that prevent the use of cooling in LMIC, including differences in population comorbidities, suboptimal intensive care, and the lack of affordable servo-controlled cooling devices. The emerging data from LMIC suggest that the incidence of coexisting perinatal infections in NE is no different to that in high-income countries, and that cooling can be effectively provided without tertiary intensive care and ventilatory support; however, the data on safety and efficacy of cooling are limited. Without adequately powered clinical trials, the creeping and uncertain introduction of cooling therapy in LMIC will be plagued by residual safety concerns, and any therapeutic benefit will be even more difficult to translate into widespread clinical use.

1. Introduction

Perinatal asphyxia associated with moderate to severe neonatal encephalopathy (NE) occurs at an approximate rate of 1–2 per 1000 live births in high-income countries [1] and 10–20 per 1000 live births in low- and middle-income countries (LMIC) [2]. Following moderate or severe encephalopathy, ~25–60% of the affected infants die and more than half of the survivors sustain significant brain injury and lifelong disability in LMIC [3]. Of the one million annual neonatal deaths caused by perinatal asphyxia, 99% occur in LMIC [4].

Therapeutic hypothermia has become the standard of care for NE in high-income countries following two decades of rigorous experimental and clinical research. This began with the demonstration of secondary energy failure and its amelioration with therapeutic hypothermia in animal models, followed by clinical trials, meta-analyses, registries, and finally its inclusion in national and international guidelines [5]. Therapeutic hypothermia reduces mortality after NE [typical relative risk (RR): 0.75; 95% confidence interval (CI): 0.64–0.88] and neurodisability in survivors at 18 months (typical RR: 0.77; 95% CI: 0.63–0.94) [6] and at school age (typical RR: 0.59; 95% CI: 0.37–0.94) [7,8]. Almost all eligible babies receive therapeutic hypothermia in the UK at present (~800 per year), and this is estimated to have saved the National Health Service a total of £125m since 2009 [9].

Given the simplicity of the intervention and the global disease burden, therapeutic hypothermia may have a considerable impact on the health and economies in LMIC. Unfortunately, in these settings the uptake of therapeutic hypothermia has been poor. Here we examine the various factors which have prevented the use of this highly effective therapy in settings which shoulder the greatest burden.

2. Issues related to healthcare infrastructure

2.1. Home deliveries and the lack of transport systems

In the 'standard model' of perinatal services practised in high-income countries, critically ill newborns are rapidly transported to resource-intensive tertiary neonatal units for therapeutic hypothermia – this is not readily applicable to the LMIC. In fact, such models are neither feasible nor desirable in LMIC, where simpler, affordable, and cost-effective interventions in primary and secondary care may be more effective in reducing neonatal mortality. In low-income countries in regions such as Sub-Saharan Africa, some communities have no access by road; communication systems are weak; many cannot afford private transport [10]; and many deliveries happen at home or in poorly equipped facilities [11]. Even in institutional deliveries, delayed maternity admissions

* Corresponding author. Address: Centre for Perinatal Neuroscience, Level 5, Hammersmith House, Department of Paediatrics, Imperial College London and Imperial College Healthcare NHS Trust, Du Cane Road, London W12 0HS, UK. Tel.: +44 203 313 8515.
E-mail address: s.thayyil@imperial.ac.uk (S. Thayyil).

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(often in prolonged or obstructed labor due to the lack of effective transport systems) may mean that the time window for initiation of therapeutic hypothermia is already lost by the time of delivery.

On the other hand, with rapidly improving standards of healthcare in urban settings and referral facilities available in transitional economies such as China, India, and Brazil, a large number of deliveries occur in hospitals, or infants may be admitted within the window period for initiation of rescue hypothermic neuroprotection. In fact, in the last two to three decades, the number of neonatal intensive care units and special care neonatal units in transitional countries such as India and China has increased exponentially [12,13]. Approximately 75% of deliveries in India now occur in hospitals, though this varies from 50% in North India to 95% in South India [14,15]. Although accurate morbidity statistics are lacking, at least one million babies are likely to suffer from encephalopathy in India every year, and up to half of these deliveries may occur in a hospital setting. If therapeutic hypothermia were available to even a small proportion of these hospitals, it may provide substantial health benefits.

2.2. The use of therapeutic hypothermia outside optimal tertiary neonatal intensive care

Interventions that are safe and highly effective within well-resourced tertiary intensive care units may not be so elsewhere. For example, the use of fluid bolus in septic shock is a routine clinical practice in well-resourced pediatric intensive care units with facilities for cardiorespiratory support and invasive monitoring of vital signs. However, in Sub-Saharan African hospitals without these facilities, the intervention was associated with increased mortality [16].

It is unclear how much intensive care support is required for the safe administration of therapeutic hypothermia. The earliest therapeutic hypothermia trials in high-income countries were conducted only in tertiary neonatal units with facilities for optimal cardiorespiratory support and neurological monitoring, and the vast majority of the babies were kept ventilated and sedated during therapy. As experience with therapeutic hypothermia has increased, it is now offered by many secondary care units in the UK; and indeed many babies (especially with moderate encephalopathy) are not ventilated, or are extubated soon after initial resuscitation while undergoing therapeutic hypothermia. Most infants undergoing therapeutic hypothermia receive sedation in the UK; however, such routine sedation was not used in the National Institute of Child health and Human Development (NICHD) cooling trial [17] and is not part of routine clinical practice in the NICHD Neonatal Research Network (NRN) in the USA (personal communication: Prof. Seetha Shankaran). In addition, studies have now shown that therapeutic hypothermia improves respiratory, renal, and other metabolic parameters in encephalopathic babies [18,19]. Thus, there is no reason to believe that therapeutic hypothermia may be ineffective without ventilatory support (although caution will need to be exercised in babies with persistent pulmonary hypertension from meconium aspiration). On the contrary, it is possible that the infants with moderate encephalopathy not requiring ventilatory support might be those who benefit most from therapeutic hypothermia in LMIC, and may achieve normal outcomes. Finally, many encephalopathic babies have a low core body temperature during first 24 h after birth [20], although this might be more apparent in babies born in low-resource settings, where radiant warmers are not routinely used [21]. It is unclear whether this hypothermia would have any neuroprotective effect, or whether rewarming these babies would cause more harm or benefit [22].

Unfortunately, the use of therapeutic hypothermia in low-resource settings has received bad publicity after a pilot study in Sub-Saharan Africa showed five-fold higher mortality in cooled babies, albeit statistically non-significant (RR: 5.0; 95% CI: 0.7–37) [21]. It remains unclear whether this was related to a lack of basic neonatal care facilities and medical/nursing expertise in this setting (for example adequate neonatal resuscitation and routine monitoring of basic physiology); inadequate cooling devices (water bottles); lack of sedation [23]; or due to the recruitment of more severely encephalopathic infants in the cooled arm. Nevertheless, therapeutic hypothermia has now disappeared from the priority list of global health researchers, with infection being highlighted as a potential cause for the increased mortality with therapeutic hypothermia [24], despite little evidence to support this. This situation is not dissimilar to the 1960s, when therapeutic hypothermia received negative publicity after a clinical trial showed an increased mortality of hypothermic preterm infants [25]. Therapeutic hypothermia then disappeared from the clinic for several decades before it was rigorously re-evaluated in high-income countries. A repeat of this history would be unfortunate, and may deprive babies in LMIC from the benefits of one of the most important and simple interventions in medicine.

3. Concerns about perinatal infection

Fetal inflammation and infection has been shown to increase brain vulnerability to hypoxia–ischemia via stimulation of immune and inflammatory responses, chemotaxis, toll-like receptors and cell death [26]. Emerging experimental data also suggest that hypothermia may not be neuroprotective after bacterial lipopolysaccharide-sensitized NE brain injury as compared to hypothermia without bacterial lipopolysaccharide [27]. Hence, therapeutic hypothermia in the presence of infection might even be deleterious as hypothermia may impair innate immune function, including neutrophil migration and function [28].

In a prospective study, Tann et al. [29] reported that the prevalence of neonatal bacteremia with a pathogenic organism among encephalopathic infants was 3.5% by blood culture alone, 6.9% by polymerase chain reaction (PCR) alone, and 8.9% by blood culture and PCR in combination. A similar incidence of coexistent bloodstream-positive infection and encephalopathy has been reported from India [30,31]. This is similar to that reported from high-income countries: 8.1% in the Infant Cooling Evaluation (ICE) trial [32], 6% in NICHD [17], 17% in the Total Body Cooling (TOBY) registry [33]. Therefore, coexistent perinatal infection is unlikely to have a role in influencing the treatment efficacy of therapeutic hypothermia for the vast majority of babies in LMIC.

4. Concerns about established brain injury

Cerebral magnetic resonance imaging (MRI) in high-income countries has shown that cerebral injury is acute and acquired perinatally, and is not established (antenatal injury) at the time of birth; hence it is amenable to therapeutic hypothermia [34]. Emerging evidence from LMIC suggests similar perinatal origins of brain injury. In a prospective study on 172 encephalopathic infants admitted to a sub Saharan neonatal unit, evidence of acute perinatal injury was seen on early cranial ultrasound (USG) in most infants, however, established brain injury was not seen in any baby [35]. Although the utility of USG in term encephalopathic infants is limited [36], these findings are similar to the cerebral MRI reported by Lally et al. from a South Indian cohort ($n = 54$), in which none of the encephalopathic babies had evidence of established brain injury. However, unlike in high-income countries, the predominant injury was in the white matter, rather than in the deep gray matter