Neuroprotection for Perinatal Hypoxic Ischemic Encephalopathy in Low- and Middle-Income Countries

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Perinatal hypoxic ischemic encephalopathy (HIE) is associated with approximately one-quarter of global neonatal deaths.[1] In 2010, there were an estimated 1.15 million cases of neonatal encephalopathy, of which 96% of were from low- and middle-income (LMI) countries.[2] In the developed world, therapeutic hypothermia is now widely accepted as the standard of care for treating newborns with moderate to severe HIE.[3] Therapeutic hypothermia has been found to reduce the risk of death or major neurodevelopmental disability at age 18 months (risk ratio [RR], 0.76; 95% CI, 0.69-0.84) and to increase survival with normal neurologic function (RR, 1.63; 95% CI, 1.36-1.95).[4,5] Recent studies have confirmed improved neurocognitive outcomes at school age.[6,7] Those studies involved predominantly developed countries. In contrast, a systematic review of 7 trials including 567 newborns from LMI countries, using mainly low-cost cooling techniques, did not show a significant reduction in neonatal mortality (RR, 0.74; 95% CI, 0.44-1.25).[8] Although the point estimate is consistent with estimates from the developed world,[4,5] the wide CI of that result means that a clinically important benefit or harm could not be excluded. Furthermore, there was insufficient long-term follow-up to allow assessment of whether hypothermia had improved neurodevelopmental outcomes.

See related article, p 58

The heterogeneity of outcomes in studies from LMI countries may be an artifact of poorly designed studies, many of which were very small.[8] The largest study in that review, which carried almost one-half of the weight in the primary outcome (neonatal mortality), may have introduced selection bias by including more boys (85%) and violated its protocol by including 20% cases with mild encephalopathy.[9] Overall, 15% of the patients in these studies had mild encephalopathy, and, consistent with this, only 12% required ventilation.[8] Newborns with mild HIE have a low risk of mortality,[10] reducing the study's power and potentially leading to a false conclusion that the intervention is not conclusive when the intervention was not applied to the correct target population. It is unclear whether the low frequency of mechanical ventilation reflects only selection for milder cases, or whether resource limitations constrained care.

Alternatively, the heterogeneity of outcomes potentially could be "real," that is, related to medical factors that impair the effectiveness of hypothermia. First, there may be biological differences in the study populations. Some evidence from a newborn rat model of hypoxic ischemic brain injury suggests that priming with infection before the injury may reduce the protective effect of mild hypothermia.[11] The rate of perinatal neonatal sepsis is higher in many LMI countries,[12] and thus might reduce the neuroprotection afforded by hypothermia. However, as reviewed recently, the rate of confirmed sepsis in Ugandan or Indian infants with encephalopathy is not materially different from that reported in recent developed world trials.[13] Second, the time of the insult before treatment is critical to the effectiveness of hypothermia,[14] and is often difficult to quantify. In LMI countries, a higher proportion of perinatal brain injury may be related to chronic antenatal insults, such as malnutrition and intrauterine growth restriction,[15] and there are often delays in providing care owing to a limited medical and nursing infrastructure.[16] Thus, in many cases, the therapeutic window may have passed by the time that treatment could be initiated.[17] Third, low-resourced or less-experienced centers may be less rigorous in using therapeutic hypothermia according to established protocols, or may use less rigorous selection criteria, which would reduce the apparent efficacy of hypothermia or increase complications.[18,19] Fourth, such countries may not be able to provide adequate neonatal intensive care, including proper monitoring, mechanical ventilation, sedation, and use of oxygen. Finally, LMI countries may be less able to afford approved devices to induce stable hypothermia within targeted goals. Nevertheless, low-cost alternative devices, such as servo-controlled fans to blow room air, ice packs, cold water bottles, mattresses made of phase-changing materials, and less expensive servo-controlled cooling blankets, are being developed.[18,20-23]

This outcome leaves LMI countries with insufficient evidence that therapeutic hypothermia is safe and protective in their current settings, and yet it is almost certainly no longer acceptable to undertake trials of hypothermia against normothermia. This ethical conundrum is not unique, and it

HIE	Hypoxic ischemic encephalopathy
LMI	Low- and middle-income
RR	Risk ratio

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is common to have a gap in evidence-based practice between high-income countries and LMI countries.

Resource limitations are understandably severe in low-income countries. Thus, at present, hypothermia should not be considered standard care in extremely poor settings, where it may be argued that primary prevention should be the primary focus. A comprehensive package of community-based low-cost interventions (eg, the Helping Babies Breathe campaign) to ensure that all infants are born with a skilled birth attendant present is likely to have a much greater effect than any secondary treatment.[24,25] Similar initiatives tailored according to the sociocultural environment to improve maternal nutritional status, improve obstetric care, and decrease infection rates will improve maternal and, consequently, neonatal outcomes. Consistent with this suggestion, a recent analysis in 78 LMI countries found that scaling up midwifery among other maternal and newborn interventions could avert up to 83% of all maternal deaths, stillbirths, and neonatal deaths. Furthermore, the inclusion of specialist care could further decrease deaths, meaning that midwifery care has the greatest effect when provided within a functional health system with effective referral and transfer mechanisms to specialist care.[26] Thus, secondary treatment and primary prevention should be balanced in countries where there is a wide range of resourcing.

Ethical Complexity and Limited Resources

In many LMI countries, poverty, endemic diseases, and a low level of investment in health care systems will affect both the ease of performing clinical trials and the selection of trials that can benefit local citizens. A further challenge is to conduct clinical trials that make use of impoverished and, at least in some cases, illiterate populations without violating ethical behavior and while protecting potential research subjects.[27] At the same time, capturing a wide spectrum of patient profiles with adequate representation of all ethnic groups is essential for global implementation of any therapy. This suggests that international collaboration between LMI and high-income countries is essential to systematically test the most promising agents. Naturally, LMI countries will need to demonstrate sufficient clinical expertise and motivation to undertake neuroprotection research, to ensure safety of the participants and a high likelihood of success for collaborative work. Such collaboration between high-income and LMI countries in the design and conduct of future trials will enhance not only the participation of LMI countries, but also the way in which results of trials are implemented.

Powering Clinical Trials of Neuroprotection

Collaboration between LMI and high-income countries may have significant benefits for the speed of development of potential treatment strategies. Assuming a target of a 20% reduction in relative risk for the primary outcome of death or major neurodevelopmental disability at age 18-24 months from the current 48%[4,5] to 38%, an α error of 0.05, and a β error of 20%, by convention, 748 newborns with moderate to severe perinatal hypoxic ischemic insult will be required to test each new therapy. Based on a 20% loss to follow-up, a sample size close to 900 participants would be needed to complete a single study. Furthermore, a single study is typically not sufficient to establish any intervention and to confirm generalizability.

Given the current incidence of 1-2 cases of neonatal encephalopathy per 1000 live births in the developed world, it will be difficult to recruit such large cohorts in high-income countries alone within a reasonable timeline.[28] Shortening the interval between drug discovery and use in clinical practice in multiple settings is a clear benefit that would be achieved by increasing study power. Surrogate endpoints for clinical trials are possible, but ultimately clinical improvement will be required to convincingly demonstrate usefulness.

Should Patients from LMI Countries Be Represented in Future Clinical Trials?

Investing in an intervention that would not be applicable to LMI countries will not help the majority of potential beneficiaries and will limit the global utility of such an intervention. Thus, the interests of newborns in LMI countries should be considered when researchers are investigating neuroprotective interventions.[2,29,30]

Simple administration and monitoring are crucial to make new interventions successful and usable in LMI countries. Ideally, any intervention would be: (1) accessible and distributable in all pharmaceutical markets; (2) inexpensive—the cost of the treatment in LMI countries directly affect parents' decision whether to continue treatment or to withdraw care; (3) easily administered, especially during transport, to prevent delays in starting a time-sensitive treatment; and (4) require minimal training for its administration and monitoring.

What Should Be Next?

At present, researchers in developed countries are evaluating the effectiveness of xenon and erythropoietin in conjunction with hypothermia, with little contribution from LMI countries.[31-33] These agents have shown promising preclinical results, but carry relatively high costs. For example, Dingley et al[31] estimated the cost of using a recirculating circuit of xenon as a way to reduce costs in conjunction with therapeutic hypothermia as $15.60 per hour, in addition to $200 for the ventilator circuit and $80 for the cuffed endotracheal tube. That figure did not include the costs of intensive care beds for ventilated newborns and long-term follow up. Thus, the final costs for such interventions remain high for LMI countries. There are added costs for knowledge translation, education, and training of medical and nursing staff. These costs may preclude their implementation in LMI countries.