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Therapeutic Hypothermia for Neonatal Hypoxic Ischemic Encephalopathy (HIE) in Low- and Middle-Income Countries (LMIC's): Challenges and Opportunities

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Introduction:

Perinatal Asphyxia is the third major cause of neonatal mortality and morbidity worldwide: more so in LMIC's which bear almost 98% of global incidence of Perinatal Asphyxia. The involvement of brain in Perinatal Asphyxia, called Hypoxic Ischemic Encephalopathy (HIE), occurs in 1 up to 3 per 1000 live births in high-income countries, and in up to 20 per 1000 live births in LMIC's [1]. Untreated HIE has very high mortality (up to 62%) and very high morbidity in survivors (Cognitive and developmental delay or learning difficulties 45%, Cerebral Palsy 29%, Blindness or vision defects 26%, Gross motor, coordination problems and epilepsy 17%, hearing loss or deafness 9%, and behavioural issues 1%) [1]. The socioeconomic and psychological consequences of these morbidities are very high; both for the sufferers and their families as well as the health system.

Therapeutic Hypothermia, induced during the first 72 hours of life, is now standard evidence based neuroprotective therapy in all NICU's worldwide for moderate to severe HIE in term and near-term infants [2-4]. TH reduces the combined risk of mortality and morbidity due to HIE by 20 to 30% [4]. The beneficial neuroprotective effects of TH persist into early and late childhood [4]. In high income countries, TH is provided by servo-controlled total body cooling machines (Teicotherm Neo. Inspiration Health Care or other similar machines) which are excellent in maintaining TH in the required range (33^{0}C to 34^{0}C). Unfortunately, these servo-controlled machines are very expensive and beyond the economic capability of LMIC's. The alternative is to use low-cost devices like ice gel packs or phase changing cooling mattresses for inducing and maintaining TH [4]. These low-cost devices are labour intensive, requiring hourly manual temperature check and adjustment of cooling support. The maintenance of temperature exactly in the very narrow required range (33^{0}C to 34^{0}C) demands very dedicated 1:1 nursing care [4]. However, the target is achievable as shown in the study by Naeem et al [6]. in this issue of IJPRHE. The message from this study is very significant and hope building for hard pressed paediatricians working in LMIC's and dealing with huge number of infants with HIE, system deficits and economic constraints.

Abate B B et al [1]. concluded in their systematic review and meta-analysis of 28 RCT's that "Low-income countries benefit the most from TH. Therefore, health professionals should consider offering therapeutic hypothermia as part of routine clinical care to newborns with hypoxic-ischemic encephalopathy especially in low-income countries". Fajardo C et al. concluded the same

from their study based on Epic Latino Neonatal Network [5]. The recommendation is clear but LMIC's have a number of challenges in implementing TH protocol [4]. The challenges in implementing TH in LMIC's extends beyond infrastructure and equipment [4]. These challenges include a large volume of out born deliveries in centres with no facilities to provide TH, home deliveries, lack of appropriately skilled and trained staff, diagnostic uncertainty, delayed referrals and almost non-existent neonatal transport facilities. In LMIC's, babies presenting with HIE are very likely to have additional co morbidities e.g. sepsis, intrauterine growth retardation, maternal malnutrition and untreated maternal illnesses like diabetes and hypertension. The challenges, their impact on LMIC's and mitigation strategies are summarised in below table.

Challenge	LMIC Impact	Mitigation Opportunity
Infrastructure	Power outages, no servo-devices	Low-cost passive cooling (ice packs)
Diagnosis/Timing	No aEEG/blood gas	Simplified scores (e.g., Thompson)
Comorbidities/Support	Sepsis, no ventilation	Selective "TH-ready" centers
Workforce	Low neonatologist and nurses density	Task-shifting + training

The large number of infants suffering from HIE in LMIC's provides a unique opportunity of research in a single, well selected, appropriately staffed and equipped perinatal centre. This opportunity is unavailable in high income countries which have to resort to a multi-centre trial to meet the sample size within the duration of the trial. Provided there is enough technical, academic and financial support, LMIC's can provide further insights into TH, both as a monotherapy as well as in combination with neuroprotective pharmacologic agents e.g. Erythropoietin, Melatonin, Magnesium Sulphate, Allopurinol etc [3]. TH in LMIC,s can also open a gateway to neuroprotective strategies in high-risk infants suffering from encephalopathies other than HIE.

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