EDITORIAL

# Therapeutic Hypothermia in Neonates: Is Phase Changing Material the Game Changer?

**SRIPARNA BASU[1] AND MANISH KUMAR[2]**

*From Departments of [1]Neonatology and [2]Pediatrics, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India.*
*[1]drsriparnabasu@rediffmail.com*

Therapeutic hypothermia (TH) is now considered the standard of care for neonatal hypoxic ischemic encephalopathy (HIE) in developed world with favorable clinical evidence in terms of reduction in mortality and improved neurological outcome on long-term follow-up [1]. However, low- and middle-income countries (LMIC), where the burden of HIE is ten folds higher with over a million annual neonatal deaths, have been bereft of the benefits of TH, primarily due to high costs associated with advanced servo-controlled cooling devices. The urgent need for an affordable cooling technology has translated into multiple trials with ice, frozen gel packs and cooling fans; albeit unsuccessfully. These well-meaning attempts were hindered by unacceptable temperature fluctuations leading to severe hypothermia and consequent adverse outcomes [2]. Selective head cooling, similarly, suffers from the drawback of hyperthermia in the rewarming phase. A meta-analysis on TH for neonatal encephalopathy in the LMICs failed to establish a statistically significant benefit in terms of reduction in neonatal mortality [3]. The authors also highlighted the paucity of clinical data to exclude significant harms or benefits of cooling therapy in resource-constraint settings.

The quest for an affordable innovation has thus brought into focus a bioengineering marvel named phase changing materials (PCM). Composed of salt hydride, fatty acids and esters, PCM is currently being used in industrial set ups and in jackets worn by firefighters. They essentially act as heat buffers through their ability to liquefy on coming in contact with a warmer object thus absorbing and storing heat. This unique property is utilized in designing neonatal bed meant for whole body cooling. Preliminary reports of usage of PCM for TH in both experimental animal models and small single-center cohorts have yielded promising results. Iwata, *et al.* [4] showed that PCM can effectively induce and maintain hypothermia in piglet model along with their superiority in providing more stable hypothermia in comparison to water bottles. Thayyil, *et al.* [5] tried whole body cooling using PCM mattresses for neonatal HIE in 17 neonates. Though not powered for clinical outcomes, this study considered PCM based cooling an option worth exploring. This interest in PCM has shaped into a multicenter trial (Hypothermia for Encephalopathy In Low Income countries: HELIX), which is currently recruiting with an aim to provide definitive answers regarding safety and efficacy of TH in LMICs [6].

Amidst this excitement for PCM, Thomas, *et al.* [7] have made an earnest attempt by garnering robust scientific evidence for role of PCM in TH. The team from Christian Medical College, Vellore have built upon their earlier single-center, retrospective study involving 41 neonates for assessing the efficacy of PCM-based device as an alternative method of providing TH [8]. In the present trial [7], the authors enrolled 103 neonates with perinatal asphyxia from eleven centers in India, to assess the feasibility and safety of TH through a PCM-based device (MiraCradle). The study documents a stable hypothermia through PCM-based cooling with temperature fluctuations less than that reported from trials using servo-controlled equipments; though induction of hypothermia was delayed. The selection of level-3 NICUs with pre-established protocols as study settings, is a commendable strategy aimed at addressing the assumption of lack of optimal neonatal care when explaining the failure of TH in LMICs. The multicentric nature of study also lends support to the claims of external validity of the protocol suggested. Another astutely planned aspect of the cooling strategy in this trial is use of PCM with different melting points aimed at providing stable hypothermia, decreasing the need for repeated nursing interventions. However, the fact that most of neonates were hypothermic at randomization somehow dilutes the observation regarding induction of hypothermia by PCM-based devices. Another notable difference of this study with trials from developed settings is the markedly lesser number neonates with severe encephalopathy, thus negating the opportunity to

assess the feasibility and safety aspects of PCM-based cooling in the severest spectrum of HIE. As acceded by authors, the lack of control group and long-term follow-up data are obvious limitations, which leave us short of a definitive answer.

In LMICs, the outcome of moderate to severe HIE is still grim with high mortality and poor long term developmental outcome. This study by Thomas, *et al.* [7] is a timely and praiseworthy effort in an endeavor for finding the elusive answers regarding safety and efficacy of TH for neonatal encephalopathy in resource constraint Indian settings. While we wait for an adequately powered clinical trial that can establish PCM as the game changing modality for the management of HIE; the goals of strengthening our obstetric and perinatal services to prevent perinatal asphyxia and its avoidable consequences should not elude our vision.

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