

## **Cooling Therapy for Neonatal Encephalopathy in Low- and Middle-income Countries**

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**R**escue hypothermic neuroprotection has now dominated publications related to neonatal encephalopathy for over a decade. Carefully designed and executed randomized controlled trials in high-income countries have conclusively shown that a controlled reduction of body temperature by 3 to 4°C soon after birth for three days reduces death and neuro-disability, and that the benefits persists into late childhood [1]. Deeper or longer cooling is not beneficial and may be harmful [2], and the benefits of delayed cooling (after 6 hours) is marginal [3]. In all high-income countries, cooling therapy is now the standard of care for babies with moderate or severe encephalopathy.

However, the cooling story is far from complete. One of the biggest unanswered questions is whether this therapy would benefit babies in low- and middle-income countries (LMICs), which shoulder the highest disease burden. Undertaking cooling trials in developing countries is challenging due to the lack of adequate research governance, and the difficulty in obtaining accurate clinical and follow-up data. It is unrealistic for clinical teams to obtain accurate hourly recordings of core body temperature in LMICs, unless data loggers are used, and the claims of accurate hourly manual temperature recording have to be taken with a pinch of salt [1]. Thus, although a number of small and low quality clinical trials have been reported from LMICs, the published data are inconclusive and the safety and efficacy of cooling in these settings remain uncertain [4].

Another key issue is the way cooling is delivered. Any method that can maintain core body temperature within the target range without wide fluctuations, in theory, should be adequate for this purpose. Interestingly, almost every low-tech cooling strategy – ice, frozen gel packs, water bottles, fans – has been reported to have similar cooling efficacy as the servo-controlled devices [1,5]. The latest in this long list is phase changing material.

Phase changing materials (PCM) are made of salt

hydride, fatty acid, and esters or paraffin, and melt at a set point. During this process they can store or release large amounts of energy, and hence, have a wide range of applications based on the set points. The use of PCM as a low-cost cooling method for developing countries was first proposed by Olsen, as a part of his PhD work at University College London and Karolinska University in 2007. In a piglet model of hypoxic ischemic injury (where the ambient temperatures were around 18 to 20°C with air conditioning), PCM effectively induced and maintained cooling in the target range. The first ever clinical trial of PCM was conducted at Calicut Medical College – the Peacock (Phase Change Material for Cooling in Kerala) trial in 2009 [5,6]. The PCM cooling mattress was manufactured by Climator with a cost of approximately £100 per mattress. Hourly rectal temperatures were recorded and stored using a data-logger, and then transferred to a database for analysis. PCM maintained core temperature within the target range, only when ambient temperature was low. Given that most tertiary neonatal units in India may have air-conditioning, this may not prove to be a major hurdle in wider use. Although it is unclear whether the nursing staff documented hourly temperature data in real time, and what the ambient temperatures were, Thomas and colleagues report that PCM can be used to administer cooling in Indian neonatal units [7].

The key question is: should we now start routine cooling therapy in India and other LMICs? Opinions are polarized. Some feel most neonatal therapies used in LMICs are based on evidence from high-income countries, and high quality, multicenter neonatal trials are rarely undertaken in these settings. So, why should this be different in cooling therapy? Moreover, is it ethical to withhold a highly effective and proven treatment that is standard of care in high-income countries [8] from the babies in LMICs, particularly as there is no alternative treatment?

Others argue that differences in population co-

morbidity, infection, and supportive care could alter the therapeutic response to cooling such that it may even be harmful [1]. Not uncommonly, direct extrapolation of the evidence from high income countries to LMICs may cause harm [9,10]. The primary duty of the clinicians is to 'do no harm first'. A large multi-country randomized controlled trial (HELIX) is now nearing completion in many centers in India, Sri Lanka and Bangladesh, and may well provide a definitive answer to this important issue.

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