Should hypoxic babies get a little cold at birth?

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Hypothermia develops consistently in infants exposed to asphyxia and cared for at room temperatures. The mechanisms include inhibition of endogenous thermogenesis by acidosis, hypoxia and inflammation and reduced body movements (Silverman & Sinclair, 1966). In the early days of neonatal intensive care, such spontaneous hypothermia was associated with greater oxygen consumption and increased mortality, at least in preterm infants. The direction of causality has been contentious, but until recently it was recommended that infants should be aggressively kept warm. For term and near-term infants with acute, evolving encephalopathy, this has been dramatically reversed in the developed world by compelling evidence from multiple controlled trials in infants with moderate to severe neonatal encephalopathy that mild induced hypothermia (33.5±0.5°C) started as early as possible in the first 6 hours after birth and continued for 72 hours significantly improves survival without disability, at least in the setting of modern neonatal intensive care. The optimal parameters for neuroprotection are well established, as recently reviewed (Wassink *et al.*, 2018). Critically, we know that deeper and or longer hypothermia does not further improve outcomes and may increase early neonatal mortality (Shankaran *et al.*, 2017).

Mild therapeutic hypothermia is a safe, cheap intervention that can be delivered in many ways, including very low tech solutions. Despite this, it has proven to be exceptionally difficult to translate to the developing world. One of the key limitations is reported in this issue: similarly to the historical experience (Silverman & Sinclair, 1966), a cohort of 14 infants with encephalopathy cared for in a sub-Saharan Africa hospital developed poorly controlled spontaneous hypothermia after birth (Enweronu-Laryea *et al.*, 2019). In this cohort, it is very striking that the mean rectal temperature in the first 24 hours, 34.2°C, is just above the target range (33 to 34°C) for therapeutic hypothermia. It is very tempting to see this spontaneous cooling as an endogenous protective response. Unfortunately, the infants' rectal temperatures were in the target range for just 18% of the time on average; and were above 34°C for more than two thirds of the time, and below 33°C for 11%. Moreover, it is reasonable to note that the average was likely in part related to the policy of initially leaving the infants uncovered except for a nappy and then covering them with a blanket if their

rectal temperature fell below 34° C, and that the policy was strengthened during the study to try to reduce the risk of deeper hypothermia.

The rather variable temperature profile is highly consistent with evidence that such spontaneous cooling is passive and not actively regulated to a new setpoint, as reviewed (Romanovsky, 2004). Consistent with the historical evidence (Silverman & Sinclair, 1966), more severe encephalopathy was associated with a greater fall in temperature and greater mortality. Given that in randomized controlled trials, hypothermia was associated with reduced risk of death (Wassink *et al.*, 2018), and few side effects, which were of limited clinical significance such as mild thrombocytopenia, it is likely that more severe asphyxia mediated both the fall in temperature and mortality. Only one infant in this cohort developed sepsis and was treated conventionally. Nevertheless, it is important to note that infection is very common in low resource settings (Tann *et al.*, 2018), and that hypothermia has dose related anti-inflammatory effects and so can impair neonatal response to infection (Wassink *et al.*, 2018). Careful assessment is essential, particularly during deeper cooling.

Thus, overall, spontaneous cooling in this sub Saharan African hospital setting was not associated with the "optimal temperature profile" that can be delivered in settings that offer standardized therapeutic hypothermia (Enweronu-Laryea *et al.*, 2019). This does not necessarily mean that it had no benefit. Although there is no strong clinical evidence, spontaneous cooling is also universally seen in rodents after hypoxia; indeed most preclinical studies of neuroprotection mainly involved active warming to prevent a fall in temperature in the 'normothermic' groups. For example, in neonatal (postnatal day 7) rats, active warming to 37°C for 5 h after hypoxia-ischemia was associated with greater cerebral infarction than cooling to 33.5°C, with no additional protection with deeper cooling (Wood *et al.*, 2016). After the period of active temperature manipulation, the pups were returned to the nest with their dam. Healthy rat pups have rectal temperatures that are typically 1 to 2 °C less than 37°C, inferring that the neonatal rats will have received milder but ongoing passive hypothermia *after* the 5 h period of active hypothermia (Wood *et al.*, 2016). This suggests that, at

least from 5 h after hypoxia-ischaemia, milder hypothermia than tested in human trials can have some benefit. This concept is consistent with the finding of neuroprotection with a reduction in temperature of just 2 to 3 °C in postnatal day 21 rats, provided that this very mild cooling was started immediately and continued for 72 hours (Wassink *et al.*, 2018).

A more subtle benefit is that a policy of allowing mild hypothermia effectively reduces the risk of hyperthermia. Increased brain temperatures are consistently highly deleterious after hypoxia-ischemia in neonatal animals, and can transform selective cell loss into overt infarction (Wood *et al.*, 2016). Indeed, in the large randomised controlled trials of therapeutic hypothermia in the developed world, intermittent pyrexia was common in the control groups who received “normothermia” and associated with worse outcomes (Wassink *et al.*, 2018). Given these considerations, as much as we would like to recommend actively managed hypothermia for neonatal encephalopathy in all situations, on balance, allowing mild spontaneous hypothermia is likely to provide some net benefit for neonatal encephalopathy in a low resource setting, provided that deeper hypothermia is avoided.

Last but not least, the temperature profile in this cohort strongly emphasizes that if we wish to develop new neuroprotective interventions for low resource settings, then just as in the developed world, all strategies must now be specifically tested to see if they can augment protection during mild hypothermia. Indeed, it may be appropriate to test different temperature profiles depending on the specific clinical setting. Therapeutic hypothermia both reduces clearance of many drugs, and acts through mild but broad suppression of deleterious pathways and so there is considerable potential for additive effects with combined therapy (Wassink *et al.*, 2018).

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