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**Response to:**

**Late Initiation of Therapeutic Hypothermia: Not the New Standard of Care (Bourque SL, Dietz RM.**

**Start Cooling as soon as possible**

Thank you for your supportive comments (1) on our letter (2), regards statistical interpretation of the Laptook et al paper publishing a trial on delayed therapeutic hypothermia (TH) treatment which you supported (3). You also present arguments in favour of allowing this late start of TH after perinatal asphyxia and we would like to comment on those.

You say (1):

‘Laptook and colleagues importantly demonstrated the feasibility and safety of late TH when early initiation of TH may not be possible. Specifically, there were no increased adverse events in the infants who underwent late TH.’

Should one offer treatment with uncertain efficacy as long as the treatment is feasible and has shown no harm? Even if harm was not shown from 96 hours of TH, starting at ~16 hours after birth in the Laptook paper, there are known disadvantages and uncertainties related to hypothermia treatment. The newborn is separated from its parents, and he/she is less likely to receive any breast milk until after rewarming. As an intensive care patient, most infants undergoing TH will be ventilated and sedated, receive antibiotics and parenteral nutrition. We do not know the long-term effects of the necessary sedative drugs delivered during TH (it is unpleasant to be cold as well as ventilated). It is known that drug levels show great individual variability (4), partly due to unpredictable liver and kidney metabolism during cooling. Animal data from different species suggest that opiates damage the immature brain including the cerebellum and starting cooling with a delay of 12 hours in rats after a severe HI insult increased injury (5). These disadvantages need to be weighed against a treatment with disputable effect.

Your next point (1) addresses two clinical problems:

‘Under-recognition of encephalopathy and delivery at centres without cooling capability coupled with prolonged transport time are potential reasons for inability to cool within 6 hours after delivery.’

The first point highlights the need for training of staff and availability of some basic monitoring equipment for cooling like rectal temperature probes for continuous temperature monitoring. Single channel aEEG equipment will document background voltage depression or seizures and help the diagnosis of encephalopathy, a web-camera or smartphone can send pictures and video of the aEEG trace and a neurological examination to the cooling centre. The cooling centre should be able to provide a second opinion fast and advise on starting passive cooling or not. A cohort study showed it was the time of starting cooling and not the time it took to reach 33.5° which is the more important. (6)

We think the effort is better used on early diagnoses with centralised review, cooling during transport and starting cooling within 6 hours after birth.

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