

Time to start hypothermia after perinatal asphyxia: does it matter?

Floris Groenendaal¹

To cite: Groenendaal F. Time to start hypothermia after perinatal asphyxia: does it matter? *BMJ Paediatrics Open* 2019;3:e000494. doi:10.1136/bmjpo-2019-000494

Received 18 April 2019
Revised 27 April 2019
Accepted 29 April 2019

Evidence from animal models of human perinatal asphyxia has demonstrated that starting moderate hypothermia within 6 hours after the hypoxic-ischaemic insult provides neuroprotection.^{1–3} One of the beneficial effects of moderate hypothermia is presumed to be a reduction of ‘secondary energy failure’ which starts 6–8 hours after resuscitation.¹⁴

Trials in (near-)term human infants confirmed the beneficial effects of cooling when started within 6 hours, and most guidelines strongly recommend starting therapeutic hypothermia as soon as possible after perinatal asphyxia and subsequent encephalopathy.⁵

In their paper in this journal Guillot *et al* suggest that starting therapeutic hypothermia before 3 hours was not associated with a difference in brain injury on MRI or a better neurodevelopmental outcome at 18 months.⁶ They based their conclusions on observations in 91 infants of whom 61 had moderate to severe hypoxic ischaemic encephalopathy (HIE) before therapeutic hypothermia was started.

The authors suggest that time to start cooling is not relevant, although in the conclusions of their paper they state that cooling should be started as soon as the indication is confirmed.

When taking a closer look at the data of the paper, it is obvious that the infants who were started early needed more resuscitation, and were referred earlier to a level III neonatal intensive care unit. This is also reflected in the severity of HIE before therapeutic hypothermia: significantly more infants with severe HIE were seen in the ‘Early’ versus the ‘Late’ group. The paper does not mention how many infants who died had an MRI performed, and what the results of these MRIs were.

Time to reach target temperature after initiation of therapeutic hypothermia was surprisingly long, more than 3 hours in the ‘Early’ group, and 3.5 hours in the ‘Late’ group. This is much longer than the 2–2.5 hours as reported by Thoresen *et al*.⁷

If the outcome is similar in the ‘Early’ versus ‘Late’ groups of Guillot *et al*, this would suggest that earlier treatment is more effective, since the infants who were cooled earlier had a more severe hypoxic-ischaemic insult as demonstrated by a significantly higher resuscitation score.

In contrast with the findings of Guillot *et al* an earlier study demonstrated a better motor outcome at 18–20 months when cooling was started before 3 hours.⁷

Using MRI different patterns of brain injury can be demonstrated after perinatal asphyxia.⁸ Signal changes in the deep grey matter are seen after a severe sentinel event such as uterine rupture or placental abruption. Lesions in the deep grey matter are commonly followed by motor impairments, in particular dyskinetic cerebral palsy.⁹ Watershed lesions occur more commonly after more prolonged, moderate fetal hypoxia and are followed by cognitive impairments specially when aggravated by hypoglycaemia.¹⁰ Follow-up until school age is required to assess long-term effects of hypothermia.

It is likely that cooling is more effective in the acute, sentinel insult than in the prolonged fetal hypoxia and therefore provides better motor protection as suggested by Thoresen *et al*.⁷ The paper by Guillot *et al* is underpowered to make this distinction, and MRI was not performed in the most severely affected infants.

A publication by Laptook *et al* focusing on therapeutic hypothermia initiated 6–24 hours after birth stated that delayed therapeutic hypothermia ‘may have benefit, but there is uncertainty in its effectiveness.’¹¹ These findings were criticised recently.¹²

After more than a decade of using moderate hypothermia as standard neuroprotective therapy there is still room for fine-tuning. We therefore agree with the final sentence of Guillot *et al* that larger studies are needed to better establish the effect of timing of therapeutic hypothermia avoiding the bias of



© Author(s) (or their employer(s)) 2019. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

Department of Neonatology, University Medical Center Utrecht and Utrecht University, Utrecht, The Netherlands

Correspondence to

Dr Floris Groenendaal; f.groenendaal@umcutrecht.nl

severity of the insult. Use of amplitude-integrated electroencephalography (aEEG) will definitely aid in stratification of severity of HIE before cooling.¹³

In addition, the paper by Guillot *et al* demonstrates that after therapeutic hypothermia still a substantial number of patients have an adverse outcome.⁶ Routine neuro-monitoring using aEEG and treatment of (subclinical) seizures will reduce the adverse neurodevelopmental outcome following HIE. Because of the still substantial number of patients with adverse outcome, research should focus on add-on treatment modalities or interventions to further improve outcome. Funding for these studies is urgently needed.

Meanwhile, based on the current evidence, therapeutic hypothermia should be started as soon as indicated to obtain the best neuroprotective results.

Contributors FG wrote this text after the invitation of *BMJPO*.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

REFERENCES

1. Gunn AJ, Gunn TR, de Haan HH, *et al*. Dramatic neuronal rescue with prolonged selective head cooling after ischemia in fetal lambs. *J Clin Invest* 1997;99:248–56.
2. Thoresen M, Bågenholm R, Løberg EM, *et al*. Posthypoxic cooling of neonatal rats provides protection against brain injury. *Arch Dis Child Fetal Neonatal Ed* 1996;74:F3–F9.
3. Thoresen M, Penrice J, Lorek A, *et al*. Mild hypothermia after severe transient hypoxia-ischemia ameliorates delayed cerebral energy failure in the newborn piglet. *Pediatr Res* 1995;37:667–70.
4. Lorek A, Takei Y, Cady EB, *et al*. Delayed ("secondary") cerebral energy failure after acute hypoxia-ischemia in the newborn piglet: continuous 48-hour studies by phosphorus magnetic resonance spectroscopy. *Pediatr Res* 1994;36:699–706.
5. Jacobs SE, Berg M, Hunt R, *et al*. Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst Rev* 2013;(1).
6. Guillot M, Philippe M, Davila J, *et al*. Influence of timing of initiation of therapeutic hypothermia on brain MRI and neurodevelopment at 18 months in infants with HIE: a retrospective cohort study. *BMJ Paediatrics Open* 2019.
7. Thoresen M, Tooley J, Liu X, *et al*. Time is brain: Starting therapeutic hypothermia within three hours after birth improves motor outcome in asphyxiated newborns. *Neonatology* 2013;104:228–33.
8. de Vries LS, Groenendaal F. Patterns of neonatal hypoxic-ischaemic brain injury. *Neuroradiology* 2010;52:555–66.
9. Kinney HC, Volpe JJ. Hypoxic-ischemic injury in the term infant: neuropathology. In: Volpe JJ, ed. *Neurology of the newborn*. 6th ed.. Philadelphia, PA: Elsevier, 2018: 484–99.
10. Martinez-Biarge M, Bregant T, Wusthoff CJ, *et al*. White matter and cortical injury in hypoxic-ischemic encephalopathy: antecedent factors and 2-year outcome. *The Journal of Pediatrics* 2012;161:799–807.
11. Laptook AR, Shankaran S, Tyson JE, *et al*. Effect of therapeutic hypothermia initiated after 6 hours of age on death or disability among newborns with hypoxic-ischemic encephalopathy: a randomized clinical trial. *JAMA* 2017;318:1550–60.
12. Walløe L, Hjort NL, Thoresen M. Why results from Bayesian statistical analyses of clinical trials with a strong prior and small sample sizes may be misleading the case of the NICHD Neonatal Research network late hypothermia trial. *Acta Paediatr* 2019;108. doi:10.1111/apa.14800. [Epub ahead of print: 29 Mar 2019].
13. Weeke LC, Vilan A, Toet MC, *et al*. A comparison of the Thompson encephalopathy score and Amplitude-Integrated electroencephalography in infants with perinatal asphyxia and therapeutic hypothermia. *Neonatology* 2017;112:24–9.