Neurocritical care for hypoxic-ischaemic encephalopathy: cooling and beyond

The use of therapeutic hypothermia is now the standard of care for infants with hypoxic-ischaemic encephalopathy (HIE). Effective treatment requires early identification and safe transfer to a regional cooling centre. This article reviews some of the latest evidence from infants who have been cooled and highlights the crucial role of neurophysiology and neuroimaging in providing important diagnostic and prognostic information.

Topun Austin
MBBS, MRCP(Paed), PhD
Consultant Neonatologist
topun.austin@nhs.net

S. Samantha O'Hare
BMBS, BMedSci, MRCPCH, MSc
Locum Consultant Neonatologist

Neonatal Unit, The Rosie Hospital, Cambridge University Hospitals NHS Foundation Trust

Keywords

cooling; therapeutic hypothermia; hypoxic-ischaemic encephalopathy; electroencephalography; neurocritical care

Key points

Austin T., O'Hare S.S. Neurocritical care for hypoxic-ischaemic encephalopathy: cooling and beyond. *Infant* 2013; 9(4): 135-38.

1. Initiation of cooling should not be delayed and temperature stability can be maintained during transport using servo-controlled systems.
2. aEEG remains extremely useful for continuous assessment of cerebral activity and in identifying seizures. MRI scans should be undertaken at the optimal time and interpreted by individuals with expertise.
3. Comprehensive long-term follow-up data on cooled infants is limited – follow-up programmes should extend beyond infancy.
4. A multi-disciplinary 'neurocritical care' approach to management will ensure high-quality, consistent and timely care.

Hypoxic-ischaemic encephalopathy (HIE) is a condition of altered neurological state resulting from a critical lack of blood flow and oxygen to the brain around birth. In the UK the incidence is estimated at between one and two per 1,000 live births[1]; globally over one million infants die each year[2]. Survivors are at high risk of developing life-long neurodisability, placing an enormous physical, psychological and financial burden on their families and society.

One of the major advances in neonatal care in recent years has been the introduction of therapeutic hypothermia to treat infants with HIE. This practice, endorsed by the National Institute for Health and Care Excellence (NICE) and the British Association of Perinatal Medicine (BAPM), follows decades of basic and clinical research[3,4]. As research is translated into clinical practice there are a number of challenges to managing these infants, particularly with regard to early identification, transfer, monitoring and imaging, all of which can impact both on their outcome and how their parents are counselled.

Resuscitation and early identification: who to cool

Identification of infants who may benefit from cooling is based on evidence of fetal compromise (low Apgar score, metabolic acidosis, continued need for resuscitation) and emerging encephalopathy (abnormal conscious level, altered tone and reflexes and/or seizures). Although most experimental studies started cooling immediately after the hypoxic-ischaemic insult, for practical purposes the main clinical trials enrolled infants within six hours of birth[5-8]. The clinical trials did not show a significant difference in neurodevelopmental outcome between those cooled early (less than four hours) and those cooled late (four to six hours); there was a trend to favour those cooled earlier[8]. Experimental evidence also suggests a lack of benefit from delayed cooling[9]. It is therefore important that infants potentially eligible for cooling are identified early and cooling commenced immediately.

Both the CoolCap and TOBY trials used amplitude-integrated electroencephalography (aEEG) to assess the severity of encephalopathy before enrolling infants[6,8]. The CoolCap study showed that at 18 months of age, the aEEG amplitude and presence of seizures were independently associated with poor outcome; in the TOBY study the outcome following cooling was not related to the severity of abnormality on the initial aEEG.

It has been reported that the early (three to six hours) predictive value of aEEG was lost with hypothermia[10]; a recent prospective study has also found that early aEEG (less than nine hours of age) was not predictive of neurodevelopmental outcome at 18-24 months of age in cooled infants[11]. However, accurate grading of encephalopathy is difficult in the hours immediately following delivery and it is important that repeated and systematic neurological evaluation is carried out and documented regularly; Sarnat, Thompson and Miller scoring systems are all useful validated tools for this purpose[12-14]. Currently there is no evidence that infants with apparently mild encephalopathy benefit from cooling. Infants who meet the criteria initially who subsequently improve within six hours remain a challenge, as enrolment into clinical trials would have

depended on the timing of initial assessment. If a decision is made to re-warm an infant whose neurology showed significant improvement in the first hours of life, it would be advisable to continue close monitoring, ideally accompanied by continuous aEEG monitoring as these infants may still go on to develop seizures. It is unclear whether re-cooling following seizures would be beneficial; they are an important group to study and significant neurodevelopmental morbidity in these infants may make us more reticent to re-warm them in the future.

Stabilisation and transfer to the regional cooling centre

There are 20 regional transport units in the UK; most teams continue passive cooling during transfer. In the East of England, the Acute Neonatal Transfer Service (ANTS) started a 24-hour emergency service in October 2009. By May 2011 they had 106 requests for transfer of babies with HIE and moved 73 infants to one of three cooling centres in the region. Thirty-three infants were not transferred for cooling, either because they did not fit the predefined TOBY register cooling criteria, or because their neurological status was so abnormal (eg fixed dilated pupils, absent corneal reflex) that further intensive support was deemed to be futile. Between October 2009 and May 2011, the time taken to achieve target temperature had reduced significantly (regression coefficient -12.8; 95%CI 19.2 to -6.5, p=0.0002) (**FIGURE 1**). There was also a trend towards earlier referral, earlier commencement of passive cooling and earlier admission to the regional cooling cot.

The experience in the East of England is similar to that in London[15] and also mirrors that of cooling during transport in other countries, which highlight the problem of overcooling[16,17] and demonstrate the importance of continuous core-temperature (rectal temperature) monitoring. Given the challenges of maintaining stable temperatures during transport, ANTS have used a servo-controlled device since March 2011. Since its introduction there has been a significant reduction in the number of infants either overcooled or not achieving target temperature on arrival at the cooling centres. Other regions have reported their experience with active cooling, and similarly found significantly improved thermal control[18,19]. In order to avoid overcooling, it would therefore be reasonable to recommend that neonatal transport teams invest in servo-controlled equipment if moving infants any significant distance.

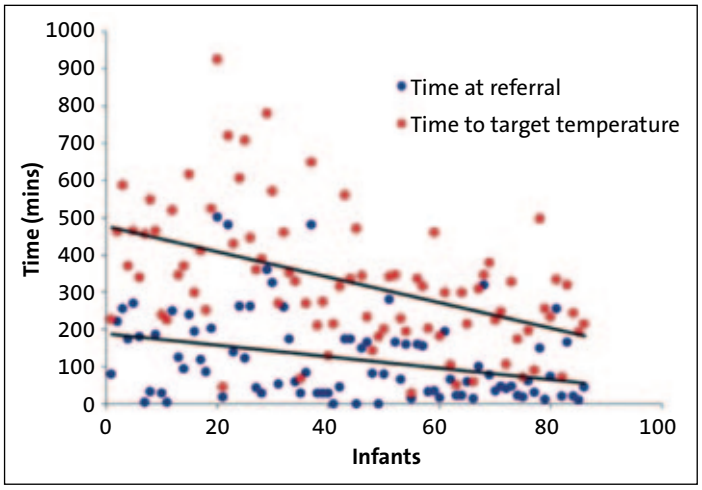

FIGURE 1 Reduction in the time at referral and time to target temperature for the first 82 infants referred to ANTS for cooling between October 2009 and September 2011.

Continuing evaluation: the role of aEEG and EEG

The BAPM statement on therapeutic hypothermia emphasised that infants receiving cooling should be: "Supported by a multidisciplinary team experienced in intensive care, neonatal electrophysiology (both aEEG and conventional EEG) and neuro-MRI (magnetic resonance imaging). Their care should be directed by clinicians experienced in the diagnosis and prognosis of perinatal brain injury"[3]. The diagnosis of HIE is often not straightforward and careful neurological assessment is essential for diagnostic and prognostic purposes.

Although the early predictive value of aEEG may be more limited, electrophysiological monitoring either with aEEG or EEG remains extremely useful for continuous assessment of cerebral activity and in identifying seizure activity. Recovery time to normal background pattern remains a strong predictor of outcome; similarly, failure to develop sleep-wake cycling by 72 hours of age is a good predictor of poor outcome[10].

Neonatal seizures are most commonly due to HIE; however they are frequently under-diagnosed and remain difficult to treat. Historically seizures have been shown to be strong predictors of death or disability and there is growing evidence that seizures themselves can worsen pre-existing injury[20]. A good comparison between aEEG and EEG in seizure detection has been reported[21], however other studies suggest that aEEG may underestimate the burden of seizures in neonates, particularly if seizures are focal in nature, originating at sites distant from the aEEG electrodes[22]. Although continuous multichannel video-EEG monitoring remains the gold standard, it relies heavily on neurophysiological expertise to interpret recordings. Automated seizure detection algorithms have been developed; to date no system has sufficient sensitivity or specificity to be recommended for routine clinical use, but it is an exciting area of active research[23].

The effect of cooling on seizures has been studied – a decreased seizure burden was reported in neonates with moderate HIE who were cooled[24]. Interestingly it has also been reported that 40% of cooled infants who had seizures had good clinical outcomes[25]. It is possible that these observations reflect some of the therapeutic benefits of cooling.

MRI following cooling

MRI and magnetic resonance spectroscopy (MRS) are useful predictors of long-term neurodevelopmental outcome[26], although the optimal timing of scanning using conventional imaging is late at seven to 10 days of age. Changes in diffusion weighted imaging and MRS can be seen earlier and may aid management, particularly with regard to withdrawal of intensive support, although MRI imaging should never be used in isolation[27]. In a sub-study of the TOBY trial, findings from 131 infants who had MRI scans were reported[28]. Fewer cerebral lesions in cooled infants were observed and the predictive value of MRI for subsequent neurological impairment was not affected by cooling. Similar results have been reported from sub-studies of the US National Institute of Child Health and Human Development (NICHD) cooling trial and Australian Infant Cooling Evaluation (ICE) trial[29,30]. Interestingly

more lesions on MRI have been reported in infants who received selective head cooling (SHC), compared to those with whole body cooling (WBC)[31].

The American Academy of Pediatrics currently recommends conventional MRI in all term infants with neonatal encephalopathy, but no similar recommendation exists in the UK[32].

A lack of standardisation with respect to timing, sequences and reporting of MRI scans may limit the diagnostic and predictive value of this technique. A more coordinated approach would ensure all infants with HIE receive high quality MRI scans and reports in a timely manner. Both EEG and MRI can be reported remotely and best practice may be to centralise expertise. More explicit national guidance is needed.

Follow-up and long-term prognosis

The number needed to treat with cooling to prevent one death from HIE is nine and to have one extra infant with normal neurological outcome at 18 months of age, is eight[33]. Although encouraging, this means there is still a significant burden of disability after cooling. To identify problems early, it is important these children receive long-term follow-up. The NICHD cooling trial recently published follow-up of infants at six to seven years of age[34]. Although the primary outcome of death or disability was not significantly different between the two groups (p=0.06), it did show a reduction in death with no increase in disability or low IQ in the cooling group. Despite a good follow-up rate the study was not powered to evaluate secondary outcomes, such as individual components of disability, cognitive and motor outcomes and overall physical and psychosocial health.

Previous long-term follow-up studies suggest that survivors of neonatal encephalopathy without major disability typically have an increased risk of subtle neurological disabilities when assessed at school age[35]. Although BAPM recommend neurodevelopmental assessment at two years of age, it is important that these infants are followed-up throughout childhood to identify more subtle problems and attention is given during schooling to additional educational needs.

Neonatal neurocritical care: an emerging specialty

Adult neurocritical care is a growing multidisciplinary sub-specialty that combines expertise in intensive care, neurology, neurosurgery and neuroradiology. Evidence suggests that specialised neurocritical care not only improves the quality of care and reduces clinical risk but also can improve long-term neurological outcome[36].

Several core principles from adult neurocritical care can be applied to management of these infants; careful attention to temperature control, oxygenation, blood pressure and glucose regulation can prevent secondary brain injury. In the East of England, the experience is that a coordinated, protocol-driven approach can improve identification and timely management of infants with HIE. Advances in neuromonitoring and neuroimaging provide important diagnostic and prognostic information. These developments suggest that the need for dedicated expertise in neonatal neurocritical care equals that for adults. Such a service has been described by clinicians at the University of California, San Francisco[37]; a multidisciplinary team including neonatologists and paediatric neurologists work alongside the attending team, providing additional clinical support, guidelines and training on a broad range of neonatal neurological conditions. The aim of this approach is to provide a comprehensive and consistent approach to the care of these infants, with the ultimate aim of improving neurodevelopmental outcomes.

- Cooling outside current criteria:
  - preterm infants*
  - postnatal collapse
  - acute perinatal stroke
  - infants cooled after six hours of age*
  - mild to moderate encephalopathy (with base deficit less than -16)
- Possible adjuncts to cooling eg Xenon*
- Seizure detection algorithms
- Standardisation of MRI imaging and reporting

* Currently the subject of randomised controlled trials

TABLE 1 Areas of active research and ongoing development.

Conclusion

The introduction of therapeutic hypothermia into clinical practice is one of the major advances in neonatal medicine in recent years. Further research is required to identify other patient groups who may benefit from cooling, as well as therapeutic adjuncts to cooling (**TABLE 1**). Alongside the continuing developments in neuromonitoring and neuroimaging, the ability to provide consistent high quality care to these vulnerable infants will stem from a coordinated and multidisciplinary 'brain orientated' approach.

Acknowledgement

The authors would like to thank the East of England Neonatal Neuroprotection Team and the Acute Neonatal Transfer Service (ANTS) for assistance in developing this article.

References

1. **Evans K., Rigby A.S., Hamilton P. et al.** The relationships between neonatal encephalopathy and cerebral palsy: a cohort study. *J Obstet Gynaecol* 2001;21:114-20.
2. **Lawn J.E., Wilczynska-Ketende K., Cousens S.N.** Estimating the causes of 4 million neonatal deaths in the year 2000. *Int J Epidemiol* 2006;35:706-18.
3. **BAPM.** *Position Statement on Therapeutic Cooling for Neonatal Encephalopathy* [Online]. 2010 Available from: www.bapm.org/publications/documents/guidelines/Position_Statement_Therapeutic_Cooling_Neonatal_Encephalopathy_July%202010.pdf [Accessed 29 May 2013].
4. **NICE.** *Therapeutic Hypothermia with Intracorporeal Temperature Monitoring for Hypoxic Perinatal Brain Injury: Guidance* [Online]. 2010. Available from: www.nice.org.uk/nicemedia/live/11315/48809/48809.pdf [Accessed 29 May 2013].
5. **Thoresen M., Penrice J., Lorek A. et al.** Mild hypothermia after severe transient hypoxia-ischaemia ameliorates delayed cerebral energy failure in the newborn piglet. *Pediatr Res* 1995;37:667-70.
6. **Gluckman P.D., Wyatt J.S., Azzopardi D. et al.** Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet* 2005;365:663-70.
7. **Shankaran S., Laptook A.R., Ehrenkranz R.A. et al.** Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med* 2005;353:1574-84.
8. **Azzopardi D.V., Strohm B., Edwards A.D. et al.** Moderate hypothermia to treat perinatal asphyxial encephalopathy. *N Engl J Med* 2009;361:1349-58.
9. **Karlsson M., Tooley J.R., Satas S. et al.** Delayed hypothermia as selective head cooling or whole body cooling does not protect brain or body in newborn pig subjected to hypoxia-ischaemia. *Pediatr Res* 2008;64:74-78.
10. **Thoresen M., Hellstrom-Westas L., Liu X. et al.** Effect of hypothermia on amplitude-integrated electroencephalogram in infants with asphyxia. *Pediatrics* 2010;126:e131-39.
11. **Shankaran S., Pappas A., McDonald S.A. et al.** Predictive value of an early amplitude integrated electroencephalogram and neurologic examination. *Pediatrics* 2011;128:e112-20.
12. **Sarnat H.B., Sarnat M.S.** Neonatal encephalopathy following fetal distress: a clinical and electroencephalographic study. *Arch Neurol* 1976;33:696-705.
13. **Miller S.P., Latal B., Clark H. et al.** Clinical signs predict 30-month neurodevelopmental outcome after neonatal encephalopathy. *Am J Obstet*

Gynecol 2004;190:93-99.
14. **Thompson C.M., Puterman A.S., Linley L.L. et al.** The value of a scoring system for hypoxic-ischaemic encephalopathy in predicting neurodevelopmental outcome. *Acta Paediatr* 1997;86:757-61.
15. **Kendall G.S., Kapetanakis A., Ratnavel N. et al.** Passive cooling for initiation of therapeutic hypothermia in neonatal encephalopathy. *Arch Dis Child Fetal Neonatal Ed* 2010;95:F408-12.
16. **Hallberg B., Olson L., Bartocci M. et al.** Passive induction of hypothermia during transport of asphyxiated infants: a risk of excessive cooling. *Acta Paediatr* 2009;98:942-46.
17. **Fairchild K., Sokora D., Scott J. et al.** Therapeutic hypothermia on neonatal transport: 4-year experience in a single NICU. *J Perinatol* 2010;30:324-29.
18. **O'Reilly K.M., Tooley J., Winterbottom S.** Therapeutic hypothermia during neonatal transport. *Acta Paediatrica* 2011;100:1084-86.
19. **Johnston E.D., Becher J.C., Mitchell A.P. et al.** Provision of servo-controlled cooling during neonatal transport. *Arch Dis Child Fetal Neonatal Ed* 2012;97:F365-67.
20. **Wirrell E.V., Armstrong E.A., Osman L.D. et al.** Prolonged seizures exacerbate perinatal hypoxic-ischaemic brain damage. *Pediatr Res* 2001;50:445-54.
21. **Shah D.K., Mackay M.T., Lavery S. et al.** Accuracy of bedside electroencephalographic monitoring in comparison with simultaneous continuous conventional electroencephalography for seizure detection in term infants. *Pediatrics* 2008;121:1146-54.
22. **Shelhaas R.A., Soaita A.I., Clancy R.R.** Sensitivity of amplitude-integrated electroencephalography for neonatal seizure detection. *Pediatrics* 2007; 120:770-77.
23. **Temko A., Thomas E., Marnane W. et al.** Performance assessment for EEG-based neonatal seizure detectors. *Clin Neurophysiol* 2011;122: 474-82.
24. **Low E., Boylan G.B., Mathieson S.R. et al.** Cooling and seizure burden in term neonates: an observational study. *Arch Dis Child Fetal Neonatal Ed* 2012;97:F267-72.
25. **Glass H.C., Kendall B.N., Bonifacio S.L. et al.** Seizures and magnetic resonance imaging-detected brain injury in newborns cooled for hypoxic-ischaemic encephalopathy. *J Perinatol* 2011;159:731-35.
26. **Rutherford M.A., Pennock J.M., Counsell S.J. et al.** Abnormal magnetic resonance signal in the internal capsule predicts poor neurodevelopmental outcome in infants with hypoxic-ischemic encephalopathy. *Pediatrics* 1998;102:323-28.
27. **Wilkinson D.** MRI and withdrawal of life support from newborn infants with hypoxic-ischaemic encephalopathy. *Pediatrics* 2010;126:e451-58.
28. **Rutherford M., Ramenghi L.A., Edwards A.D. et al.** Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic-ischaemic encephalopathy: a nested substudy of a randomised controlled trial. *Lancet Neurol* 2009;9:39-45.
29. **Shankaran S., Barnes P.D., Hintz S.R. et al.** Brain injury following trial of hypothermia for neonatal hypoxic-ischaemic encephalopathy. *Arch Dis Child Fetal Neonatal Ed* 2012;97:F398-404.
30. **Cheong J.L.Y., Coleman L., Hunt R.W.** Prognostic utility of magnetic resonance imaging in neonatal hypoxic-ischaemic encephalopathy. *Arch Pediatr Adolesc Med* 2012;166:634-40.
31. **Sarkar S., Donn S.M., Bapuraj J.R.** Distribution and severity of hypoxic-ischaemic lesions on brain MRI following therapeutic cooling: selective head versus whole body cooling. *Arch Dis Child Fetal Neonatal Ed* 2012;97:F335-39.
32. **Ment L.R., Bada H.S., Barnes P. et al.** Practice parameter: neuroimaging of the neonate: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2002;58:1726-38.
33. **Edwards A.D., Brocklehurst P., Gunn A.J. et al.** Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. *BMJ* 2010;340:c363.
34. **Shankaran S., Pappas A., McDonald S.A.** Childhood outcomes after hypothermia for neonatal encephalopathy. *N Engl J Med* 2012;366:2085-92.
35. **Marlow N., Rose A.S., Rands C.E. et al.** Neuropsychological and educational problems at school age associated with neonatal encephalopathy. *Arch Dis Child Fetal Neonatal Ed* 2005;90:F380-87.
36. **Suarez J.I.** Outcome in neurocritical care: advances in monitoring and treatment and effect of a specialized neurocritical care team. *Crit Care Med* 2006;34:232-38.
37. **Glass H.C., Bonifacio S.L., Peloquin S. et al.** Neurocritical care for neonates. *Neurocrit Care* 2010;12:421-29.