Should neonatal encephalopathy now be treated with cooling?

The use of selective and systemic induced mild hypothermia for the treatment of neonatal encephalopathy has been the subject of several randomised controlled trials over recent years. The largest of these, the TOBY Study, has recently completed recruitment. This article discusses the current status of hypothermia and how its use might evolve in the near future.

Brenda W Strohm
RGN
TOBY Study Research Nurse/Co-ordinator
National Perinatal Epidemiology Unit
University of Oxford
brenda.strohm@npeu.ox.ac.uk

Denis V Azzopardi
MD, FRCP, FRCPCH
Senior Lecturer in Paediatrics and Neonatal Medicine, Faculty of Medicine,
Hammersmith Campus,
Imperial College, London

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Key points

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1. A summary of recently published randomised controlled trials of neonatal hypothermia is presented.
2. Research published to date indicates some benefit may be conferred by cooling babies with moderate neonatal encephalopathy. In practice not all clinicians find this evidence convincing, whilst others are inclined to offer cooling to appropriately selected patients.
3. Until the TOBY Study reports its findings at the end of 2008, uncertainty about cooling as a treatment for neonatal encephalopathy remains.
4. The future for administration of hypothermia outside the trial setting in the UK is considered.
5. Proposals for the establishment of a UK Cooling Register are detailed.

Over recent years there has been increasing interest in the use of mild, induced hypothermia or 'cooling' for the treatment of neonatal encephalopathy (NE) resulting from a presumed hypoxic-ischaemic insult occurring very close to birth[1-4]. In the UK NE occurs in 2-3 per 1000 births, and has a considerable impact on affected babies and their families, as well as making significant demands on healthcare and educational resources[5,6]. Without an effective treatment, management of babies with NE has traditionally consisted of stabilisation using standard intensive care measures and control of seizures by anticonvulsant medication. Therefore, identification and development of a safe and effective treatment of NE has been a long standing goal of clinicians and researchers interested in neuroprotection.

Following promising experimental and clinical pilot studies of cooling, randomised controlled trials in neonates were started[7-12]. Two major studies have already reported their results[13,14], while the TOBY Study (Whole body hypothermia for the treatment of perinatal asphyxial encephalopathy; TOBY: Total Body Hypothermia[15]) concluded its active recruitment phase in November 2006. The primary outcome of TOBY is death or neurodevelopmental disability at 18 months of age; therefore full findings and results will not be available until the end of 2008 when all 18 month follow-up assessments have been completed and analysis can take place.

Whilst TOBY was recruiting infants, there was agreement among neonatologists in the UK that cooling should only be provided as a treatment within the context of a trial, and the TOBY Study benefited from widespread support. As a result recruitment to TOBY exceeded expectations and TOBY is the largest study of treatment with cooling so far. However, it was recognised that when recruitment ended, there would be uncertainty about the management of babies with NE. Should cooling become an evolving and emerging treatment to be used with caution, or should practice revert to symptom management only, until the results of TOBY are available to provide evidence on which to base future practice?

This article will look at the current evidence regarding cooling, the management of babies with NE when recruitment to the TOBY Study is no longer an option, and proposals for a register of cooling in the UK.

Results of cooling studies for perinatal asphyxial encephalopathy

The published studies into the use of cooling as a therapy show improvement in survival without disability at 12-18 months of age but there is debate about the strength of the research evidence[16]. Outside the UK some neonatal units are keen to offer cooling for all babies with moderate or severe NE; others are more cautious, and warn against its indiscriminate use[17].

Details of the currently published studies of cooling are summarised in **TABLE 1**.

None of the studies have reported outcome beyond 18 months of age or were sufficiently large to determine the effect of hypothermia on specific individual outcomes. The study by Eicher was a pilot study of 65 infants randomised to total body hypothermia to 33°C for 48 hours. Unfortunately the study only reported outcomes to 12 months of age and 32% of survivors were not followed up[10]. However,

Study author	Cooled controls (n)	Hypothermia method	Temp (core)	Duration hypothermia (hours)	Primary outcome	Follow-up period
Akisu[27]	11:10 (21)	selective	36.5	72	CSF analysis, CT, EEG	4-10 days
Gunn[9]	12:10 (22)	selective	35.5/36	72	adverse events, neurological	6-12 months
Eicher[10]	32:33 (65)	systemic	33	48	death + severe disabilities	12 months
Gluckman[13]	116:118 (234)	selective	34-35	72	death + severe disabilities	18 months
Shankaran[14]	102:106 (208)	systemic	33.5	72	death + moderate + severe disabilities	18 months
Lin[28]	32:30 (62)	selective	34-35	72	CT, Brazelton	7-10 days
Zhou[29]	23:27 (50)	selective	34.5	72	Cardiac function	NA

TABLE 1 Summary of trials of hypothermia that have reported so far.

	Death/ disability at 18 months	Good outcome
Cooled	104	106
Control	137	76
TOTAL	241	182

Probability of good outcome following treatment with cooling is number of cooled infants with good outcome/total number of cooled infants = 51% (Combined data from Gluckman[13] and Shankaran[14])

TABLE 2 Probability of outcome following treatment with cooling.

that study also reported significant harmful effects of cooling: there was an increased dependence on vasopressors and volume support, lower platelet counts and prolonged thrombin times[11]. These complications may be related to the lower target temperature in Eicher's study since they were not observed in the larger studies, which had aimed for a higher core temperature.

The studies of Shankaran[14] and Gluckman[13], were reasonably large and well carried out but there were several important differences between them – the amplitude integrated EEG (aEEG – a simplified form of EEG) was used for selecting infants in Gluckman's study but not in Shankaran's and the studies used different methods of inducing and maintaining hypothermia. Gluckman's Coolcap study used a specially developed cap which allowed cooled fluid to circulate around the baby's head, while systemic temperature was maintained at 34.5°C with an overhead radiant heater. Shankaran's study employed whole body cooling using a specially modified commercially available servo-controlled cooling mattress.

In addition whilst in Coolcap the primary outcome was the occurrence of death or severe disability, infants with moderate disabilities were also included in the composite outcome in Shankaran's study. These differences in study design prevent a direct comparison between the two forms of cooling: selective head cooling and whole body cooling, and one cannot assume that they have identical effects. Indeed, two recent small studies suggested different distribution of abnormalities on magnetic resonance imaging between infants that received head cooling with mild whole body cooling, or whole body cooling only[18,19].

Gluckman[13] reported that after correcting for severity of encephalopathy, hypothermia was associated with improvement in survival without severe disability at 18 months of age, but no benefit was observed in the most severely asphyxiated babies, as categorised by the aEEG at randomisation. The Shankaran study reported a 23% absolute risk reduction of death or disability following systemic cooling to 33.5°C for 72 hours after asphyxia (number needed to treat, 4). Although this appears to be a large reduction in adverse outcome, despite treatment with cooling infants with NE are still at high risk of death or disability at 18 months of age as indicated in **TABLE 2**.

The entry criteria of the Gluckman, Shankaran and TOBY trials are summarised in **TABLE 3** for comparison. As TOBY entry criteria are similar to the Gluckman and Shankaran studies, the TOBY results will be able to be included in future meta-analyses.

An important finding that has emerged from the large trials is that several infants in the control (normothermia) groups experienced episodes of hyperthermia exceeding 38°C, which is potentially harmful, and might confound the trial results[14]. Examples of temperature control in infants in the TOBY Study are shown in **FIGURES 1 AND 2**.

Meta analysis of currently published cooling studies

By combining the results of trials the power is increased so that the effect of hypothermia on individual outcomes of interest can be assessed. Systematic analyses of the studies of cooling have been carried out[3, 20, 21].The meta analyses shown in **FIGURES 3 AND 4** suggest that hypothermia has a small beneficial effect on survival and neurodevelopmental outcome, but more data are required to confirm these observations.

Despite findings yielded by these studies there are still many questions about the use of cooling awaiting answers: what level of hypothermia is most effective and safe, when is it effective and in which babies, how long should hypothermia last, how may it be induced, maintained and reversed; what are the risks?

Current opinion on treatment with cooling

Most experts believe that current on-going trials of cooling should continue to be supported so that it should later be possible to precisely determine the therapeutic efficacy of cooling. An international workshop on the status of

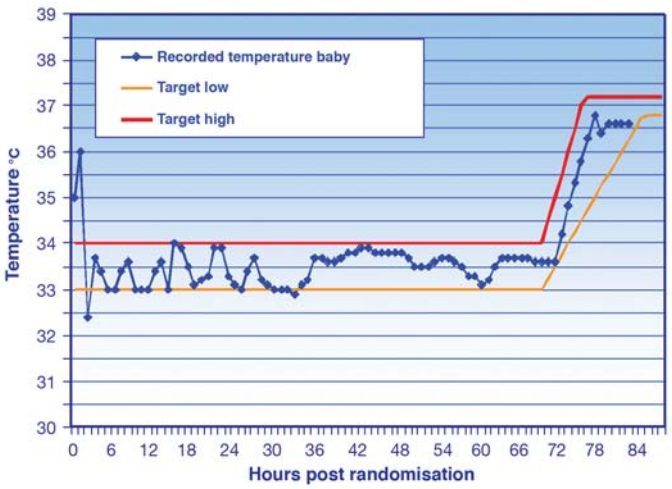

FIGURE 1 Graph showing temperature control of a TOBY baby during cooling and rewarming.

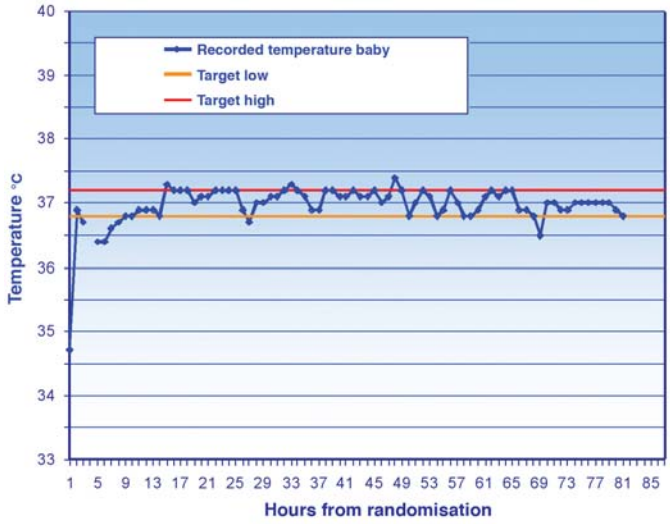

FIGURE 2 Graph showing temperature control of a control (normothermic) TOBY baby.

cooling as a treatment convened by the National Institute of Child Health and Human Development in Washington USA (May 2005)[17] concluded that: ongoing studies should be completed to add to existing knowledge about safety and efficacy; and studies into cooling should strive to conduct further follow-up studies on their recruits to investigate longer-term outcomes. This would yield more detailed information on neurodevelopment and cognitive skills than that available at 18 months of age; early results may even be reversed on later assessment. Another important recommendation was that any future use of cooling as a treatment outside of a trial should be documented in a register that would provide information on the extent to which cooling was used, the demand for it, standards of care, and outcomes. This additional data would add to the existing pool of information, and provide scope for further analysis and research opportunities.

TOBY – what next?

Early in 2006, in anticipation of the TOBY recruitment period coming to an end later in the year, enquiries were already being received from clinicians regarding future treatment of babies whom they would have previously assessed for eligibility for the TOBY trial.

An important step in planning how to proceed was to request guidance from the TOBY Data Monitoring Committee (DMC) following their meeting in October 2006, when all data available to date would be reviewed along with any serious adverse events that had been identified and reported. Providing no contraindications to the continued use of cooling were found, the TOBY researchers identified the following areas that required action:

- Development of a protocol and clinical guidelines, for use by both experienced TOBY clinicians and novice practitioners
- Training in the use of cooling.
- Establishment of a register and relevant documentation, e.g. data collection form, for patients treated with cooling for NE.
- Dissemination of information to all NICUs.

The TOBY research group intends to carry out further assessment of outcome on TOBY recruits, at approximately 6 years of age, and to carry out further studies of cooling in combination with one or more additional interventions.

	Gluckman[13]	Shankaran[14]	Toby[15]
Method of cooling	Head cooling with mild whole body to rectal temp 34.5°C	Whole body cooling to oesophageal temp 33.5°C	Whole body cooling to rectal temp 33.5°C
Gestation	≥36+0 weeks	≥36+0 weeks	≥36+0 weeks
Apgar scores*	≤5 @ 10 minutes	≤5 @ 10 minutes	≤5 @ 10 minutes
Blood pH*	<7 within 60 minutes of birth	≤7 within 60 minutes of birth	<7 within 60 minutes of birth
Base deficit*	≥16	≥16	≥16
Resuscitation* duration	at least 10 minutes	at least 10 minutes	at least 10 minutes
Signs of NE	Yes	Yes (using specified criteria)	Yes
CFM	Yes	No	Yes
Study size	218	208	>300 (see TOBY website for current recruitment)

* Not all clinical criteria needed to be present (details provided in originial papers).

TABLE 3 Comparison of entry criteria in trials of cooling.

Proposed administration of cooling prior to publication of the TOBY results

Protocol and clinical guidance

In order to standardise practice and build on the lessons learnt from TOBY, a treatment protocol and guidelines for clinicians undertaking cooling were developed (accessible from www.npeu.ox.ac.uk/tobyregister). These will help to ensure that cooling is delivered safely and effectively, to agreed standards. The guidance was based on the TOBY protocol, and gives details on the assessment of infants, application of cooling, monitoring and supportive therapy and investigations.

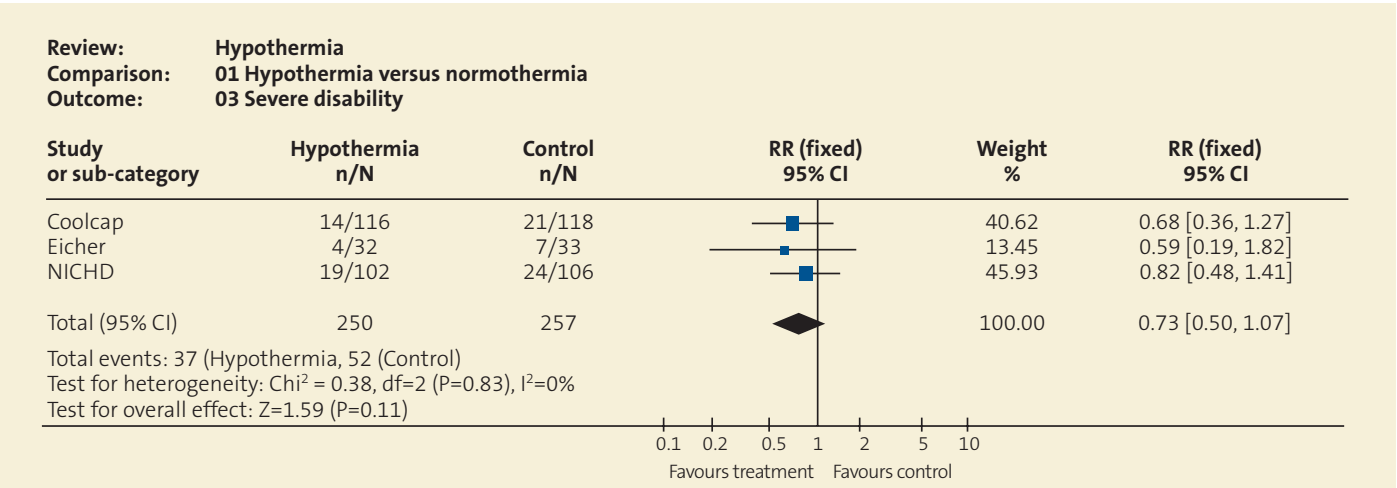

FIGURE 3 Meta analysis of studies of the effect of treatment with mild/moderate hypothermia on severe disability at 12-18 months of age. Studies included are: Gluckman (Coolcap)[13], Eicher[10] and Shankaran (NICHD)[14]. Only infants with severely abnormal psychomotor or mental developmental scores are included in analysis.

Purposely designed data forms are provided to aid monitoring and to allow further analysis of treatment with cooling.

Training

Although therapeutic hypothermia is a relatively simple procedure, it should not be undertaken lightly, and staff involved in offering hypothermia should be adequately trained. Inadequate monitoring or unfamiliarity with the cooling equipment may result in inadvertent excessive hypothermia or hyperthermia, which may be harmful[8, 11]. Specific training should be provided about: patient selection; cooling and re-warming procedures; use and interpretation of aEEG; monitoring, identifying and reporting adverse events.

Current capacity to offer cooling in the UK

There are approximately 35 UK neonatal units currently equipped to provide cooling within the TOBY Study, and other units may also wish to offer cooling now that TOBY recruitment has ended. As a result of the large number of participating centres in the UK and the frequent discussion of cooling at academic meetings, most UK clinicians are aware of the potential of treatment with cooling following perinatal asphyxia. Although it is difficult to predict the likely demand for treatment with cooling, probably more babies with less severe encephalopathy will be referred for treatment when recruitment is completed. It is possible that centres may not have the capacity to offer cooling on every occasion, because the cooling equipment is already in use. Neonatal networks need to assess the likely demand for cooling, and plan appropriately.

Consent issues

The consent procedures that applied to TOBY[22] during recruitment no longer apply so stringently if cooling is now offered as part of standard clinical care following perinatal asphyxia. However, parents should be involved in discussions about their baby's treatment, and assent to its implementation. Possible side effects should be brought to their attention, and it is naturally good practice to document such discussions accurately in the hospital notes. In practice to avoid delay, clinicians are likely to initiate cooling and later obtain assent for continuing treatment with cooling, but practice may vary between hospital trusts because of local clinical governance procedures.

Use of cerebral function monitoring during treatment with cooling

Assessment of aEEG with the cerebral function monitor (CFM) was required for trial entry into TOBY. However after completion of trial recruitment, to avoid delay, clinicians may wish to initiate

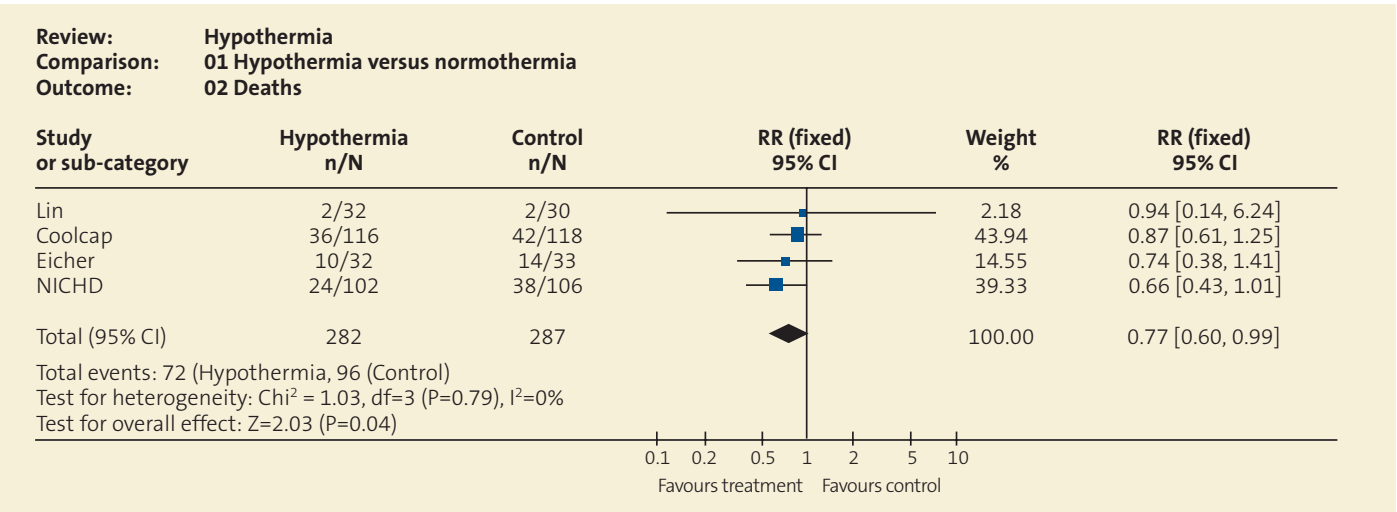

FIGURE 4 Meta analysis of studies of the effect of treatment wth mild/moderate hypothermia on mortality. Studies included are: Lin[28], Gluckman (Coolcap)[13], Eicher[10] and Shankaran (NICHD)[14].

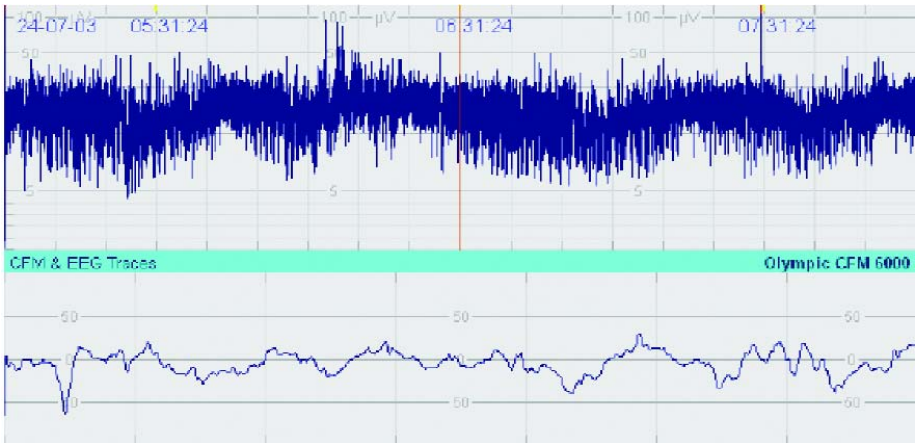

FIGURE 5 Normal CFM voltage. The upper margin of the trace is above 10 microvolts and the lower margin is greater than 5 microvolts. Sleep wake cycling can be observed.

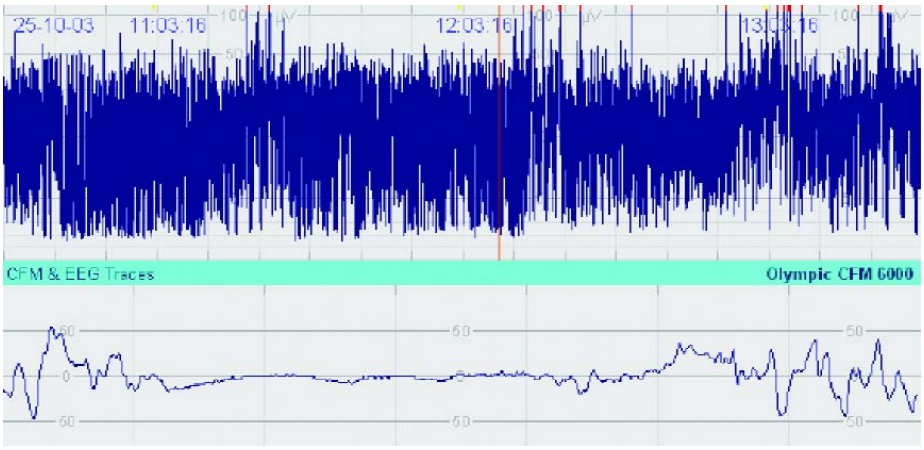

FIGURE 6 Moderately abnormal CFM. EEG shows discontinuity. The upper margin of the trace is greater than 10 microvolts and the lower margin is less than 5 microvolts.

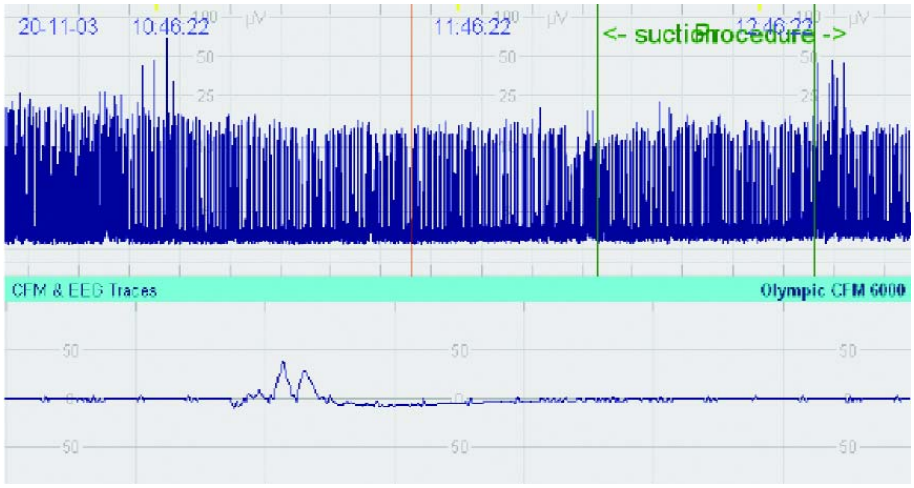

FIGURE 7 Severely abnormal CFM. EEG shows brief burst on isoelectric background. The upper margin of the trace is less than 10 microvolts. The lower margin is usually less than 5 microvolts but on occasion the lower margin may be raised above 5 microvolts because of interference from ECG or other artefacts.

cooling before recording the aEEG. Outside the context of the TOBY Study, cerebral function monitoring will be helpful to confirm the neurological status of the baby, and determine whether cooling should be started, or if already started, whether it should continue. A severely depressed aEEG, (EEG equivalent is very low voltage or isoelectric EEG) persisting for 24 hours after birth, indicates a very poor prognosis and that further treatment with cooling is probably futile, although this data is from non cooled infants[23]. The CFM is also useful in identifying non-clinical seizures and aiding decisions about anticonvulsant therapy, especially if the raw EEG can be displayed. Consequently, neonatal units choosing to start offering cooling are encouraged to perform cerebral function monitoring during treatment with cooling.

FIGURES 5, 6 AND 7 show examples of three CFM traces: normal, moderately abnormal and severely abnormal[24].

Establishment of a register and relevant documentation

To encourage uniform practice, and collect further clinical data related to treatment with cooling, a register of UK babies treated with cooling is being established by the TOBY Study group at the National Perinatal Epidemiology Unit. Participation in a register does not require written consent if patient identifiers[25] are not used and collection of data is more likely to be complete if consent procedures are not required. Therefore the proposed register will be anonymised, and written consent will not be sought.

The aims of the UK Cooling Register

The aims of the register will be to:

- Determine the likely demand in the UK for treatment of newborn infants with cooling. This would be important information for the National Institute for Clinical Excellence (NICE) to consider when evaluating whether cooling should become standard treatment following perinatal asphyxial encephalopathy. The Department of Health recently commissioned a review of NE, which proposed that national surveillance of NE should be considered[26]. The register would provide useful information for setting up the surveillance and could later become part of the surveillance programme.
- Identify adverse events associated with treatment with cooling. Although no severe adverse events related to cooling have been reported in the clinical trials so far, relatively few babies received cooling in these studies (approximately 250 infants) so that uncommon events may have been missed. Adverse events may be more likely to occur when cooling is carried out outside the context of a clinical trial.
- Ensure uniform clinical management to a high standard in a high risk group of infants. Until now no specific treatment for infants with asphyxial encephalopathy was available. A register will ensure

that this high risk group of infants are treated to a specified protocol which would minimise the risk of inappropriate or inadequate treatment, and maximise the benefit of treatment with cooling. This would also lessen the risk of accusation of negligence, a relatively common occurrence in these cases.

- Support clinical trials of neuroprotection following asphyxia. The promising results of clinical trials of cooling and the successful enrolment of infants into the TOBY trial confirm that it is feasible to carry out clinical trials of emergency interventions very soon after birth, and that clinically significant improvement in outcome is possible. The TOBY Study group is poised to carry out further trials of promising new treatments in combination with cooling. A register co-ordinated by the Toby office would widen participation, and improve the speed of research, which would lead to earlier integration of research findings into clinical practice.

Follow-up and longer term outcomes

Infants that warrant treatment with cooling require routine follow-up by their paediatricians, but participation in the register will endorse the need for neuro-developmental assessment at around two years of age. In addition, another assessment should be performed at around six years of age, in order to identify outcomes that cannot be detected at 18-24 months of age, and once again add to trial data. Use of appropriate assessment tools at each stage will enable comparison and analysis of the data within the register and by meta-analysis with data derived from trials.

Conclusion

Despite best obstetric practice, NE due to a perinatal asphyxial insult remains a relatively common and severe complication in full term newborns in the UK. Mild cases are likely to recover spontaneously with monitoring and minimal support, with the prospect of a good outcome. At the other extreme there will occasionally be very severe cases in which attempts at neuroprotection are likely to be futile and death or severe impairment is inevitable. For the moderate and less severe cases in between however, neonatologists will welcome the chance to offer a treatment that is already supported by some evidence, is economical to provide and has the potential to minimise impairment following asphyxial insult. If the promising results are confirmed by the findings from TOBY and other studies, the impact of such a treatment on the babies, their families and NHS resources in the shorter and longer terms will be considerable. However, the experience gained from the studies of cooling in adults with trauma or stroke suggest that we must await further data before recommending that cooling becomes standard therapy for NE. In the meantime there is an opportunity to exploit the knowledge, skills and motivation that have developed within the TOBY Study group. Taking this opportunity will ensure that when treatment with cooling is chosen, it will be administered safely, competently and efficiently, with procedures in place that can identify and address difficulties should they arise, while promoting good practice. Data collection via the register to monitor how and to what extent cooling is used will provide information that will allow healthcare managers, planners and educators to allocate resources accordingly.

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