Cooling for neonatal encephalopathy in 2010

This article provides an overview of the role therapeutic cooling now plays in the treatment of neonatal encephalopathy in the UK. Following the publication of the TOBY Study in October 2009, two meta-analyses were produced and the National Institute for Health and Clinical Excellence (NICE) conducted a consultation on therapeutic hypothermia in order to publish new guidance, which was issued in May 2010. The British Association for Perinatal Medicine (BAPM) is drafting recommendations and increasing numbers of neonatal units are providing cooling treatment. Transport of infants to cooling centres is becoming more frequent and as a result transport protocols are being developed. Research continues to study the administration of cooling treatment in combination with other therapies as well as the long-term outcomes of cooling.

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Key points

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1. New guidance on cooling to treat neonatal encephalopathy was published by NICE in May 2010.
2. All newborns treated with cooling should be registered with The UK TOBY Cooling Register (www.npeu.ox.ac.uk/tobyregister)
3. The number of UK neonatal units offering cooling as a treatment for neonatal encephalopathy is steadily increasing.
4. Referral of newborns to cooling centres has led to the development of protocols on management during transport and passive cooling.
5. Longer-term follow-up of children treated with cooling will confirm whether benefits from treatment are maintained into childhood.

Historically the journey to the current position on cooling has been long and far from smooth, with fluctuating interest that has increased to a peak over the last twenty years[1].The potential of moderate induced hypothermia as a treatment for neonatal encephalopathy has occupied an increasing number of researchers working with both animals and human infants since the 1950s. The focus of the research eventually broadened to include not only short-term recovery but also longer-term neurodevelopmental outcomes. The need for ongoing follow-up of cooled infants has been recognised and recommended as a strategy by clinicians closely involved with the development of this treatment[2].

The publication of the results of the TOBY Study in October 2009[3] was eagerly anticipated by those who hoped it would confirm their existing confidence in the benefits cooling has to offer, as well as by those who wanted more evidence to support its use. When the findings from the two previously published major trials of hypothermia[4,5] to treat perinatal asphyxial encephalopathy were reinforced by the TOBY results, the role of cooling in current and evolving neonatal care was undoubtedly strengthened.

The UK TOBY Cooling Register

When the TOBY Study closed recruitment in December 2006, all those equipped to cool babies within the trial setting were faced with a period of uncertainty about how to treat a baby whom they would previously have recruited to TOBY and treated according to the allocation. While the follow-up assessments were being completed, it would be at least two years until analysis could take place leading to the publication of the findings; in the event it was three years. Many clinicians involved in cooling wished to offer cooling treatment (**FIGURE 1**) during these intervening months, however there was also a smaller group of clinicians who took the decision not to cool electively until evidence from TOBY's results could guide them.

FIGURE 1 An infant is whole-body cooled using a servo-controlled body-wrap system.

The UK TOBY Cooling Register was therefore established at that point so that cooling treatment provided during this interim period could be audited and clinical guidance based on the TOBY Study protocol could be provided.

Those involved in the UK TOBY Cooling Register[6] have witnessed at first hand the growth in the number of hospitals offering

cooling as a treatment, and consequently the improved access to this treatment for babies across the UK. When the TOBY Study[3] closed recruitment in December 2006, there were areas of the UK where there was no easily accessible cooling centre for considerable distances. At that time referring hospitals were not likely to start passive cooling while an infant was awaiting retrieval by the cooling centre, thus missing the important window of opportunity in which to intervene before secondary energy failure and further cell damage took their toll[7]. If distance meant retrieval would be delayed, then referral was probably not even considered.

The UK TOBY Cooling Register[6] records demonstrate the steady increase in the number of units offering cooling to neonates (**FIGURE 2**), as well as the associated increase in the number of registered treatment episodes (**FIGURE 3**).

Anecdotally, Register personnel are aware of neonatal units, where the purchase of cooling equipment has been hampered by financial considerations and Trust procedures regarding new and evolving treatments. This has applied to both the acquisition of equipment to initiate a cooling programme as well as adding to or updating existing cooling equipment. As cooling now moves closer to becoming standard care, then this process should become easier, especially if evidence of demand can be demonstrated through local audits. Compared to some neonatal treatments or equipment, cooling is not expensive. A study of cost-effectiveness[8] concluded that cooling becomes more cost effective in the context of national incidence data or when projected over an extended time period. (The national incidence of neonatal encephalopathy and Cooling Register data on patient throughput in cooling centres were used to estimate the cost per infant per centre per year for cerebral function monitoring and total body cooling.) This study did not include costs borne by parents and carers, or related to education services and medico-legal proceedings. In monetary terms the cost of a servo-controlled cooling system is considerably less than a state-of-the-art incubator or ventilator, ie ~£8,500 and ~£15,000 respectively[9].

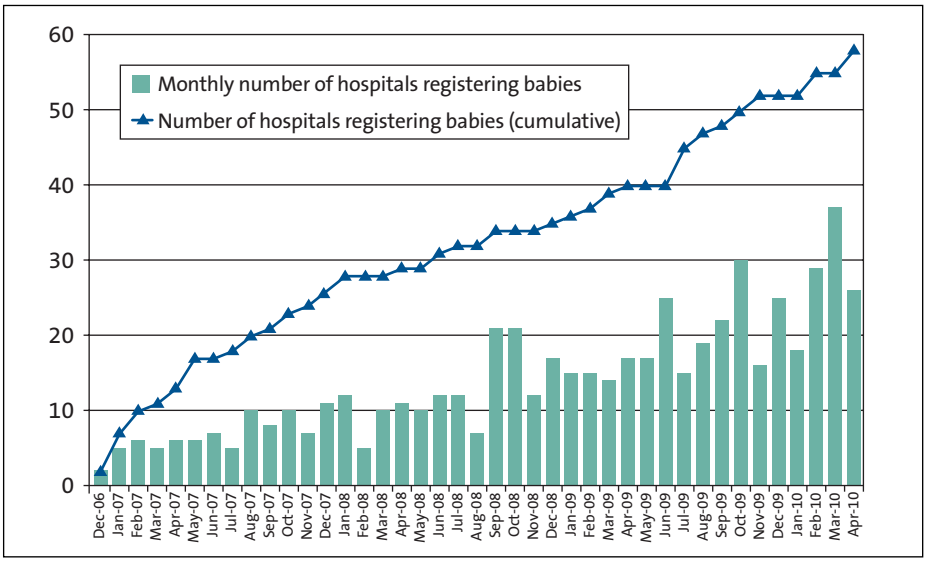

FIGURE 2 Monthly and cumulative numbers of hospitals registering cooled babies, December 2006 - April 2010.

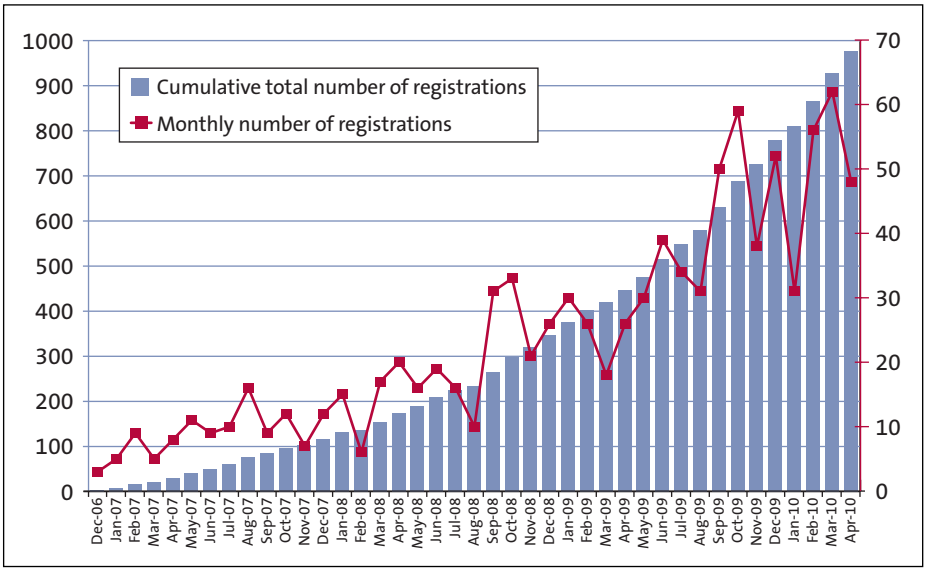

FIGURE 3 Monthly and cumulative numbers of registered cooled babies, December 2006 - April 2010.

Meta-analyses of published data

When the results from TOBY are added to those of other major published randomised controlled trials (RCTs), it is apparent that treatment with cooling increases the number of children surviving without severe disability following perinatal asphyxia. In February and March 2010, two meta-analyses[10,11] of published trial data were published and both concluded that mortality, combined outcome of survival or disability, incidence of cerebral palsy and survival without disability are all significantly improved as a result of moderate hypothermia.

The homogeneity of these findings reported in the two meta-analyses is striking (**TABLE 1**), given that the studies included and the numbers of participants in each category differ to varying degrees.

These two papers identify other clinical questions to which definitive answers would be welcome regarding:

- the difference in outcomes between babies who experience moderate compared to severe encephalopathy
- the difference in outcomes in relation to the depth of cooling, and the method employed to induce and maintain cooling, ie whole body cooling or selective head cooling.

The method of cooling employed is not considered to affect the benefits bestowed by cooling, by Edwards and colleagues. Shah maintains that cooling using a target core temperature of ≤34°C is more likely to result in significantly improved outcomes. Edwards and co-workers conclude that while infants with moderate encephalopathy are most likely to benefit from improved outcomes, the treatment of babies with severe encephalopathy will be beneficial only in some cases and clinical

Outcome	Edwards et al Risk ratio [95% CI] (number of studies/ number of participants)	Shah Risk ratio [95% CI] (number of studies/ number of participants)
Mortality	0.78 [0.66-0.93] (10/1320)	0.78 [0.65-0.92] (12/1390)
Neurodevelopmental disability in survivors	0.71 [0.56-0.91] (3/520)	0.67 [0.54-0.84] (6/687)
Rate of cerebral palsy in survivors	0.69 [0.54-0.89] (3/518)	0.65 [0.48-0.88] (3/518)
Mental Developmental Index <70	0.71 [0.54-0.92] (3/493)	0.70 [0.54-0.90] (4/522)
Psychomotor Developmental Index <70	0.73 [0.56-0.95] (3/484)	0.70 [0.54-0.90] (4/512)
Blindness/severe visual deficit	0.56 [0.33-0.96] (3/507)	0.59 [0.35-0.98] (4/535)

TABLE 1 Comparison of selected results from two meta-analyses of published cooling studies.

judgment is required when deciding whether treatment is likely to be futile.

End-of-life decisions in cooled babies

If treatment does appear to be futile, it is appropriate to consider the question of withdrawal of intensive care and the transition to palliative end-of-life care even after a baby has started cooling treatment.

Participation in a randomised controlled trial must not override the treatment that is considered to be in the baby's best interests. Clinicians caring for babies enrolled in clinical trials still have ultimate responsibility to determine the care provided to those babies, which may include deviation from a trial protocol. Such a decision needs to be justified and documented in the hospital and trial records; researchers will report these cases when publishing their results.

It was certainly an initial concern among TOBY researchers that allocation to cooling treatment might encourage continued intensive care, which would not have been maintained otherwise; this could result in increased survival at the cost of higher rates of severe disability.

Shah's meta-analysis showed that there was no difference in the adoption of a palliative-care approach between the two groups. The UK TOBY Cooling Register received data on 58 babies (when data had been received on a total of 605 babies), whose cooling treatment had been stopped earlier than the recommended 72 hours, to allow palliative care to commence (unpublished data). This indicates that clinicians do not allow cooling treatment to delay the discussion of other options with the parents and their colleagues[12].

Safety issues – now and later

The increasing number of cooling treatments administered and recording of subsequent outcomes will provide more accurate evidence of the safety or associated risks of cooling.

Cooling a baby or passively allowing a baby's temperature to fall is all too easy to do; indeed, neonatal clinicians and nursing staff dedicate considerable time and effort to achieving and maintaining normothermia and avoiding hypothermia. The provision of a safe but therapeutic level of cooling for appropriate babies should be undertaken by trained staff, who are aware of the safety issues and how to avoid complications related to cooling and rewarming.

Moderate hypothermia is not without risk and overcooling brings increased risks; therefore continuous rectal temperature monitoring is recommended throughout the treatment period to ensure accurate temperature control in the desired range[13]. Overcooling is associated with inadequate temperature monitoring, thus there is general consensus that continuous rectal monitoring is required as soon as the decision to initiate cooling is acted upon[14-16]. This includes during transport, when the danger of overcooling due to inadequate monitoring is currently most likely to occur[17,18].

Cooling presents additional challenges in the management of medications, with its impact on drug metabolism, clearance and distribution necessitating added vigilance. Toxicity levels should be monitored where possible and clinical signs should be interpreted with awareness of the possible impact cooling may have on them. Caution must also apply during rewarming when physiological functions are adjusting[19].

In order to identify all potential adverse events; clinicians should:

- be aware of known risks
- be open to recognising the potential link between complications and the cooling/rewarming process
- report such adverse events appropriately – UK TOBY Cooling Register in the UK[6], Vermont Oxford Neonatal Encephalopathy Register in the US[20].

Follow-up in childhood

With the addition of this new and evolving treatment to the neonatologist's arsenal, it is important to continue to monitor the development of children who were cooled as newborns. Collection of outcome data over longer periods, at around two years of age and on into school age, is vital if the full implications of cooling treatment are to be revealed.

Neurodevelopmental assessment at 18-24 months has its limitations: potential difficulties that are identified at that age may no longer be present when the child reaches school age. It is also possible that the more detailed and subtle assessment that can be undertaken at school age will elicit problems that could not be identified in a two-year-old. Neonatologists need to know that the treatment provided at birth does not prove to be detrimental to development in the longer-term, despite the benefits demonstrated in the shorter-term.

TOBY Study participants are now undergoing assessments at age 6-7 years, by taking part in the TOBY Children Study. This study is funded by the Medical Research Council, as was the original TOBY Study; results will not be available until 2013 at the earliest. While the follow-up of trial participants will provide a detailed comparison of the cooled intervention and non-cooled control groups, the numbers will be relatively small. By the time the TOBY Children Study reports its findings, many hundreds of babies will have been treated with cooling worldwide and mostly outside of clinical trials. Longer-term surveillance of registered cooled babies through infancy

and on into childhood is a valuable resource that should be utilised.

Areas for further research

At present cooling is being adopted more and more as an accepted, and often expected, mode of treatment for term babies with neonatal encephalopathy. Parallel to this, research continues in two distinct areas:

- How to further improve the administration of cooling, either by examining factors such as depth and timing of cooling, or by combining it with an additional treatment in the perinatal period.
- Finding out whether the apparent improvements identified in survivors at 18 months of age are in fact maintained through childhood into school age, with follow-up studies on trial cohorts being undertaken. It is feasible that in the future these children will go on to be studied as adolescents and even as adults.

Hypothermia with additional interventions

The possibility of combining cooling with an additional medication or treatment to improve the treatment effect has been considered since the benefit of cooling alone has become apparent.

Erythropoietin

It has been proposed that erythropoietin could be either an alternative to, or adjunct treatment with, hypothermia. A safety and efficacy study of recombinant human erythropoietin, administered on alternate days for two weeks in term babies with moderate or severe HIE, demonstrated reduced risk of disability for infants with moderate HIE[21]. Two different doses of erythropoietin, 300 U/kg and 500 U/kg, or conventional care were randomly allocated to participants in this double-blind study; both sub-groups in the treatment arm showed benefit. Erythropoietin had already been used for anaemia of prematurity and the safety and efficacy of a low dose regimen had already been demonstrated.

An internet search of registered current trials showed a further dosing and safety study due to start[22], but no trials studying hypothermia combined with erythropoietin were identified.

Xenon

Inhaled xenon gas has been used in anaesthetics[23] for 50 years. Simultaneous research into delivering xenon to neonates for use as neuroprotection is under way at the University of Bristol[24] and University College London[25]. The first baby to be treated with xenon combined with cooling was reported in April 2010, in Bristol[26].

Medical Research Council (MRC) funding has been secured by TOBY researchers for a randomised controlled trial of cooling with inhaled xenon compared to cooling alone; recruitment is due to start during 2010[27].

NICE guidance

An overview of 'therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury' was prepared in April 2008 and was available on the NICE Interventional Procedures Program pages from June 2008. There was a four-week consultation period at that time but with the publication of the TOBY results imminent, the development of guidelines was deferred, so that the latest evidence from the largest randomised controlled trial of cooling could be used. After the TOBY findings were published a second consultation was instigated in January 2010[28]. NICE guidance was published in May 2010, recommending the use of therapeutic cooling in 'carefully selected neonates', by experienced staff trained in its use. Registration of all cooled infants with the UK TOBY Cooling Register is encouraged.[29] In addition NICE published information that was written to 'help parents or carers whose baby has been offered this procedure to decide whether to agree to it or not'[30].

Conclusion

Hypothermia is a rapidly growing mode of treatment and is used not only in the setting of the neonatal unit but also in adult intensive care. It is also being considered in contexts other than HIE. The NEST Study is a randomised controlled trial examining its use as prophylactic neuroprotection during extra-corporeal membrane oxygenation (ECMO) in babies; recruitment was completed in March 2010 and neurodevelopmental assessment at two years is well under way[31]. There has also been a safety study of hypothermia for the treatment of advanced necrotising enterocolitis (NEC) in preterms[32]. In addition, hypothermia is recommended post-adult cardiac arrest in adults[33].

It is likely that we still have some way to go on the learning curve, but only with the benefit of hindsight will we be able to look back to 2010 and realise how much we have learned and how much we still do not know. Continued data collection on treatment episodes and subsequent outcomes over several years will be required before all aspects of treatment with hypothermia are fully supported by evidence.

The time has surely come for moderate hypothermia for neonatal encephalopathy to become integrated into established neonatal and two-year outcome databases.

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