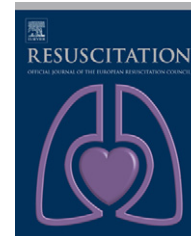




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REVIEW

Therapeutic hypothermia in neonates. Review of current clinical data, ILCOR recommendations and suggestions for implementation in neonatal intensive care units[☆]

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Received 4 November 2007; received in revised form 17 March 2008; accepted 10 April 2008

KEYWORDS

ILCOR guidelines;
Neonatal asphyxia;
Neonatal encephalopathy;
Therapeutic hypothermia

Summary Recent evidence suggests that the current ILCOR guidelines regarding hypothermia for the treatment of neonatal encephalopathy need urgent revision. In 2005 when the current ILCOR guidelines were finalised one large (CoolCap trial, $n=235$) and one small RCT ($n=67$), in addition to pilot trials, had been published, and demonstrated that therapeutic hypothermia after perinatal asphyxia was safe. The CoolCap trial showed a borderline overall effect on death and disability at 18 months of age, but significant improvement in a large subset of infants with less severe electroencephalographic changes. Based on this and other available evidence, the 2005 ILCOR guidelines supported post-resuscitation hypothermia in paediatric patients after

Abbreviations: ILCOR, International Liaison Committee on Resuscitation; aEEG, amplitude integrated EEG.

[☆] A Spanish translated version of the summary of this article appears as Appendix in the final online version at [doi:10.1016/j.resuscitation.2008.04.027](https://doi.org/10.1016/j.resuscitation.2008.04.027).

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cardiac arrest, but not after neonatal resuscitation. Subsequently, a whole body cooling trial supported by the NICHD reported a significant overall improvement in death or disability. Further large neonatal trials of hypothermia have stopped recruitment and their final results are likely to be published 2009–2011.

Many important questions around the optimal therapeutic use of hypothermia remain to be answered. Nevertheless, independent meta-analyses of the published trials now indicate a consistent, robust beneficial effect of therapeutic hypothermia for moderate to severe neonatal encephalopathy, with a mean NNT between 6 and 8. Given that there is currently no other clinically proven treatment for infants with neonatal encephalopathy we propose that an interim advisory statement should be issued to support and guide the introduction of therapeutic hypothermia into routine clinical practice.

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Introduction

Post-resuscitation moderate to severe acute neonatal encephalopathy in infants born at term is associated with a high rate of death or devastating long-term disabilities. There has been no significant improvement in the risk of this tragic event over recent decades and only supportive care is routinely available at present. The possibility that mild cooling might be beneficial has tantalised clinicians for over 300 years.¹ In the present review we critically review the available clinical evidence for therapeutic hypothermia in relation to the relevant 2005 recommendations of the International Liaison Committee on Resuscitation (ILCOR). These recommendations are updated every five years, as evidence changes.²

Current ILCOR recommendation²

Consensus on science

A reduction of body temperature by 2–3°C (modest hypothermia) following cerebral hypoxia-ischaemia reduces cerebral metabolic and biochemical abnormalities and cerebral injury and improves function in experimental neonatal models (LOE 6).^{3–5} In adults, induced hypothermia (temperature of 32–34°C) for 12–24 h improves neurological outcome after cardiac arrest due to ventricular arrhythmias but not after trauma or stroke (LOE 7).⁶ In a multi-centre trial involving newborns with suspected asphyxia (indicated by need for resuscitation at birth, metabolic acidosis, and early encephalopathy), selective head cooling to achieve a rectal temperature of 34–35°C was associated with a nonsignificant reduction in the overall number of survivors with severe disability at 18 months but a significant benefit in the subgroup with moderate encephalopathy (LOE 2).⁷ Infants with severe electroencephalographic (EEG) suppression and seizures did not benefit from treatment with modest hypothermia (LOE 2).⁷ A second small controlled pilot study in asphyxiated infants with early induced systemic hypothermia that achieved a rectal temperature of 33°C resulted in fewer deaths and disability at 12 months (LOE 2).⁸ Modest hypothermia is associated with bradycardia and elevated blood pressure that do not usually require treatment, but a rapid increase in body temperature may cause hypotension (LOE 5).⁹ Profound hypothermia (core temperature <33°C) may cause arrhythmia, bleeding, thrombosis, and sepsis, but these complications have not been reported in infants treated with modest hypothermia (LOE 2).^{7,8,10,11}

ILCOR treatment recommendation

There are insufficient data to recommend the routine use of systemic or selective cerebral hypothermia after resuscitation of infants with suspected asphyxia. Further clinical trials are needed to confirm that treatment with cooling is beneficial, to identify infants who will benefit most, and to determine the most effective method and timing of cooling.

New data and information following the 2005 ILCOR statement

In October 2005 a second large randomised controlled trial (RCT) was published,¹⁰ in which 208 infants were treated with whole body cooling at a rectal temperature of 33.5 ± 0.5°C or normothermia for 72 h. Entry criteria were similar to those of the CoolCap trial,⁷ except that only clinical and not aEEG criteria were used (see Table 1). This study found a significant improvement in the composite outcome of death or moderate to severe disability at 18 months of age in the treatment group (Table 2).

Following presentation of the NICHD trial data at the annual meeting of the Pediatric Academic Societies, the Committee on Fetus and Newborn (COFN), American Academy of Pediatrics¹² and the National Institute of Child Health and Human Development¹³ unanimously emphasised the need for additional data and established a long list of currently unanswered questions. Both committees concluded that these gaps in knowledge prevented a general recommendation to apply therapeutic hypothermia as a generally available tool in the treatment of asphyxiated near-term and term infants at that time. Both the COFN and the Workshop participants recommended that hypothermia, if offered, should be used only under published protocols, as indicated in the CoolCap⁷ and the NICHD¹⁰ trials or as part of ongoing controlled trials with appropriate follow up.

A number of independent systematic meta-analyses have since been published. The first in 2006 examined only the three large trials on therapeutic hypothermia for neonatal encephalopathy,^{7,8,10} and reported a significant overall improvement in primary outcome (i.e. a reduction in death or disability at 18 months of age) but did not make a general treatment recommendation.¹⁴ The second, which included data from all published RCT's to early 2007 ($n=5$) evaluating either death or neurodevelopmental disability at ≥18 months after hypothermia by selective head cooling or whole body cooling in term neonates (a combined total of 552 randomised infants) reported a significant effect of therapeutic hypothermia on the primary composite outcome of death or disability (RR: 0.78, 95% CI: 0.66, 0.92, NNT: 8,

Table 1 Entry criteria of the CoolCap⁷ and the NICHD¹⁰ study

	Entry criteria	
	CoolCap study ⁷	NICHD ¹⁰
	pH <7.0 or base deficit ≥ 16 or APGAR score ≤ 5 (10') or need for resuscitation at 10 min	pH <7.0 or base deficit ≥ 16 if blood gas not available or pH 7.01–7.15 or base deficit 10–15.9: need for history of acute perinatal event and APGAR score ≤ 5 (10') or need for resuscitation at birth and continued for 10 min
	Moderate to severe clinical encephalopathy Abnormal aEEG trace or seizures	Moderate to severe clinical encephalopathy or seizures Signs of fetal distress
Predicted mortality or severe disability in the standard treatment group	70%	50%
Observed mortality or severe disability in the standard treatment group	66%	62%

95% CI: 5, 20) as well as on the single outcomes of mortality (RR: 0.75, 95% CI: 0.59, 0.96) and neurodevelopmental disability at 18–22 months (RR: 0.72, 95% CI: 0.53, 0.98).¹⁵ A third meta-analysis including eight randomised or quasi-randomised trials also supported the safety and efficacy of therapeutic hypothermia with a NNT of six for overall death or disability.¹⁶ Finally, the most recent Cochrane Review on therapeutic hypothermia in neonates reached similar conclusions, with a NNT of seven for overall death or disability at 18–22 months, without recommending application in clinical practice.¹⁷

In addition to the published trials discussed above, a large multicentre trial in mainland China has reported the effect of head cooling to a nasopharyngeal temperature of 34 °C. This study enrolled 187 infants with severe asphyxia (Apgar $\leq 3/5$ at 1/5 min, pH ≤ 7.0 or base deficit ≤ -16 mM) and moderate to severe encephalopathy. Death or severe disability at 18 months of age was significantly ($p = 0.02$) reduced in cooled infants (28/88), compared to controls (35/69) (Shao Xiaomei, oral presentation Hot Topics In Neonatology, Washington, DC, December 4, 2006).

In 2007, April 30, the European neo.nEuro.network study 'Induced hypothermia in asphyxiated newborns' (whole

body cooling to 33.5 °C, PI: Georg Simbruner, University of Innsbruck, personal communication) was terminated after recruiting 129 asphyxiated infants, because '*the current evidence of the benefits of therapeutic hypothermia did not justify further randomisation*'. Preliminary data are supportive of the results of the published studies described above and point to decreased mortality and improved neurologic outcome of surviving infants in the hypothermia group. Complete follow-up data are expected to be available in late 2008.

The Medical Research Council funded 'TOBY' trial in the UK stopped recruitment according to schedule after enrolling 325 severely asphyxiated babies in November 2006 (whole body cooling to 33.5 °C) and outcome results are expected to be first presented in late 2008 (PI: Denis Azzopardi, Imperial College London).

Finally, the ICE (infant cooling evaluation, whole body cooling to a mean of 33.0 °C for 72 h) trial in Australasia and Canada terminated recruitment on July 27th 2007 due to a 'lack of equipoise' at a sample size of 218 (PI: Susan Jacobs, Royal Women's Hospital Melbourne, personal communication). Follow-up data are estimated to be available in 2010.

Table 2 Death, disability, and other adverse outcome of the CoolCap,⁷ NICHD,¹⁰ and Eicher⁸ study

	CoolCap ⁷		NICHD ¹⁰		Eicher ⁸	
	Cooled	Control	Cooled	Control	Cooled	Control
Adverse outcome	59/108 (55%)	73/110 (66%)	45/102 (44%)	64/103 (62%)	14/27 (52%)	21/25 (84%)
Death	36/108 (33%)	42/110 (38%)	24/102 (24%)	38/106 (37%)	10/32 (31%)	14/33 (42%)
Disability in survivors	23/72 (32%)	31/68 (46%)	21/78 (27%)	26/65 (40%)		
Severe neuromotor disability	14/72 (19%)	21/68 (31%)	15/77 (19%)	19/64 (30%)	4/17 (24%)	7/11 (64%)
MDI <70	21/70 (30%)	24/61 (39%)	20/74 (27%)	24/62 (39%)	4/17 (24%)	5/12 (42%)
Visual impairment	7/72 (10%)	11/64 (17%)	5/75 (7%)	9/63 (14%)		

Adverse outcome: death or severe disability at 18 months (CoolCap); death or moderate or severe disability at 18 months (NICHD); death or severe motor scores at 12 months (Eicher). Data are number (%). MDI: Bayley Mental Developmental Index score at 18 and 12 months respectively.

This shows that no new published, peer reviewed data from further large trials will be available until 2009–2011 at the earliest. Even then it is critical to appreciate that these trials were not designed to address most of the remaining open questions related to the optimal use of therapeutic hypothermia. Rather these additional RCT's will primarily provide further data on the basic effect of the modality itself. Direct, randomised trials to examine different cooling strategies will by definition require very large numbers of patients, and many more years before any information becomes available. Thus, the central ethical question now is: how much more certainty do we need before a general treatment recommendation is given versus how many more infants we potentially deny an improved chance of survival and reduced disability?

Given that the published trials were well conducted,¹⁵ additional information that would support a decision include the numerical robustness of the current meta-analysis, the apparent consistency of any beneficial effects between trials and between the components of outcome, and additional information from other measures of outcome.¹⁴ Numerically, the efficacy of hypothermia seems to be solidly established by the recent meta-analyses.^{14–17} Even if at one extreme, there was no apparent effect of cooling among the next 400 children to be randomised, then the cumulative meta-analysis of the three main trials¹⁴ would continue to show a significant overall effect, relative risk (RR) 0.85, 95% CI 0.76–0.96, $p=0.01$. Indeed, Shah et al. calculated that 1500 infants with no effect of hypothermia would need to be recruited into RCT's in order to nullify the outcome of the current data.¹⁶ Thus, the consolidated finding that hypothermia can significantly and safely improve the medium term outcome of moderate to severe HIE is highly robust. We note that these calculations do not include the as yet unpublished data from the Chinese RCT cited above.

Next, as shown in Table 2, the two major RCT's published to date had highly similar effects both overall, and for the different components of outcome. A particular concern before these trials were completed was that treatment might enable more severely damaged infants to survive with handicap. In the event, reassuringly, an overall reduction in mortality was accompanied by a reduction in disability among survivors that was comparable for each of the different measures of disability (Table 2). Further supportive information comes from magnetic resonance imaging studies that suggested both head cooling and total body cooling were associated with a reduced incidence of basal ganglia/thalamic brain lesions and this was most significant in patients with moderate injury by aEEG criteria.¹⁸

Despite early concerns, hypothermia has proven to be remarkably safe, at least in the intensive care environment.¹⁹ Current meta-analyses suggest that the only consistent effects of hypothermia are clinically benign physiological sinus bradycardia, and increased thrombocytopenia.^{16,17} There seems to be a borderline increase in inotrope requirements, but no increase in the incidence or degree of hypotension or other major adverse events.¹⁷ In particular, no increase in haemorrhagic complications was reported in either of the two large randomised trials.^{7,10} The smaller study from Eicher et al. did suggest such an increase, although it was clinically manageable, and no severe intracranial haemorrhage was reported.⁸ It is still unclear whether this is a specific problem associated with the lower target rectal temperatures in that trial (33°C), or simply a chance finding. It is reassuring that in piglet studies where the cortex was cooled significantly (to <30°C) no cerebral haemorrhages were seen,²⁰ and a recent retrospective case series suggests that hypothermia

may be safe even down to rectal temperatures as low as 30°C.²¹

At the same time it is critical to recognise that many important questions about therapeutic hypothermia remain to be answered.¹³ In particular, the optimal depth, duration and mode of delivery of cooling, the impact of time of initiation within the first six postnatal hours on outcome, whether we can better target treatment to babies who are likely to benefit or not, and the effectiveness or otherwise of the combination with additional therapeutic strategies must be explored. For example, there are some, limited, imaging data to suggest differential improvements on MRI after head cooling compared with whole body cooling,^{18,22} although the overall impact of these modalities on death or disability has been comparable. Intriguingly, despite the markedly greater rate of adverse outcome in infants with severe clinically assessed encephalopathy, this was not associated with any apparent effect on the response to hypothermic treatment.^{10,23} In contrast, the CoolCap trial suggested that aEEG monitoring could identify a subgroup of infants with profound suppression of aEEG amplitude and onset of seizures at the time of randomisation who did not respond.⁷ Although these findings are suggestive, it would be premature to use this or any other parameter to identify infants who are 'too severe' to treat, until the findings have been replicated by several studies.¹⁹

Despite these questions, similar issues may be raised about many other treatments currently in use in neonatology. As reviewed above, the published results to date strongly indicate that there is already a clear overall benefit for a subset of moderately to severely asphyxiated infants with either cooling modality, and that treatment has not been associated with any clinically significant side-effects or potential risks for those infants who may not benefit from hypothermia. We may reasonably conclude then that the evidence available to date is more than sufficient to strongly support the introduction of therapeutic hypothermia into clinical practice, while waiting for new studies to address the many remaining questions around the optimal use of hypothermia. The strength of this evidence, the numbers of patients randomised and the consistency of these trials are all at least as good if indeed not better than the two papers that were the basis for changing adult cardiac arrest guidelines.^{6,24}

In the personal experience of the authors, a growing number of infants are already being treated according to the personal strategy of the attending physician. According to a recent survey of directors of neonatal intensive care units 6.4% of respondents in the United States currently use therapeutic hypothermia.²⁵ In the United Kingdom all 25 centres currently offering therapeutic hypothermia report their data to the UK TOBY cooling register. A general treatment recommendation, including practical guidelines, would make it much easier to achieve consistent delivery of known effective therapeutic strategies. It is likely that once hypothermia can be used as a routine, without requirement for informed consent, that further improvements in outcomes should be achieved. For example, we strongly believe that currently available scientific data convincingly show that hypothermia should be offered to infants with moderate to severe encephalopathy as soon as possible after birth. The animal work on which a duration of 72 h and a maximum delay of 5.5 h before initiating hypothermia is based,²⁶ showed far greater histological and electrophysiological protection if hypothermia was initiated within 1.5 h than if it was started 5.5 h after the cerebral insult.

These data have immediate implications for the many affected infants who are born outside of centres that can

offer intensive care. In principle it would be highly desirable to avoid active rewarming during transport to increase the chance of treatment benefit; further, rapid warming has been associated with cardiovascular instability in a few cases⁹ and may have adverse cerebral effects.²⁷ This should not compromise assessment at the referral (tertiary) hospital. In particular, since in practice, mild hypothermia has a minimal acute effect on aEEG recordings,²⁸ aEEG may still be used after transfer to the referral hospital. At the same time, the authors are already aware of episodes of uncontrolled hypothermia during transport of very ill infants prior to admission. Although the results of the ICE trial which specifically tested the possibility of cooling during transport will be of considerable value, there is evidence that passive but carefully monitored hypothermia during transport can be accomplished safely.²⁹ Clearly, management during transport must be an important focus of staff training.

Suggestions for practical implementation

We propose that intensive care nurseries should now consider adopting one of the validated protocols for the selection of term infants with HIE (see Table 1), be appropriately equipped and train staff to offer hypothermia according to the protocol of the currently published large hypothermia trials.^{7,10} Given the practical limitations on any future formal trials, it is vital that strict protocols, including universal follow up should be adopted. Because HIE is a relatively uncommon condition, it will be highly desirable where possible to centralise this treatment to larger intensive care units. This would have the two-fold benefit of first increasing local expertise in the use of hypothermia, and secondly helping to facilitate the ability of large consortia of neonatal units to examine incremental modifications to the treatment protocols such as the length or degree of hypothermia. Thus, infants suffering from perinatal asphyxia can be offered more than just symptomatic treatment, without geographic restrictions, while allowing progressive refinement of techniques and improvements in outcome, analogous to the strategy used to develop paediatric cancer therapy. With the data presently available, there is no longer any reasonable justification to deny this apparently efficacious treatment for those who most urgently need it.

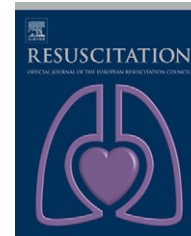
Conflict of interest statement

There are no conflicts of interest or financial interests to reveal.

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EDITORIAL

Hypothermia as a therapeutic intervention in term infants with neonatal encephalopathy—Is it ready for prime time?

KEYWORDS

Therapeutic hypothermia;
Neonatal encephalopathy;
Neuroprotection

The findings contained in the two recently completed multi-centre neonatal studies demonstrating a beneficial effect of induced modest hypothermia in reducing death and neurodevelopmental deficits at follow-up is an important observation.^{1,2} There have been several reviews and meta-analyses of these two studies as well as additional pilot data,^{3–5} and the general consensus is that the number needed to treat to show benefit in one infant is in the range of six to eight infants.^{6–9} The article in this issue of *Resuscitation* is another enthusiastic review on the topic and the authors take an additional step by recommending that hypothermia should be offered as standard of care in every neonatal intensive care unit.¹⁰

While the data are indeed exciting, there are many unanswered questions that demand further research. First, in the Cool Cap study, hypothermia was of significant benefit only in a subcategory of infants, i.e. those who presented with moderate encephalopathy and no seizures.¹ In the whole body cooling study there was benefit only when a composite outcome of death and moderate/severe encephalopathy was viewed and not when these outcomes were analysed individually.² Second, irrespective of the method of cooling, approximately 50% of hypothermic treated infants either died or exhibited significant neurodevelopmental deficits at follow-up. When the data were analysed as a function of the initial degree of severity, the only significant effect of hypothermia was in those infants who presented with moderate encephalopathy, and only as it related to death or moderate to severe neurodevelopmental disability or severe cerebral palsy.⁶

Another important recent observation relates to the detection of artefact noted on the 'raw EEG' which is now a standard part of new cerebral function monitors that record the amplitude integrated EEG (aEEG).^{11,12} The artefact is presumed to be related to muscular activity or respiratory effort, and results in an upward shift of the amplitude into a normal band range and may falsely exclude infants who have overt clinical evidence of moderate/severe encephalopathy. Importantly, the aEEG was a major criterion for entry into the Cool Cap study.¹ It is unclear how many of the 98 infants excluded from enrolment in the Cool Cap study because aEEG criteria were not met, were secondary to artefact, which in turn may have influenced the outcome.

There are numerous additional gaps in knowledge, e.g. the severity of encephalopathy at which the risk versus benefit ratio favours hypothermia, the optimal mode of achieving cooling and the duration of cooling for maximum neuroprotection. Since hypothermia appears to be most effective when induced close to the time of the primary insult, reducing the time from birth to induction of hypothermia, which was approximately 4.5 h in the two large studies, is a priority.^{13,14} There are few data on the changing neurological examination during cooling. The Cool Cap study demonstrated a negative effect of seizures on outcome, yet the seizure burden during cooling is unknown. This should also be an important priority for future evaluation.^{15–17}

The problem is further magnified when it is estimated that neonatal encephalopathy secondary to intrapartum hypoxia-ischaemia evolves in less than one in a 1000 term deliveries. Thus most neonatal intensive care units will treat

just two or three of these cases annually. Clearly, these numbers are insufficient to achieve competency with the technique and/or enhance treatment outcomes even if data are submitted to a national registry.

These issues raise the question of whether the glass is half empty (need more research) or half full (treat everywhere). How should the neonatal community proceed with the question of offering hypothermia as a treatment option while preserving the critical need for further research? One possible solution being adopted in the greater New York Metropolitan region is to establish regional cooling centres. The goal is for each centre to develop a dedicated team consisting of a neonatologist, neurologist, preferably with EEG expertise, and a core of neonatal nurses, to develop and follow a consistent protocol and receive referrals from neighbouring hospitals. The latter should facilitate a more rapid transfer and earlier time to induction of hypothermia. In this manner, regional cooling centres will be able to work in unison in offering hypothermia to all eligible babies while concurrently developing additional strategies to improve outcome. Translating this concept into practical terms, if applied to the New York region where there are 120,000 annual deliveries and seven proposed regional cooling centres, each would treat between 16 and 20 babies each year. This consolidated distribution of numbers should facilitate the development and implementation of randomized studies. We urge others to consider this concept, which should serve as a bridge to those who are advocating hypothermia to all infants while preserving the critical need for additional research.

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