NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury

Hypoxic perinatal brain injury is caused by lack of oxygen to a baby's brain during labour and/or delivery. It can lead to death or permanent brain damage. Therapeutic hypothermia aims to cool the brain (soon after birth and for several days) to prevent permanent brain damage. Hypothermia may be induced by whole body cooling (using a mattress or blanket filled with cooled fluid or air) or by head cooling (using a cap filled with cooled fluid or air). Throughout the procedure, the baby's temperature is measured using a thermometer inside the body (either the rectum or the gullet), to help ensure that cooling is both adequate and not excessive. After cooling, the body temperature is gradually returned to normal.

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in April 2008.

Procedure name

- Therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury

Specialty societies

- Royal College of Paediatrics and Child Health
- British Association of Perinatal Medicine.

Description

Indications and current treatment

Hypoxic perinatal brain injury is caused by a decrease in the amount of oxygen supplied to an infant's brain close to the time of birth (usually during labour and/or delivery). It can result in stillbirth or neonatal death. Infants who survive may develop an abnormal neurological state known as hypoxic-ischaemic encephalopathy (HIE) which can lead to severe lifelong disability or death. Hypoxic perinatal brain injury is also associated with multi-organ failure affecting the heart, lungs, liver and kidneys in some infants.

Hypoxic perinatal brain injury is characterised by fetal distress, metabolic acidosis and the need for artificial ventilation from birth. The initial diagnosis of hypoxic perinatal brain injury is made using a combination of clinical features, birth history and, if available, paired umbilical arterial and venous blood gas measurements. Amplitude-integrated electroencephalography (aEEG) may also be used.

A variety of instruments have been used to measure the degree of disability among children who survive hypoxic perinatal brain injury. These include the Bayley Psychomotor Development Index Score, the Bayley Mental Developmental Index Score, the Mental Development Index Score, and the Gross Motor Function Classification System.

Currently there is no specific treatment for hypoxic perinatal brain injury. Therapy focuses on supportive care after injury has occurred.

What the procedure involves

Therapeutic hypothermia aims to cool the brain to several degrees below the baseline temperature, usually between 33°C and 35°C, with the intention of preventing continuing neuronal loss that occurs in the days after brain injury.

Hypothermia may be induced by selective cooling of the head using a cap placed over the infant's head, or by whole body cooling using a blanket or mattress. Cold water or air is circulated through the cap, blanket or mattress to achieve the desired temperature. A rectal or nasopharyngeal thermometer is used to measure the intracorporeal temperature as a proxy for brain temperature.

Treatment is started as soon as possible after diagnosis and continues for a few days. After this time, the infant is slowly warmed to normal body temperature.

Efficacy

A systematic review and meta-analysis of eight randomised controlled trials (RCTs) and a total of 638 infants compared selective head cooling or whole body cooling to standard care. Overall there was a lower risk of death in

cooled infants compared with infants who had standard care (relative risk [RR]: 0.74, 95% confidence interval [CI]: 0.58 to 0.94) and of major neurodevelopmental disability (of survivors at 18 months of age from four RCTs) (RR: 0.68; 95% CI: 0.51 to 0.92)[1].

Restricting the meta-analysis to studies using whole body cooling, cooled infants had lower risks of both death and major neurodevelopmental disability than control infants (RRs: 0.66, 95% CI: 0.47 to 0.93 and 0.60, 95% CI: 0.40 to 0.92 respectively). In the meta-analysis of studies using selective head cooling, there was no statistically significant difference between the groups[1].

The first two studies[2, 3] described in the following section were included in the systematic review and meta-analysis referred to above.

In an RCT of selective head cooling (n = 234), 13% (15/116) of cooled infants died during the 76-hour cooling period compared with 16% (19/118) of control infants in the same time period. Of 218 infants who were followed-up, after 18 months, 55% (59/108) of cooled infants and 66% (73/110) of control infants had died or were severely disabled (odds ratio [OR]: 0.61, 95%CI: 0.34 to 1.09)[2].

In an RCT of whole body cooling (n = 208), 13% (13/102) of cooled infants died during the 72-hour cooling period compared with 10% (11/106) of control infants in the same time period. Of 205 infants who were followed-up, after 18 to 22 months, 44% (45/102) of cooled infants and 62% (64/103) of control infants had died or had moderate or severe disability (RR: 0.72, 95% CI: 0.45 to 0.95)[3].

In an additional RCT of 50 infants (that did not meet inclusion criteria for the systematic review), 78% (18/23) of cooled infants and 70% (19/27) of control infants had normal neurological development (assessed by Infant Mental Developmental Assessment Scale) at six months of age[4].

Safety

The systematic review reported increased risks of sinus bradycardia (RR: 5.96, 95% CI 2.15 to 6.49), thrombocytopaenia (RR: 1.55, 95% CI 1.14 to 2.11) and hypotension requiring inotropic treatment (RR: 1.17, 95% CI 1.00 to 1.38) in cooled infants compared with infants who had standard care[1].

In the RCT of 234 infants, there was a similar incidence of most adverse events in the cooled and control groups except minor cardiac arrhythmia (mostly sinus bradycardia) which was more common in cooled infants than control infants (9%, 10/116 and 1%, 1/118 respectively; p value = 0.004)[2].

In the RCT of 208 infants, the incidence of serious adverse events was similar in the cooled and control groups. Hypotension requiring treatment was more common in the cooled group than the control group (42% [42/102] and 33% [35/106] respectively), as was hypocalcaemia (28% [28/102] and 19%

[20/106] respectively; p values not reported). In addition, 4 infants in the cooled group had various skin changes which resolved spontaneously[3].

The RCT of 50 infants found no significant differences between the cooled and control groups in blood pressure, cardiac function, renal function or other adverse outcomes. However, cooled infants had a significant decrease in heart rates at 24, 48 and 72 hours compared with controls ($p < 0.05$)[4].

There were two additional case reports of adverse events associated with therapeutic hyperthermia. In the first report, an infant who underwent whole body cooling using a water-filled mattress developed sclerema on his back, in the area in contact with the cooling mattress. The sclerema resolved without scarring after three months[5]. In the second report, an infant who underwent whole body cooling using ice packs applied to the skin developed subcutaneous fat necrosis where the ice packs were applied. At nine months of age, asymptomatic firm nodules with no calcification were present[6].

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury. Searches were conducted of the following databases, covering the period from their commencement to 02/04/08: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy).

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with hypoxic perinatal brain injury.
Intervention/test	Therapeutic hypothermia with intracorporeal temperature monitoring.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on approximately 690 infants from one systematic review, two RCTs that were included in the systematic review, an additional RCT and two case reports.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

There is currently no NICE guidance related to this procedure.

Table 2 Summary of key efficacy and safety findings on therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury

Abbreviations used: MDI, mental development index; HIE, hypoxic-ischaemic encephalopathy, GMF, gross motor function, PDI, psychomotor development index;

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Jacobs et al (2007) [1]

Study type: systematic review
Country: international
Study period: not reported
Study population: newborn infants
n = 638 (8 RCTs)
Sex: not reported

Inclusion criteria:
• evidence of birth asphyxia (Apgar score ≤5 at 10 minutes; mechanical ventilation or resuscitation required at 10 minutes or cord or arterial pH <7.1) and
• evidence of encephalopathy and
• no major congenital abnormalities.

Technique:
• Method of cooling: whole body (6 studies) or selective head cooling (2 studies) vs standard care (no cooling).
• Duration of cooling: 72 hours (7 studies) or 48 hours (1 study)
• Degree of cooling: various target temperatures ranging from 32.5–36.5°C
• Warming: 0.5°C per hour for 4 hours (6 studies), 0.5°C every second hour for 8 hours (1 study), spontaneous warming at room temperature for up to 12 hours (1 study).

Follow-up: various

Conflict of interest: none reported</td>
<td><u>All outcomes are for cooled group vs standard care</u>
Death or major neurodevelopmental disability at age 18–22 months
<table>
<tr><th></th><th>Rel. risk (95% CI)</th><th>Risk diff. (95% CI)</th></tr>
<tr><td>Total
(8 studies)</td><td>0.76
(0.65–0.89)</td><td>-0.15
(-0.24– -0.07)</td></tr>
<tr><td colspan="3">Subgroup analysis: method of cooling</td></tr>
<tr><td>Head
(4 studies)</td><td>0.85
(0.69–1.05)</td><td>-0.09
(-0.21–0.03)</td></tr>
<tr><td>Whole body
(4 studies)</td><td>0.69
(0.55–0.86)</td><td>-0.21
(-0.33– -0.09)</td></tr>
</table>
Death within first 18 months of life
<table>
<tr><th></th><th>Rel. risk (95% CI)</th><th>Risk diff. (95% CI)</th></tr>
<tr><td>Total
(8 studies)</td><td>0.74
(0.58–0.94)</td><td>-0.09
(-0.16– -0.02)</td></tr>
<tr><td colspan="3">Subgroup analysis: method of cooling</td></tr>
<tr><td>Head
(4 studies)</td><td>0.83
(0.59–1.16)</td><td>-0.05
(-0.14–0.04)</td></tr>
<tr><td>Whole body
(4 studies)</td><td>0.66
(0.47–0.93)</td><td>-0.13
(-0.23– -0.02)</td></tr>
</table>
Major neurodevelopmental disability in survivors at age 18–22 months
<table>
<tr><th></th><th>Rel. risk (95% CI)</th><th>Risk diff. (95% CI)</th></tr>
<tr><td>Total
(4 studies)</td><td>0.68
(0.51–0.92)</td><td>-0.13
(-0.23– -0.03)</td></tr>
<tr><td colspan="3">Subgroup analysis: method of cooling</td></tr>
<tr><td>Head
(2 studies)</td><td>0.77
(0.51–1.17)</td><td>-0.09
(-0.24–0.05)</td></tr>
<tr><td>Whole body
(2 studies)</td><td>0.60
(0.40–0.92)</td><td>-0.17
(-0.31– -0.03)</td></tr>
</table>
</td>
<td>Adverse events

Only adverse events with statistically significant differences in cooled infants compared to standard care infants are reported here.

• Increased sinus bradycardia (5 studies; RR: 5.96, 95% CI 2.15 to 6.49),
• Increased hypotension requiring inotropes (borderline significance) (5 studies; RR: 1.17, 95% CI 1.00 to 1.38)
• Increased thrombo-cytopaenia (4 studies; RR: 1.55, 95% CI 1.14 to 2.11)</td>
<td>Apgar score: method of assessing newborns' heart rate, respiratory effort, muscle tone, skin color, response to catheter in nostril (10 = infant is in the best possible condition, 0–3 = infant needs immediate resuscitation).

Major neurodevelopmental disability was defined as:
• cerebral palsy,
• developmental delay (Bayley or Griffith mental development assessment > 2 standard deviations below the mean),
• intellectual impairment (IQ > 2 standard deviations below the mean),
• blindness (< 6/60 in both eyes),
• sensorineural deafness requiring amplification.

There was no evidence of heterogeneity in all outcomes (I-squared = 0%) except for major neurodevelopmental disability by method of cooling (mild heterogeneity - 16%)</td>
</tr>
</table>

Abbreviations used: MDI, mental development index; HIE, hypoxic-ischaemic encephalopathy, GMF, gross motor function, PDI, psychomotor development index;

Study details

Shankaran et al (2005)3

Study type: **RCT**
Country: USA (multi-centre)
Study period: July 2000 – May 2003
Study population: newborn infants **n = 208**

Sex: not reported

Inclusion criteria:
- gestational age ≥ 36 weeks & enrolled within 6 hours of birth
- poor respiratory effort at birth and need for resuscitation or
- diagnosis of encephalopathy,
- blood pH ≤ 7.0 or base deficit 10–15.9mmol/L within 60 mins of birth
- no major congenital abnormalities.

Treatment assignment: random allocation by telephone, stratified by centre.

Technique: whole body cooling to an oesophageal temperature of 33.5°C for 72 hours using a Blanketrol cooling blanket (Cincinatti Sub-Zero). Infants were slowly warmed to 36.5°C (0.5°C per hour) over 6 hours. Control infants received standard care.

Follow-up: **20 months (median)**

Conflict of interest: none stated

Key efficacy findings

Death or disability at age 18–22 months (number of infants)

	Cooled group (n = 102)	Control group (n = 106)	Adjusted relative risk (95% CI)
Died or moderate or severe neuro-developmental disability *(prim. outcome)*	44% (45)	62% (64)	0.72 (0.45–0.95)
Died	24% (24)	37% (38)	0.68 (0.44–1.05)
Bayley MDI score <70	25% (19)	39% (24)	0.71 (0.43–1.17)
Bayley PDI score <70	27% (20)	35% (22)	0.80 (0.48–1.33)
Disabling cerebral palsy	19% (15)	30% (19)	0.68 (0.38–1.22)
Blindness	7% (5)	14% (9)	0.50 (0.17–1.44)
Severe hearing impairment	4% (3)	6% (4)	0.54 (0.10–3.02)

Relative risks were adjusted for study centre. Percentages were based on the number of infants for whom data were available.

Mortality

Time period	Cooled group	Control group
72-hour intervention period	13% (13/102)	10% (11/106)
Hospital course	19% (19/102)	27% (29/106)

Key safety findings

Adverse events

	Cooled group (n = 102)	Control group (n = 106)
During 72-hour intervention period		
Mean heart rate	109bpm	140bpm
Cardiac arrhythmia	0	0
Persistent acidosis	1	2
Bleeding	0	0
Skin changes	4% (4/102)	0
During hospital course		
Hypotension requiring treatment	42% (42/102)	33% (35/106)
Cardiac arrhythmia	2% (2/102)	1% (1/106)
Persistent pulmonary hypertension	25% (25/102)	22% (23/106)
Hepatic dysfunction	20% (20/102)	15% (16/106)
Bloodstream infection	5% (5/102)	6% (6/106)
Disseminated intravascular coagulopathy	18% (18/102)	11% (12/106)
Hypoglycaemia	12% (12/102)	15% (16/106)
Hypocalcaemia	27% (28/102)	19% (20/106)

There was a similar incidence of serious adverse events in both groups.

Comments

This study is included in the Cochrane systematic review (Jacobs et al 2007)

3 infants were lost to follow-up.

Severe disability was defined as one of:
- GMF level 3–5
- Bayley MDI <70
- hearing impairment requiring aids
- blindness.

Moderate disability was defined as:
- Bayley MDI 70–84 and
- GMF level 2, or
- hearing impairment with no amplification, or

persistent seizure disorder.

Abbreviations used: MDI, mental development index; HIE, hypoxic-ischaemic encephalopathy, GMF, gross motor function, PDI, psychomotor development index;

Study details

Gluckman et al (2005) 2

Study type: **RCT**
Country: international (multi-centre)
Study period: July 1999 – Jan 2002
Study population: newborn infants
n = 234

Sex: not reported

Inclusion criteria:
- gestational age ≥ 36 weeks
- Apgar score ≤ 5 10 minutes after birth or continued need for resuscitation or severe acidosis (pH <7 pr base deficit 16 mmol/L in any blood sample within 60 mins of birth)
- evidence of encephalopathy
- abnormal aEEG
- no major congenital abnormalities.

Treatment assignment: random allocation stratified by centre.

Technique: selective head cooling to a rectal temperature of 34–35°C for 72 hours using a CoolCap cooling cap (Olympic Medical) (n = 116). After cooling infants were slowly warmed to 36.8–37.2°C (0.5°C per hour) over 6 hours. Control infants received standard care (n =

Key efficacy findings

Death or severe disability at age 18 months

	Cooled group	Control group	Odds ratio (95% CI)
Died or severe neurodevelopmental disability *(primary outcome)*	55% (59/108)	66% (73/110)	0.61 (0.34–1.09)
Died	33% (36/108)	38% (42/110)	0.81 (0.47–1.41)
Severe neuromotor disability (GMF level 3–5)	19% (14/72)	31% (21/68)	0.54 (0.25–1.17)
Bayley MDI score <70	30% (21/70)	39% (24/61)	0.66 (0.32–1.36)
Bayley PDI score <70	30% (21/69)	41% (23/56)	0.63 (0.30–1.31)
Bilateral cortical visual impairment	10% (7/72)	16% (11/64)	0.52 (0.19–1.39)

Mortality

Time period	Cooled group	Control group
76-hour monitoring period	13% (15/116)	16% (19/118)
First week of life	23% (27/116)	22% (26/118)

Secondary outcomes

There were no significant differences between the study groups in the odds ratio of the following outcomes:
- multi-organ dysfunction
- multiple disabilities
- bilateral sensorineural hearing loss
- epilepsy

Key safety findings

Adverse events

	Cooled group	Control group
Scalp oedema*	28% (32/116)	1% (1/118)
Mean heart rate during 72-hour cooling period *	114bpm	145bpm
Major cardiac arrhythmia	0	0
Major venous thrombosis	0	2% (2/118)
Severe hypotension	3% (3/112)	3% (3/116)
Minor cardiac arrhythmia (mostly sinus bradycardia)*	9% (10/112)	1% (1/118)
Abnormal renal function	65% (73/112)	70% (83/118)
Systemic infection	3% (3/112)	3% (3/118)
Coagulopathy	19% (21/112)	14% (17/118)
Hypoglycaemia	13% (14/112)	17% (20/118)
Hypocalcaemia	44% (49/112)	43% (51/118)

* *Significant difference between groups*

1 cooled infant (who died of other causes) had skin breakdown and local haemorrhage under the cooling cap.

Comments

This study is included in the Cochrane systematic review (Jacobs et al 2007)

4 infants allocated to cooling were not cooled and 1 infant allocated to standard care was cooled briefly.

Safety data are based on all infants that were enrolled (n = 234). Efficacy data are based on 218 infants that were followed up. (8 infants in each group were lost to follow-up.)

Severe neurodevelopmental disability was defined as one of:
- GMF level 3–5
- Bayley MDI < 70

bilateral cortical visual impairment.

118). **Follow-up: 18 months** Conflict of interest: study funded by manufacturer	***Sub-group analyses*** Of infants with severe aEEG changes at baseline (n = 46), there was no significant difference between study groups in death or severe neuromotor disability. Of all other infants (i.e. with moderate aEEG changes; n =172), there were significant differences between study groups in severe neuromotor disability and in combined death and severe disability.		

Abbreviations used: MDI, mental development index; HIE, hypoxic-ischaemic encephalopathy, GMF, gross motor function, PDI, psychomotor development index;

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Zhou et al (2002)[4]

Study type: RCT

Country: China

Study period: July 1999 – Dec 2000

Study population: newborn infants

n = 50

Sex: not stated

Inclusion criteria:
• gestational age ≥ 37 weeks
• Apgar score < 5 at 5 minutes
• abnormal electrocardiography or clinical depression of nervous system within 6 hours of birth
• no major congenital abnormalities.

Treatment assignment: random allocation

Technique: selective head cooling to a nasopharyngeal temperature of 34°C for 72 hours using a cap of circulating water (Hengyuan, China) (n = 23). After cooling infants were spontaneously warmed in 12 hours to a normal temperature. Control infants received standard care (n = 27).

Follow-up: 6 months

Conflict of interest: none stated</td>
<td>Mortality

No deaths reported.

Neurodevelopmental outcomes

<table>
<tr><th></th><th>Cooled group</th><th>Control group</th></tr>
<tr><td>Abnormal CT scan at 5–7 days</td><td>100%</td><td>100%</td></tr>
<tr><td>Abnormal CT scan at 3 months</td><td>17% (4/23)</td><td>33% (9/27)</td></tr>
<tr><td>Abnormal EEG at baseline</td><td>74% (17/23)</td><td>67% (18/27)</td></tr>
<tr><td>Abnormal EEG at 3 months</td><td>17% (4/23)</td><td>30% (8/27)</td></tr>
<tr><td>Normal development at 6 months*</td><td>78% (18/23)</td><td>70% (19/27)</td></tr>
</table>
* As assessed by the Infant Mental Developmental Assessment Scale (the authors do not provide a description of this scale)</td>
<td>There was a significant decrease in heart rates at 24, 48 and 72 hours in cooled infants compared to controls ($p < 0.05$).

There were no significant differences between the groups in blood pressure, cardiac function, renal function or other adverse outcomes.</td>
<td>This study did not meet inclusion criteria for the systematic review (it did not describe method of treatment allocation and did not report any of the pre-specified outcomes).</td>
</tr>
</table>

Abbreviations used: MDI, mental development index; HIE, hypoxic-ischaemic encephalopathy, GMF, gross motor function, PDI, psychomotor development index;			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Navarini-Meury et al (2007)[5] Study type*:* ***case report*** Country: *Switzerland* Study period: *not reported* Study population: *new born infant delivered at term with birth asphyxia* ***n = 1*** Sex: *male* Technique: *whole body cooling using a water-filled mattress to 34.5°C for 72 hours* Follow-up: *not stated* Conflict of interest*: none reported*		The infant survived without apparent brain damage but developed sclerema on his back, in the area in contact with the cooling mattress. The sclerema resolved without scarring after three months	

Abbreviations used: MDI, mental development index; HIE, hypoxic-ischaemic encephalopathy, GMF, gross motor function, PDI, psychomotor development index;			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Wiadrowski et al (2001)[6] Study type*: **case report*** Country: *Australia* Study period: *not reported* Study population: *new born infant delivered at term with birth asphyixia* ***n = 1*** Sex: *female* Technique: *surface cooling using ice packs applied to the skin. Temperature (monitored via a rectal probe) was kept at 32–33°C for 24 hours, then raised to 35 degrees and then 37degrees over a 3 day period* Follow-up: ***9 months*** Conflict of interest*: none reported*		Pink woody odematous change was noted on the thighs and back of the infant, corresponding to the sites of applications of the ice packs. First noted at approximately 24 hours after birth and progressively worsening over 4 days. Subcutaneous fat necrosis was histologically diagnosed at 6 days. The infant was treated by rehydration, diuretics, prednisolone, etidronate and low-calcium, low- vitamin D diet. At 9 months asymptomatic firm nodules were present and no calcification was present.	

Validity and generalisability of the studies

- The studies varied in the method of cooling (some used selective head cooling and some used whole body cooling) as well as in the degree of cooling and the method used to monitor temperature.
- The systematic review also included studies with different cooling methods, selection criteria and outcome measures.
- Outcomes were assessed to a maximum follow-up of about 18 months only.

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Dr Denis Azzopardi, Prof David Edwards, Prof Henry Halliday, Prof Malcolm Levene, Prof Marianne Thoresen, Prof Andrew Whitelaw. Royal College of Paediatrics and Child Health.

- Two Specialist Advisers thought the procedure was established practice and three thought it was novel and of uncertain safety and efficacy.
- All Advisers thought that there was no appropriate comparator because standard intensive care with normothermia was the only alternative.

Safety

- Theoretical or anecdotal adverse events included: hypotension, overcooling, pulmonary hypertension, infection, cardiac arrhythmia, bleeding, thrombosis, pneumonia, biochemical disturbance, tissue necrosis and acidosis.
- Three Specialist Advisers commented that there were no uncertainties about safety (when published protocols are used and if target temperature is maintained). The major safety concern was the potential for overcooling in routine clinical practice.

Efficacy

- Key efficacy outcomes included: decreased mortality and absence of neurodevelopmental disability (including both motor and cognitive disability) at 18 months–2 years and at 6–7 years, educational performance, and changes on MRI before discharge.
- Two Specialist Advisers commented that there was uncertainty about the efficacy of this procedure despite a systematic review because of lack of rigorous, large, randomised controlled trials. Two Advisers thought that there was no uncertainty about the efficacy of this procedure.
- Uncertainties about efficacy included: whether selective head cooling or whole body cooling is better, which is the optimum target temperature, which infants should be selected for treatment (those with moderate or severe asphyxia), when treatment should begin and whether there are long-term benefits.

- One Adviser stated that efficacy was likely to be better if infants with birth asphyxia were not warmed before they were cooled (that is if time before cooling is stared is shorter) and two Advisers stated that servocontrolled equipment is preferable to avoid temperature swings.

Other comments

- Most Advisers thought that training in the use of cooling equipment and aEEG was important but that this was relatively simple.
- Two Advisers thought that there would be legal implications of not offering this procedure and that this procedure would diffuse throughout level 3 neonatal intensive care units within a few years.
- An Adviser stated that there was uncertainty about whether to offer the procedure before the results of the TOBY trial were available. Another thought that depending on the results of the TOBY trial, this procedure would become standard care.
- Two Advisers thought that the potential impact of the procedure on NHS was moderate and two thought it was major.

Issues for consideration by IPAC

- Two Specialist Advisers thought that 'intracorporeal temperature monitoring' should be removed from the title because it could be misleading (i.e. temperature monitoring does need to be invasive) and would be simpler. Another Adviser thought that the indication section of the title should be 'for full-term or near full-term infants suffering from birth asphyxia'.
- The Total Body Hypothermia (TOBY) trial completed recruitment in December 2006. Results (with 1–2 year follow-up) are expected in December 2008. No interim analysis was carried out. One Adviser (the lead investigator of the TOBY trial) thought that guidance should not be produced until the results are available, and most Advisers commented that many clinicians were waiting for the TOBY trial results to answer uncertainties about efficacy.
- Several Advisers and the Cochrane systematic review mentioned two additional trials which are due to publish results within the next two years: the nnn-Hypothermia multi-centre trial in Europe (results due late 2008) and the ICE trial in Australia (results due late 2009).
- The TOBY group has set up a national register of cooling (http://www.npeu.ox.ac.uk/tobyregister).

References

1. Jacobs S, Hunt R, Tarnow M et al. (2007) Cooling for newborns with hypoxic ischaemic encephalopathy. The Cochrane Library

2. Gluckman PD, Wyatt JS, Azzopardi D et al. (2005) Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: Multicentre randomised trial. Lancet 365: 663–670.

3. Shankaran S. L. (2005) Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. New England Journal of Medicine 353: 1574–1584.

4. Zhou W-H, Shao X-M, Yun C et al. (2002) Safety study of hypothermia for treatment of hypoxic-ischemic brain damage in term neonates. Acta Pharmacologica Sinica 23: 64–68.

5. Navarini-Meury S, Schneider, J, Buhrer, C. (2007) Sclerema neonatorum after therapeutic whole-body hypothermia. Archives of Disease in Childhood Fetal & Neonatal Edition 92 (4) F307.

6. Wiadrowski TP, Marshman G. (2001) Subcutaneous fat necrosis of the newborn following hypothermia and complicated by pain and hypercalcaemia. Australasian Journal of Dermatology 42 (3) 207–210.

Appendix A: Additional papers on therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Akisu M. (2003) Selective head cooling with hypothermia suppresses the generation of platelet-activating factor in cerebrospinal fluid of newborn infants with perinatal asphyxia. Prostaglandins Leukotrienes and Essential Fatty Acids 69 (1) 45–50.	n = 21 (RCT) Follow-up: not stated	No evidence of severe adverse events related to hypothermia. No cooled infants and 2 control infants (20%) died after 72 hours of life. No cooled infants and 3 control infants (30%) had clinical seizure activity. No cooled infants and 4 control infants (40%) had abnormal EEG patterns (P < 0.05).	Larger studies included in table 2.
Azzopardi D, Robertson NJ, Cowan FM et al. (2000) Pilot study of treatment with whole body hypothermia for neonatal encephalopathy. Pediatrics 106: 684–694.	n = 10 Follow-up: not stated	3 infants (30%) died after intensive care was withdrawn. 1 infant had continuing neurological abnormalities at 6 months of age. 6 infants had normal neurological outcome on follow-up examination.	More recent study from same centre included in table 2.
Battin MR. (2001) Neurodevelopmental outcome of infants treated with head cooling and mild hypothermia after perinatal asphyxia. Pediatrics 107 (3) 480-484.	n = 40 RCT Follow-up: 18 months	3 infants died in each study group: 12% of cooled infants and 20% of control infants. 6/22 cooled infants and 1/12 control infants had impaired mental development or severe cerebral palsy at 18 months.	Larger studies included in table 2.
Battin MR. (2003) Treatment of term infants with head cooling and mild systemic hypothermia (35.0°C and 34.5°C) after perinatal asphyxia. Pediatrics 111: 244–251.	n = 13 (+ 13 controls) Follow-up: not stated	1 cooled infant died 2 days after rewarming, and 3 control infants died. 6 cooled infants (46%) and 5 control infants (38%) had normal EEG at 1 week.	More recent study from same centre included in table 2.
Bhat MA. (2006) Re: Therapeutic hypothermia following perinatal asphyxia. Archives of Disease in Childhood: Fetal and Neonatal Edition 91 (6) F464.	n = 35 (RCT)	No significant difference in mortality between cooled infants (15%) and controls (33%; p > 0.05). Cooled infants were less likely to have abnormal	Data were reported in a letter to the journal not a full text original article.

		neurological examination at discharge ($p < 0.001$; raw data not reported).	
Compagnoni G. (2002) Hypothermia reduces neurological damage in asphyxiated newborn infants. Biology of the Neonate 82: 222–227.	n = 10 (+ 11 controls) Follow-up: 18 months	No evidence of severe adverse events related to hypothermia. Significant ($p < 0.05$) reduction of major neurologic abnormalities at follow-up and abnormal MRI in cooled group.	Larger studies included in table 2.
Debillon T. (2003) Whole-body cooling after perinatal asphyxia: A pilot study in term neonates. Developmental Medicine and Child Neurology 45 (1) 17–23.	n = 25 Follow-up: 2 weeks	7 infants died. 13 infants (52%) had normal cerebral signal on MRI. Thrombocytopenia developed in 12 infants, including 7 with disseminated intravascular coagulation.	Larger studies included in table 2.
Eicher DJ, Wagner CL, Katikaneni LP et al. (2005) Moderate hypothermia in neonatal encephalopathy: Efficacy outcomes. Pediatric Neurology 32 (1) 11–17	n = 65 (RCT) Follow-up: 12 months	Death or severe motor disability at 12 months of age: cooled group: 52% (14/27), control group: 84% (21/25) [p = 0.019]	Larger studies included in table 2.
Eicher DJ, Wagner CL, Katikaneni LP et al. (2005) Moderate hypothermia in neonatal encephalopathy: Safety outcomes. Pediatric Neurology 32 (1) 18–24	n = 65 (RCT) Follow-up: 12 months	Cooled infants had a significantly higher incidence of bradycardia, requirements for plasma and platelet transfusions stridor, tremors and seizures and had lower heart rates during treatment. 1 infant had an acute drop in blood pressure which responded to treatment. 1 infant had a rebleed into a previous haemorrhage site (possibly related to the hyperthermia treatment).	Larger studies included in table 2.
Gebauer CM. (2006) Hemodynamics among neonates with hypoxic-ischemic encephalopathy during whole-body hypothermia and passive rewarming. Pediatrics 117: 843–850.	n = 7 Follow-up: not stated	Whole-body hypothermia resulted in reduced cardiac output, which reached normal levels at the end of passive rewarming.	Larger studies included in table 2.
Gunn AJ. (2008) Therapeutic Hypothermia Changes the Prognostic Value of Clinical Evaluation of Neonatal Encephalopathy. Journal of Pediatrics 152: 55–58.	n = 234 Follow-up: 4 days	Hypothermia did not affect severity of encephalopathy at day 4. In infants with moderate encephalopathy at day 4, those cooled had a higher rate of favorable outcome (31/45 infants, 69%, p = .006) compared with standard care (12/33, 36%).	Secondary analysis of a study included in table 2.
Gunn AJ, Gluckman PD, and	n = 22	There were no significant	More recent study

Gunn TR. (1998) Selective head cooling in newborn infants after perinatal asphyxia: a safety study. Pediatrics 102 (4 Pt 1) 885–892.	Follow-up: not stated	differences in the incidence of adverse events between the three groups of infants.	from same centre included in table 2.
Inder TE, Hunt RW, Morley C et al (2004) Randomized trial of systemic hypothermia selectively protects the cortex on MRI in term hypoxic-ischemic encephalopathy. Journal of Pediatrics 145 (6) 835–837.	n = 27 (RCT) Follow-up: not stated	Cooled infants had less cortical gray matter signal abnormality MRI (1 cooled infant, 8% vs 7/14 control infants, 50%); p = .036).	Larger studies included in table 2.
Kilani RA. (2002) The safety and practicality of selective head cooling in asphyxiated human newborn infants, a retrospective study. Journal Medical Libanais 50: 17–22.	n = 14 (+ 12 controls) Follow-up: not stated	No significant differences in adverse effects between the groups.	Larger studies included in table 2.
Lin Z-L, Yu H-M, Lin J et al. (2006) Mild hypothermia via selective head cooling as neuroprotective therapy in term neonates with perinatal asphyxia: An experience from a single neonatal intensive care unit. Journal of Perinatology 26 (3) 180-184.	n = 58 (RCT) Follow-up: 10 days	Signs of moderate to severe encephalopathy on computed tomography scan at 5 to 7 days: 13% (4/30) of cooled infants vs 64% (18/28) of control infants (p < 0.01)	Larger studies included in table 2.
Rutherford MA. (2005) Mild hypothermia and the distribution of cerebral lesions in neonates with hypoxic-ischemic encephalopathy. Pediatrics 116: 1001–1006.	n = 34 (+ 52 controls) Follow-up: not stated	Cooling was not associated with unexpected or unusual cerebral lesions and the prevalence of intracranial hemorrhage was similar across study groups. Cooling was associated with a decrease in basal ganglia and thalamic lesions (which are predictive of abnormal outcome).	Larger studies included in table 2.
Schulzke SM, Rao S, Patole SK. (2007) A systematic review of cooling for neuroprotection in neonates with hypoxic ischemic encephalopathy - Are we there yet? BMC Pediatrics 7 (30).	Systematic review n = 5 RCTs (552 infants) Follow-up: 18–22 months	Outcomes in cooled infants vs controls: Death or disability: RR: 0.78, 95% CI: 0.66–0.92) Death: RR: 0.75, 95% CI: 0.59–0.96 Neurodevelopmental disability aged 18-22 months: RR: 0.72, 95% CI: 0.53–0.98	Another systematic review of the same studies is included in table 2.
Shah PS. (2007) Hypothermia to treat neonatal hypoxic ischemic encephalopathy: Systematic review. Archives of Pediatrics and Adolescent Medicine 161 (10) 951-958.	Systematic review n = 8 RCTs (safety), 4 RCTs, 497 infants (efficacy)	Outcomes in cooled infants vs controls: Death or disability: RR: 0.76, 95% CI: 0.65–0.88) Death: RR: 0.74, 95% CI: 0.58–0.94	Another systematic review of 6 of the same studies is included in table 2.

	Follow-up: ≥ 12 months of age		
Shankaran S, Laptook A et al (2002) Whole-body hypothermia for neonatal encephalopathy: animal observations as a basis for a randomized, controlled pilot study in term infants. Pediatrics 110 (2 Pt 1) 377–385.	n = 19 (RCT) Follow-up: not stated	2 (22%) cooled died after life support was withdrawn. 3 (30%) control infants died (1 after life support was withdrawn) 43% (3/7) of cooled infants and 43% (3/7) of control infants had abnormal MRI at follow-up (44 week postmenstrual age).	Larger studies included in table 2.
Simbruner G. (1999) Induced brain hypothermia in asphyxiated human newborn infants: A retrospective chart analysis of physiological and adverse effects. Intensive Care Medicine 25 (10) 1111–1117.	n = 21 (+ 15 controls) Follow-up:	4 cooled infants (19%) and 4 control infants (27%) died (not significant). There was no significant difference in neurological score within the first 2 days of life between the groups.	Larger studies included in table 2.
Thoresen M. (2000) Cardiovascular changes during mild therapeutic hypothermia and rewarming in infants with hypoxic-ischemic encephalopathy. Pediatrics 106: 92–99.	n = 9 Follow-up: not stated	Cooling reduces heart rate and increases blood pressure (but not hazardously).	Larger studies included in table 2.
Whitelaw A and Thoresen M. (2001) Clinical experience with therapeutic hypothermia in asphyxiated infants. Developmental Medicine & Child Neurology - Supplemental 86: 30–31.	n = 9 Follow-up: not stated	Same study population and conclusion as previous study.	Larger studies included in table 2.
Wyatt JS. (2007) Determinants of outcomes after head cooling for neonatal encephalopathy. Pediatrics 119: 912–921.	n = 218 Follow-up: 18 months	n/a	Another study reporting on the same infants and outcomes is included in table 2 (Gluckman et al 2005).
Zanelli SA, Naylor M, Dobbins N et al. (2008) Implementation of a 'hypothermia for HIE' program: 2-year experience in a single NICU. Journal of Perinatology 28 (3) 171–175.	n = 21 Follow-up: not stated	4 infants (19%) died in the first 4 days after birth after ventilatory support was withdrawn. 15 infants (71%) had EEG-defined moderate or severe encephalopathy at 1–3 days of age. 5 infants (23%) had abnormal MRI at 3–24 months follow-up.	

Appendix B: Related NICE guidance for therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury

There is currently no NICE guidance related to this procedure.

Appendix C: Literature search for therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury

Database	Date searched	Version searched
Cochrane Library	02/04/2008	Issue 1, 2008
CRD databases (DARE & HTA)	02/04/2008	Issue 1, 2008
Embase	02/04/2008	1980 to 2008 Week 13
Medline	02/04/2008	1950 to March Week 3 2008
Premedline	02/04/2008	April 01, 2008
CINAHL	03/04/2008	1982-present
British Library Inside Conferences	-	-
NRR	-	2007 Issue 2
Controlled Trials Registry	02/04/2008	-

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 exp Hypoxia-Ischemia, Brain/
2 Fetal Hypoxia/
3 Asphyxia Neonatorum/
4 Anoxia/
5 Apgar Score/
6 Respiratory Distress Syndrome, Newborn/
7 exp Brain Injuries/
8 (brain$ adj3 injur$).tw.
9 (anoxi$ or anoxemia$ or hypoxi$ or hypoxemia$ or asphyxi$ or encephalopath$).tw.
10 (apgar$ adj3 scor$).tw.
11 (respirator$ adj3 distres$ syndrom$).tw.
12 or/1-11
13 exp Hypothermia, Induced/
14 Cryotherapy/
15 (Therapeut$ adj3 hypother$).tw.
16 (cool$ adj3 (brain$ or body$ or head$ or neonatal$)).tw.
17 (cool$ adj3 (cap$ or blanket$ or mattress$)).tw.

18	(hypotherm$ adj3 induc$).tw.
19	cryothera$.tw.
20	or/13-19
21	Infant, Newborn/
22	(infant$ adj3 newbor$).tw.
23	Perinat$.tw.
24	neonat$.tw.
25	(Fetus$ or Fetal$ or Foetus$ or Foeta$).tw.
26	or/21-25
27	12 and 20 and 26
28	Animals/
29	Humans/
30	28 not (28 and 29)
31	27 not 30