Cooling for newborns with hypoxic ischaemic encephalopathy (Review)

Jacobs SE, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG

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[Intervention Review]

Cooling for newborns with hypoxic ischaemic encephalopathy

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ABSTRACT

Background

Newborn animal studies and pilot studies in humans suggest that mild hypothermia following peripartum hypoxia-ischaemia in newborn infants may reduce neurological sequelae without adverse effects.

Objectives

To determine the effect of therapeutic hypothermia in encephalopathic asphyxiated newborn infants on mortality, long-term neurodevelopmental disability and clinically important side effects.

Search strategy

The standard search strategy of the Neonatal Review Group as outlined in The Cochrane Library (Issue 2, 2007) was used. Randomised controlled trials evaluating therapeutic hypothermia in term newborns with hypoxic ischaemic encephalopathy were identified by searching the Oxford Database of Perinatal Trials, the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2007), MEDLINE (1966 to June 2007), previous reviews including cross-references, abstracts, conferences, symposia proceedings, expert informants and journal hand searching.

Selection criteria

Randomised controlled trials comparing the use of therapeutic hypothermia with standard care in encephalopathic newborn infants with evidence of peripartum asphyxia and without recognisable major congenital anomalies were included. The primary outcome measure was death or long-term major neurodevelopmental disability. Other outcomes included adverse effects of cooling and 'early' indicators of neurodevelopmental outcome.

Data collection and analysis

Three review authors independently selected, assessed the quality of and extracted data from the included studies. Authors were contacted for further information. Meta-analyses were performed using relative risk and risk difference for dichotomous data, and weighted mean difference for continuous data with 95% confidence intervals.

Main results

Eight randomised controlled trials were included in this review, comprising 638 term infants with moderate/ severe encephalopathy and evidence of intrapartum asphyxia. Therapeutic hypothermia resulted in a statistically significant and clinically important reduction in the combined outcome of mortality or major neurodevelopmental disability to 18 months of age [typical RR 0.76 (95% CI 0.65, 0.89), typical RD -0.15 (95% CI -0.24, -0.07), NNT 7 (95% CI 4, 14)]. Cooling also resulted in statistically significant reductions in mortality [typical RR 0.74 (95% CI 0.58, 0.94), typical RD -0.09 (95% CI -0.16, -0.02), NNT 11 (95% CI 6, 50)] and in neurodevelopmental disability in survivors [typical RR 0.68 (95% CI 0.51, 0.92), typical RD -0.13 (95% CI -0.23, -0.03)]. Some adverse effects of hypothermia included an increase in the need for inotrope support of borderline significance and a significant increase in thrombocytopaenia.

Authors' conclusions

There is evidence from the eight randomised controlled trials included in this systematic review (n = 638) that therapeutic hypothermia is beneficial to term newborns with hypoxic ischaemic encephalopathy. Cooling reduces mortality without increasing major disability in survivors. The benefits of cooling on survival and neurodevelopment outweigh the short-term adverse effects. However, this review comprises an analysis based on less than half of all infants currently known to be randomised into eligible trials of cooling. Incorporation of data from ongoing and completed randomised trials (n = 829) will be important to clarify the effectiveness of cooling and to provide more information on the safety of therapeutic hypothermia, but could also alter these conclusions. Further trials to determine the appropriate method of providing therapeutic hypothermia, including comparison of whole body with selective head cooling with mild systemic hypothermia, are required.

PLAIN LANGUAGE SUMMARY

Cooling for newborns with hypoxic ischaemic encephalopathy

There is evidence that induced hypothermia (cooling) of newborn babies who may have suffered from a lack of oxygen at birth reduces death or disability, without increasing disability in survivors. This means that parents should expect that cooling will decrease their baby's chance of dying, and that if their baby survives, cooling will decrease his/her chance of major disability. A lack of oxygen before and during birth can destroy cells in a newborn baby's brain. The damage caused by the lack of oxygen continues for some time afterwards. One way to try and stop this damage is to induce hypothermia - cooling the baby or just the baby's head for hours to days. This treatment may reduce the amount of damage to brain cells. This review found that there is evidence from trials to show that induced hypothermia helps to improve survival and development at 18 months for term newborn babies at risk of brain damage. The results of ongoing trials may or may not confirm these favourable results. More research is also needed on the different methods of cooling.

BACKGROUND

In technically developed countries, peripartum asphyxia affects 3 - 5 per 1000 live births with subsequent moderate or severe hypoxic ischaemic encephalopathy (HIE) in 0.5 - 1 per 1000 live births (Levene 1986). HIE is a major problem worldwide as 10 - 60% of affected infants die, and at least 25% of survivors have long-term neurodevelopmental sequelae (Vannucci 1990). There are no specific treatments proven to decrease brain damage from HIE. Hypothermia is a clinically feasible manoeuvre that may improve the outcome of neonates with HIE.

Recent clinical and experimental studies have demonstrated that neuronal death occurs in two phases following a reversible hypoxic-ischaemic global insult (Gluckman 1992; Lorek 1994; Penrice 1996). If the insult is severe, there may be immediate 'primary neuronal death' related to cellular hypoxia with exhaustion of the cell's high energy stores (primary energy failure). After a latent period of at least six hours, the secondary phase of 'delayed neuronal death' begins (Williams 1991). The mechanisms involved in delayed neuronal death include hyperaemia, cytotoxic oedema, mitochondrial failure, accumulation of excitotoxins, active cell death (analogous to developmental apoptosis), nitric oxide synthesis, free radical damage and cytotoxic actions of activated microglia (Inder 2000). The delayed phase is associated with encephalopathy and increased seizure activity, and accounts for a significant proportion of the final cell loss even after very severe insults.

In term infants with evidence of intrapartum hypoxia and moderate to severe encephalopathy, magnetic resonance spectroscopy studies are consistent with this biphasic model of neuronal death. These studies demonstrate normal cerebral oxidative metabolism shortly after birth followed by 'secondary energy failure', the degree of which predicts outcome (mortality and neurodevelopmental outcome at both one and four years of age) (Roth 1997; Roth 1992). Therefore, a therapeutic 'window of opportunity' exists in the interval following resuscitation of the asphyxiated newborn before the secondary phase of impaired energy metabolism and injury.

There are a number of postulated mechanisms by which hypothermia may be neuroprotective. Hypothermia may modify cells programmed for apoptosis, leading to their survival. In neonatal piglets, 12 hours of mild hypothermia after resuscitation significantly decreased the number of apoptotic cells, but not the number of necrotic cells (Edwards 1995). Hypothermia may also protect neurons by reducing cerebral metabolic rate, attenuating the release of excitatory amino acids (glutamate, dopamine), ameliorating the ischaemia-impaired uptake of glutamate and lowering production of toxic nitric oxide and free radicals (Globus 1995).

Several term and preterm animal experimental models have demonstrated that a reduction in brain temperature of 2 - 3 degrees Celsius immediately following a hypoxic-ischaemic insult reduces energy expenditure, improves subsequent performance testing and/or reduces histological neuronal loss (Laptook 1994; Laptook 1997; Thoresen 1995; Gunn 2001). In the term fetal lamb, a significant reduction in histological neuronal loss was seen with extradural temperatures below 35 degrees Celsius (Gunn 1997a). Temperature modelling calculations also suggest that lowering an infant's core temperature to below 35 degrees Celsius is required to produce any reduction in the deep brain temperature (Van Leeuwen 2000).

For many decades, deep hypothermia to less than 28 degrees Celsius has been shown to be valuable for neuroprotection during cardiac arrest for open-heart and neurosurgical procedures. There are three Cochrane systematic reviews of the effect of systemic cooling on outcome of human adults following head injury (Alderson 2004), acute stroke (Correia 1999) and coronary artery bypass surgery (Rees 2001). There is currently no evidence from randomised controlled trials or these systematic reviews to support the use of hypothermia for treatment of either head injury or acute stroke, or for prevention of neurological injury after coronary artery bypass surgery. In addition, hypothermia may be harmful by increasing the risk of sepsis (Alderson 2004), as well as perioperative myocardial dysfunction and mortality (Rees 2001).

Mild hypothermia appears to be well tolerated in a variety of experimental animal models, as well as in adult human studies (Gunn 1997b, Thoresen 1995; Thoresen 1996; Haaland 1997; Marion 1997). There were no reported serious adverse effects in four pilot studies of hypothermia in human newborns (Gunn 1998; Azzopardi 2000; Thoresen 2000; Shankaran 2002). Adverse effects, such as sinus bradycardia, increased blood pressure and increased oxygen requirement, were all transient and reversible with rewarming (Thoresen 2000).

Therapeutic hypothermia aims to lower the temperature of the vulnerable deep brain structures, the basal ganglia, to 32 - 34 degrees Celsius. Two methods are being evaluated in newborn infants with HIE: whole body cooling and selective head cooling with mild systemic hypothermia. The rationale for selective head cooling is that the newborn infant's brain produces 70% of total body heat and that systemic hypothermia may be physiologically harmful to the sick neonate. Therefore, the adverse effects of systemic cooling may be minimised by selectively cooling the brain more than the body (Gunn 1998). However, a theoretical modelling of cooling investigating temperature distribution within the neonatal head found that the only situation that resulted in a significant reduction in deep brain temperature was when the core body temperature was lowered to 34 degrees Celsius, implying that it is necessary to reduce systemic temperature to achieve deep brain cooling (Van Leeuwen 2000). Whole body cooling relies on core body and deep brain temperatures being similar.

Identification of infants with hypoxic-ischaemic brain injury at risk of future disability who may benefit from hypothermia is challenging. It may be particularly difficult to distinguish between encephalopathy secondary to intrapartum hypoxia and that related to antepartum factors (Badawi 1998a; Badawi 1998b) or underlying congenital abnormalities not easily recognisable at birth (Felix 2000). Recent newborn animal and adult human studies are consistent with the potential for rescue hypothermia being greatest following moderate, rather than severe, hypoxic-ischaemic insults (Marion 1997; Haaland 1997). Aspects of cooling therapy that remain controversial include: how soon after the insult or birth does cooling need to be started, what level of hypothermia is required, what method (selective head cooling vs. whole body cooling) should be used and what is the duration of cooling required.

Effective therapies are urgently required to prevent neurosensory impairment following peripartum asphyxia. This systematic review reviews the evidence to determine whether therapeutic hypothermia reduces adverse outcome in encephalopathic asphyxiated newborn infants.

OBJECTIVES

To determine the effect of therapeutic hypothermia on death and long-term neurodevelopmental disability, and to ascertain clinically important side effects in newborn infants with HIE.

Secondary objectives include assessment of the adverse effects of cooling and effects on early prognostic indicators of adverse outcome. Subgroup analyses were planned on the basis of:

1. Severity of HIE (mild, moderate, severe) (Sarnat 1976; Finer 1981)

2. Inclusion criteria:

a) Preterm (< 35 weeks gestation) vs. term or near-term (≥ 35 weeks gestation)

b) Electrophysiological plus clinical criteria vs. clinical criteria alone

3. Timing of commencement of intervention (< 3 hours vs. 3 - 6 hours vs. > 6 hours)

4. Method of cooling (whole body vs. selective head cooling with mild systemic hypothermia)

5. Degree of cooling [core temperature (or surrogate eg rectal temperature) ≤ 34.5 vs. > 34.5 degrees Celsius]

6. Duration of cooling (≤ 48 hours vs. > 48 hours)

7. Quality of outcome assessment [high quality (> 18 months with formal psychological testing and review by developmental paediatrician for diagnosis of cerebral palsy) vs. lower quality].

METHODS

Criteria for considering studies for this review

Types of studies

All randomised and quasi-randomised studies comparing the use of therapeutic hypothermia with standard care were included.

Types of participants

1. Newborn infants
2. Evidence of peripartum asphyxia, with each enrolled infant satisfying at least one of the following criteria:
a) Apgar score of 5 or less at 10 minutes
b) Mechanical ventilation or resuscitation at 10 minutes
c) Cord pH < 7.1, or an arterial pH < 7.1 or base deficit of 12 or more within 60 minutes of birth
3. Evidence of encephalopathy according to Sarnat staging (Sarnat 1976; Finer 1981):
a) Stage 1 (Mild): hyperalertness, hyper-reflexia, dilated pupils, tachycardia, absence of seizures.
b) Stage 2 (Moderate): lethargy, hyper-reflexia, miosis, bradycardia, seizures, hypotonia with weak suck and Moro.
c) Stage 3 (Severe): stupor, flaccidity, small to midposition pupils which react poorly to light, decreased stretch reflexes, hypothermia and absent Moro.
4. No major congenital abnormalities recognisable at birth

Types of interventions

Cooling (whole body or selective head cooling) vs. no cooling (standard care).

Types of outcome measures

The primary outcome measure was death or long-term (> 18 months) major neurodevelopmental disability [cerebral palsy, developmental delay (Bayley or Griffith assessment more than 2 SD below the mean) or intellectual impairment (IQ more than 2 SD below mean), blindness (vision < 6/60 in both eyes), sensorineural deafness requiring amplification].
Secondary outcomes included:
1. Each component of the primary outcome:
a) Mortality
b) Major neurodevelopmental disability
c) Cerebral palsy
d) Developmental delay or intellectual impairment
e) Blindness
f) Sensorineural deafness requiring amplification
2. The incidence of adverse effects of cooling:
a) Heart rate
i) Sinus bradycardia (heart rate < 80/minute)
ii) Prolonged QT interval
iii) Arrhythmia requiring medical intervention and/or cessation of cooling
b) Blood pressure
i) Hypotension (mean arterial pressure < 40 mmHg)
ii) Need for inotrope support
c) Full blood examination
i) Anaemia (Hb<100 g/L ± Hct < 30)
ii) Leukopaenia (WCC < 5 x 10^9/L)
iii) Thrombocytopaenia (platelet count < 150 x 10^9/L)
d) Coagulation
i) Any coagulopathy
ii) Coagulopathy resulting in major thrombosis or haemorrhage
e) Hypoglycaemia (< 2.6 mmol/L)
f) Hypokalaemia (< 3.5 mmol/L)
g) Elevated lactate (number > 2 mmol/L)
h) Renal impairment
i) Urea (maximum mean ± SD)
ii) Creatinine (maximum mean ± SD)
iii) Oliguria (less than 1 ml/kg/hour)
i) Culture proven sepsis (positive blood, CSF or bladder tap urine culture)
3. 'Early' indicators of neurodevelopmental outcome:

a) Severity of encephalopathy (Sarnat staging) (Sarnat 1976; Finer 1981)
b) Severity of electroencephalogram (EEG) abnormality:
i) Severe: isoelectric or burst-suppression pattern
ii) Moderate: low voltage or discontinuous background
iii) Mild: electrographic seizures, dysmaturity
c) Seizures (and number of anticonvulsants)
d) Diffusion weighted imaging (DWI) on early MRI (< day 4)
e) Basal ganglia, posterior limb of internal capsule (PLIC) and/or white matter (WM) injury, parasagittal neuronal necrosis on late MRI (> day 4).
f) Standardised neurological assessment day seven (Dubowitz 1998)
g) Days to full sucking feeds

Search methods for identification of studies

The standard search strategy of the Neonatal Review Group as outlined in The Cochrane Library (Issue 2, 2007) was used. This included searches of the Oxford Database of Perinatal Trials, the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2007), MEDLINE {Silver Platter - 1966 to June, 2007: Infant, Newborn (explode) [MeSH heading] and Asphyxia (explode) [MeSH heading] or Hypoxic Ischaemic Encephalopathy and Hypothermia (explode) [MeSH heading]}, previous reviews including cross-references, abstracts, conferences, symposia proceedings, expert informants and journal hand searching. No language restrictions were applied.

Data collection and analysis

This systematic review followed the Cochrane Collaboration methodology according to guidelines of the Neonatal Review Group. Three review authors independently identified the studies to be included, assessed the quality of the studies and extracted the data. Methodological quality assessment was based on 1) blinding of randomisation, 2) blinding of intervention, 3) completeness of follow-up and 4) blinding of outcome measurement. When necessary, additional information and clarification of published data was requested from the authors of individual trials. Meta-analyses were performed using the fixed effects model. Relative risk (RR) and risk difference (RD) were calculated for dichotomous data and weighted mean difference (WMD) for continuous data, with 95% confidence intervals (CI) for all analyses. The number needed to treat (NNT) and associated 95% CI were determined for a statistically significant reduction in the RD. Heterogeneity was examined using the I squared test.
Outcome data are reported and analysed in this review for all randomised participants with known outcomes. Those with missing outcome data are excluded from analysis. For the primary outcome, death or major disability, a sensitivity analysis was performed to allow for the additional uncertainty arising from missing outcome data (Gamble 2005).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.
Eight randomised controlled trials met inclusion criteria for this review (Gunn 1998; Shankaran 2002; ICE 2002; Akisu 2003; Eicher 2005; Gluckman 2005; Shankaran 2005; Lin 2006). Six were performed as pilot studies, three in single centres [New Zealand (Gunn 1998), Turkey (Akisu 2003) and China (Lin 2006)] and the others at multiple centres in Australia (ICE 2002) and North America (Shankaran 2002; Eicher 2005). Two large multicentred randomised controlled trials have been published, one international (Gluckman 2005) and the other from the NICHD network in North America (Shankaran 2005).
All eight trials included term newborn infants with moderate or severe encephalopathy and evidence of intrapartum hypoxia-ischaemia without obvious congenital abnormalities.
Infants in all studies were randomised with initiation of the intervention by six hours of age [mean age at entry range: 1.9 hours (Akisu 2003) to 4.6 hours (Gluckman 2005)]. Four studies used head cooling devices in conjunction with whole body cooling (Gunn 1998; Akisu 2003; Gluckman 2005; Lin 2006), while the other four used whole body cooling alone (Shankaran 2002; ICE 2002; Eicher 2005; Shankaran 2005). The duration of hypothermia was 72 hours in all but one study that cooled infants for 48 hours (Eicher 2005). Six studies rewarmed infants by 0.5 degrees Celsius per hour with the rewarming period of four hours (Akisu 2003; Eicher 2005; Gluckman 2005; Gunn 1998; Shankaran 2002; Shankaran 2005), one study rewarmed infants by 0.5 degrees Celsius every second hour with a duration of 8 hours for rewarming (ICE 2002) and one study allowed infants to rewarm spontaneously at room temperature, such that rewarming took up to 12 hours (Lin 2006).
Mortality was ascertained up to latest follow-up in all studies, ranging from 10 days of age (Lin 2006), to hospital discharge (Shankaran 2002; ICE 2002; Akisu 2003) or to neurodevelopmental assessment at 12 months (Eicher 2005) or 18 - 22 months (Gunn 1998; Gluckman 2005; Shankaran 2005). Decisions to withdraw care were reported to precede death in five trials (ICE 2002, Shankaran 2002, Eicher 2005, Shankaran 2005, Lin 2006). Gunn, Gluckman and Shankaran (2005) presented short and long-term outcomes to 18 - 22 months, but Shankaran (2002), ICE, Akisu and Lin reported short-term morbidity to 10 days of age or discharge from hospital. Eicher reported both short-term morbidity and 12 month neuromotor outcome.

One trial reported industry sponsorship (Gluckman 2005); Olympic Medical (Seattle, WA, USA) provided financial and administrative support and equipment and monitored data for accuracy but was not involved in study design, data interpretation or publication. In the other included studies, there was no disclosure of sponsorship from industry.

Gunn 1998 reported the short-term medical outcomes of 22 term infants with hypoxic ischaemic encephalopathy (10 controls randomized to normothermia and 12 randomised to hypothermia) in a randomised controlled pilot study (Gunn 1998). The first six randomised hypothermic infants received minimal cooling (36.0 - 36.5C, n = 6) and then the next six mild cooling (35.5 - 35.9C, n = 6) as part of this 'safety' study. The study continued and the 18 month outcome of these 22 infants, together with a further 18 infants [nine randomised (three normothermic controls, with six allocated to hypothermia to 34.5 - 35.4C) and nine non-randomised (two controls, seven cooled to 34 - 35C)] were reported in a subsequent publication (Battin 2001). The combined results of the 31 randomised infants (13 normothermic controls, 18 allocated to hypothermia) are presented (Gunn 1998), with individual patient data provided by the authors. The non-randomised patients were not included in this review. There was one further report of short-term medical outcomes arising from these studies that included the 13 randomised control infants with six infants randomised to 34.5 - 35.4C and the seven non-randomised infants at 34 - 35C (Battin 2003). For the purpose of this systematic review, all randomised infants in the various reports (Gunn 1998; Battin 2001; Battin 2003) are included in the study referred to as Gunn 1998. This study did not report whether any infants had treatment withdrawn prior to death. Eighteen month neurodevelopmental outcome assessment using the BSID was performed by a psychologist blinded to treatment allocation. Neurodevelopmental outcomes were determined from Table 2 in Battin 2001, and comprised randomised infants (normothermia, numbers 1 - 13; hypothermia, numbers 16 - 33) ascertained from the author. Adverse neurodevelopmental outcome was defined by Gunn 1998 as BSID MDI or PDI < 70.

Shankaran 2002 reported the short-term medical outcomes to hospital discharge of 19 term infants with peripartum asphyxia and either seizures or moderate/ severe encephalopathy (Shankaran 2002). There were 10 controls and nine infants randomised to 34.5C by means of a servo-controlled cooling blanket. Withdrawal of care preceded three of five deaths (2/2 cooled and 1/3 standard care).

ICE 2002 reported short-term morbidity to hospital discharge of 17 near-term infants with moderate or severe encephalopathy and intrapartum hypoxia-ischemia with two of the following criteria: Apgar score $\leq$ 5 at 10 minutes, ongoing resuscitation with the need for ventilation at 10 minutes, cord or arterial blood gas within one hour of birth with pH < 7.1 and/or base deficit in excess of 12. Infants were excluded if they had congenital abnormalities, weighed < 2000 grams, required > 0.8 FiO2 or were considered to be 'in extremis' with death imminent (ICE 2002). Decisions to withdraw life support preceded all 4 deaths.

Akisu 2003 reported the short-term medical outcomes to discharge from hospital of 21 term infants with peripartum asphyxia and encephalopathy defined as stupor, hypotonia or abnormal neonatal reflexes. Eleven infants had their temperature lowered by cooling caps with cold water at 5 - 10C placed around the scalp for 72 hours. The left external auditory canal and rectal temperatures were monitored to maintain the external auditory canal temperature at 33 - 33.5C with the rectal temperature at 36 - 36.5C with the servo-mechanism of the radiant warmer. Ten control infants had their rectal temperature maintained at 36 - 36.5C with the servo-mechanism of radiant warmer. An additional seven non-randomised term control infants without asphyxia were not included in this review (Akisu 2003). Decisions to withdraw care were not reported.

In two consecutive publications, Eicher 2005 reported in-hospital morbidity with mortality and neurodevelopmental outcomes to 12 months of age in 53/65 (81.5%) near-term infants with peripartum hypoxia-ischaemia and encephalopathy (two of: posturing, seizures, autonomic dysfunction, or abnormalities of tone, reflexes or state of consciousness). Thirty-two infants had their temperature lowered by the initial application of ice to head and body for up to two hours that was then maintained at 32.5 - 33.5C (rectal) on a servo-controlled cooling blanket for 48 hours. Thirty-three control infants had their rectal temperature maintained at 36.5 - 37.5C by servo-controlled radiant warmer (Eicher 2005). Eighteen of 24 deaths were preceded by withdrawal of care (9/10 cooled and 9/14 standard care). Neurodevelopmental outcome was assessed using the BSID, CAT/CLAMS or Vineland examinations at 12 months of age by the developmental team blinded to study group assignment. Severe neuromotor disability was defined by Eicher 2005 as BSID PDI < 70. This study was considered to be of lower quality because the neurodevelopmental outcome assessment was at 12 months rather than 18 - 24 months.

Gluckman 2005 reported mortality and severe neuromotor disability to 18 months of age in 218/234 (93%) near-term infants born with evidence of peripartum hypoxia-ischaemia, moderate or severe encephalopathy or clinical seizures and moderate or severely abnormal background or seizures on amplitude integrated electroencephalography. One hundred and sixteen infants had their temperature lowered by head cooling by cooling cap (Olympic Medical Cool Care System) while receiving care on a radiant warmer servo-controlled to the infants' abdominal skin temperature adjusted to maintain the rectal temperature at 34 - 35C for 72 hours. One hundred and sixteen infants received standard care on the radiant warmer servo-controlled to infant's abdominal skin temperature that was adjusted to maintain rectal temperature at 36.8 - 37.2C (Gluckman 2005). This study did not report withdrawal of care in deaths. The 18 month neurodevelopmental assessment (neurological examination, visual and auditory assessment and BSID) was performed by certified staff and developmen-

tal psychologists blinded to treatment group assignment. Severe neurodevelopmental disability was defined by Gluckman 2005 as gross motor function (GMF) level 3 - 5, Bayley MDI < 70, or bilateral cortical visual impairment. In this review, we subtracted "died" from "died or severe disability at 18 months" as reported in Table 3 of Gluckman 2005 to obtain major neurodevelopmental disability.

Shankaran 2005, for the NICHD Neonatal Research Network, reported mortality and moderate/severe disability at 18 - 22 months in 205/208 (98.5%) term and near-term infants less than 6 hours of age with either (a) pH ≤ 7.0 or base deficit ≥ 16 mmol/L on cord blood or blood gas within one hour of birth, or (b) if no blood gas or if pH 7.01 - 7.15 mmol/L or base deficit 10 - 15.9 then additional criteria required: acute perinatal event (late or variable decelerations, cord prolapse, cord rupture, uterine rupture, maternal trauma, haemorrhage or cardiorespiratory arrest) AND either 10 minute Apgar score ≤ 5 or assisted ventilation initiated at birth and continued for at least 10 minutes and encephalopathy (on standardized neurologic examination by a certified examiner) or clinical seizures. Infants were excluded if they were unable to be enrolled by six hours of age, had major congenital abnormalities or growth restriction (birth weight ≤ 1800 grams), had consent refused by parent or neonatologist, or were moribund. One hundred and two infants were placed on a pre-cooled infant blanket (Blanketrol II Hyper-Hypothermia System, Cincinnati Sub-Zero) servo-controlled to oesophageal temperature of 33 - 34C for 72 hours; a second blanket was included in the cooling system to diminish oesophageal temperature variability. One hundred and six infants received standard care with skin temperature servo-controlled to abdominal skin temperature 36.5 - 37C (Shankaran 2005). Withdrawal of care preceded death in 39 of the 62 deaths (12/24 cooled and 27/38 standard care). Trained developmental examiners blinded to treatment group assignment performed the 18 - 22 month neurodevelopmental assessment of growth, vision, hearing, neurologic examination and development using the BSID. Severe disability was defined by Shankaran 2005 as any of the following: GMF level 3 - 5, Bayley MDI <70, hearing impairment requiring hearing aids, or blindness. As a component of their primary outcome, Shankaran 2005 reported "moderate or severe disability." However, as shown in Table 4 of Shankaran 2005, among the 45 and 64 cooled and control infants who died or had moderate or severe disability, 43 and 62 respectively either died or had MDI < 70 at followup at 18 - 22 months. Thus, the vast majority of survivors, if not all, who met the Shankaran 2005 criteria for moderate or severe disability in fact had severe disability by their definition. We used the numbers reported by Shankaran 2005 for moderate or severe disability to define major neurodevelopmental disability in this review.

Lin 2006 reported short-term outcomes to 10 days of age including mortality, moderate to severe brain injury on CT scan and neurobehavioural assessment. Thirty-two infants had their temperature lowered by a cooling cap device (Tianyuan Scientific Development Inc. Changchun, China) shielded under radiant warmer with output to maintain rectal temperature at 34 - 35C for 72 hours. The 30 infants who received standard care had intermittent measurement of their rectal temperature, although the target temperature was not stated. Aspects of the medical treatment were standardized such that all infants received prophylactic phenobarbitone (loading and maintenance) and dopamine (5 mcg/kg/min) throughout the 72 hour study period (Lin 2006). Decisions to withdraw life support preceded the four deaths.

Four of the nine excluded trials were observational case series without controls (Azzopardi 2000; Debillon 2003; Thoresen 2000; Horn 2006). Three others were retrospective cohort studies with historical controls (Simbruner 1999; Compagnoni 2002; Kilani 2002; Lista 2004). Another 'randomised' study did not describe the method of allocation and did not report any of our prespecified outcomes (Zhou 2002).

One further randomised controlled trial comprising 157 infants (88 cooled, 69 control) awaits further assessment (Shao 2006). This study was published in conference proceedings and attempts to obtain further information from the authors were unsuccessful.

There are at least three other randomised controlled trials of whole body cooling in term infants with HIE that have completed recruitment (ICE; nnn-Hypothermia; TOBY). These include 672 term infants with HIE who are currently being followed and will be assessed at 18 - 24 months of age. Therefore, there are a further 829 term infants with HIE to be included in future updates of this review.

Risk of bias in included studies

The method of randomisation/allocation concealment in six studies was achieved by means of computer generated numbers either in opaque sealed envelopes (Gunn 1998; ICE 2002; Gluckman 2005) or obtained centrally from a Data Coordinating Centre (Shankaran 2002; Shankaran 2005) or web-based system (Eicher 2005). In one study, the method of randomisation and allocation concealment may have been adequate, but details of the computer generated randomisation protocol was unclear (Akisu 2003). Allocation concealment was inadequate in one study (Lin 2006) because it used quasi-randomisation by odd or even day of admission. Following randomisation of 31 infants, Gunn et al obtained ethics approval to sequentially cool a further seven non-randomised infants who are not included in this review (Battin 2001). A further seven non-randomised control term infants without asphyxia in one study were also not included in this review (Akisu 2003).

Due to the nature of the intervention, the care-givers in these trials could not be blinded. Importantly, no study reported that the assessors of short-term outcomes were blinded to treatment allocation; this may have resulted in ascertainment bias. Short-term follow-up was complete in all studies. Neurodevelopmental outcome to 12 months was incomplete (81.5%) in one trial (Eicher 2005). Longer-term neurodevelopmental outcomes (18 - 22 months)

were reported in 100% (Gunn 1998), 93% (Gluckman 2005) and 98% (Shankaran 2005) of survivors, with masking of neurodevelopmental outcome assessors to study group assignment (Gunn 1998; Eicher 2005; Gluckman 2005; Shankaran 2005). The quality of the neurodevelopmental outcome assessment was considered to be high in three studies that followed survivors to at least 18 months of age (Gunn 1998; Gluckman 2005; Shankaran 2005) and lower in the study that had incomplete follow up to 12 months (Eicher 2005).

Effects of interventions

Six hundred and thirty-eight near-term infants with moderate or severe encephalopathy and evidence of intrapartum asphyxia were enrolled in eight randomised controlled trials to determine the effect of therapeutic hypothermia on mortality (Gunn 1998; Shankaran 2002; ICE 2002; Akisu 2003; Eicher 2005; Gluckman 2005; Shankaran 2005; Lin 2006), short-term medical (Gunn 1998; Shankaran 2002; ICE 2002; Akisu 2003; Eicher 2005; Gluckman 2005; Shankaran 2005) and longer-term neurodevelopmental outcomes (Gunn 1998; Eicher 2005; Gluckman 2005; Shankaran 2005).

THERAPEUTIC HYPOTHERMIA VS. STANDARD CARE (ALL INFANTS) (COMPARISON 01)

Death or major neurodevelopmental disability in survivors assessed (Tables 01.01, 01.02):

Death or major neurodevelopmental disability in survivors assessed by quality of follow-up (Table 01.01):

Data which permitted the assessment of the effect on this composite outcome were available from four trials (Gunn 1998; Eicher 2005; Gluckman 2005; Shankaran 2005). There was a total of 506 participants, of whom 287 either died or had major neurodevelopmental disability at follow-up assessment. Two of the trials (Shankaran 2005; Eicher 2005) found a significant reduction in the incidence of death or major neurodevelopmental disability in the hypothermia groups. Meta-analysis of all four trials found a significant reduction in death or major neurodevelopmental disability in survivors [typical RR 0.76 (95% CI 0.65, 0.89), typical RD -0.15 (95% CI -0.24, -0.07), NNT 7 (95% CI 4, 14)]. There was no evidence of heterogeneity (I squared 0%). In the three trials with high quality follow-up (Gunn 1998; Gluckman 2005; Shankaran 2005), the reduction in death or major disability was statistically significant [typical RR 0.79 (95% CI 0.67, 0.93), typical RD -0.13 (95% CI -0.22, -0.04), NNT 8 (95% CI 4, 25)]. The effect was also significant in the one trial with lower quality follow-up (Eicher 2005).

Data were missing for the primary outcome for this review, death or major disability, in a few participants in three trials: Eicher 2005 (5 cooled, 8 control), Gluckman 2005 (8 cooled, 8 control), Shankaran 2005 (0 cooled, 3 control). After allowing for uncertainty due to these missing outcome data (Gamble 2005), the reduction in the risk of death or major disability was maintained: uncertainty interval for risk difference -0.24, -0.04 (data not shown).

Death or major disability in survivors assessed by method of cooling (Table 01.02):

Meta-analysis of the two trials that used selective head cooling with mild systemic hypothermia (Gunn 1998; Gluckman 2005) failed to show a statistically significant effect [typical RR 0.85 (95% CI 0.69, 1.05), typical RD -0.09 (95% CI -0.21, 0.03)] . Meta-analysis of the two trials (Eicher 2005; Shankaran 2005) that used whole body cooling demonstrated a significant reduction in death or disability in the hypothermia groups [typical RR 0.69 (95% CI 0.55, 0.86), typical RD -0.21 (95% CI -0.33, -0.09)]. There was no evidence of heterogeneity of effect (I squared 0%).

Mortality by method of cooling (Table 01.03):

Eight trials reported on mortality (Gunn 1998; Shankaran 2002; ICE 2002; Akisu 2003; Eicher 2005; Gluckman 2005; Shankaran 2005; Lin 2006). There were 638 infants and 185 deaths in total. Only one of the trials (Shankaran 2005) found a statistically significant effect, a reduction in mortality in the hypothermia group. The meta-analysis of all eight trials demonstrated a significant reduction in mortality in the hypothermia groups [typical RR 0.74 (95% CI 0.58, 0.94), typical RD -0.09 (95% CI -0.16, -0.02), NNT 11 (95% CI 6, 50)]. The effect was consistent across trials, with no important heterogeneity (I squared 0%).

Meta-analysis of the four trials (Gunn 1998; Akisu 2003; Gluckman 2005; Lin 2006) that used selective head cooling with mild systemic hypothermia did not show a statistically significant effect on mortality [typical RR 0.83 (95% CI 0.59, 1.16), typical RD -0.05 (95% CI -0.14, 0.04)]. However, meta-analysis of the four trials that used whole body cooling (ICE 2002; Shankaran 2002; Eicher 2005; Shankaran 2005) demonstrated a significant reduction in mortality in the hypothermia groups [typical RR 0.66 (95% CI 0.47, 0.93), typical RD -0.13 (95% CI -0.23, -0.02); NNT 8 (95% CI 4, 50)]. This effect was consistent within this group, with no important heterogeneity (I squared 0%).

Major neurodevelopmental disability (Tables 01.04 - 01.06):

Major neurodevelopmental disability by quality of follow-up (Table 01.04):

Four trials reported on neurodevelopmental disability (Gunn 1998; Eicher 2005; Gluckman 2005; Shankaran 2005). There were 506 randomized infants with known outcomes, of whom 117 had major neurodevelopmental disability. The meta-analysis failed to show a statistically significant effect [typical RR 0.79 (95% CI 0.57, 1.09), typical RD -0.05 (95% CI -0.13, 0.02)]. There was no evidence of heterogeneity of effect (I squared 0%).

Major neurodevelopmental disability in survivors assessed by quality of follow-up (Table 01.05):

Four trials reported effect on this outcome (Gunn 1998; Eicher 2005; Gluckman 2005; Shankaran 2005). There was a total of 336 survivors with neurodevelopmental follow-up, of whom 117 had major neurodevelopmental disability. Meta-analysis of all four

trials demonstrated a significant reduction in major neurodevelopmental disability among survivors in the hypothermia groups [typical RR 0.68 (95% CI 0.51, 0.92), typical RD -0.13 (95% CI -0.23, -0.03)]. There was mild heterogeneity of treatment effect (I squared 9%). Among the three trials with high quality follow-up (Gunn 1998; Gluckman 2005; Shankaran 2005), there was a significant reduction in major neurodevelopmental disability in the hypothermia groups [typical RR 0.73 (95% CI 0.53, 0.99), RD -0.11 (95% CI -0.22, -0.01)]. In the one trial with lower quality follow-up (Eicher 2005) there was a also significant reduction in major disability in the hypothermia group.

Major neurodevelopmental disability in survivors assessed by method of cooling (Table 01.06):

Meta-analysis of the two trials that used selective head cooling with mild systemic hypothermia (Gunn 1998; Gluckman 2005) failed to show a statistically significant effect [typical RR 0.77 (95% CI 0.51, 1.17), typical RD -0.09 (95% CI -0.24, 0.05)]. However, meta-analysis of the two trials that used whole body cooling (Eicher 2005; Shankaran 2005) demonstrated a significant reduction in major neurodevelopmental disability among survivors in the hypothermia groups [typical RR 0.60 (95% CI 0.40, 0.92), typical RD -0.17 (95% CI -0.31, -0.03)]. There was mild heterogeneity of treatment effect in these two trials (I squared 16%).

Cerebral palsy in survivors assessed by method of cooling (Table 01.07):

Three trials reported effect on this outcome (Gunn 1998; Gluckman 2005; Shankaran 2005). There was a total of 306 survivors, of whom 90 had cerebral palsy. Meta-analysis of the three trials showed no significant effect of hypothermia on cerebral palsy [typical RR 0.74 (95% CI 0.52, 1.05), typical RD -0.09 (95% CI -0.19, 0.01)].

Neuromotor delay in survivors assessed (Table 01.08-01.10):

Four trials reported effect on neuromotor outcome (Gunn 1998; Eicher 2005; Gluckman 2005; Shankaran 2005) . There was a total of 311 survivors, of whom 111 had neuromotor delay on the PDI more than 2 SD below the mean using the BSID. Meta-analysis of the four trials demonstrated a reduction in neuromotor delay on PDI in the hypothermia groups that was of borderline statistical significance [typical RR 0.73 (95% CI 0.53, 1.00), typical RD -0.10 (95% CI -0.21, 0.00)]. There was no evidence of heterogeneity of effect (I squared 0%). Neuromotor delay in survivors assessed was not significant when only high quality studies were analysed [typical RR 0.79 (95% CI 0.56, 1.11), typical RD -0.08 (95% CI -0.18, 0.03)].(TABLE 01.08).

Meta-analysis of the two trials that used selective head cooling with mild systemic hypothermia (Gunn 1998; Gluckman 2005) failed to show a statistically significant effect [typical RR 0.81(95% CI 0.51, 1.29), typical RD -0.07 (95%CI -0.22, 0.08)]. Also, meta-analysis of the two trials that used whole body cooling (Eicher 2005; Shankaran 2005) did not demonstrate a statistically significant reduction in neuromotor disability in the hypothermia groups [typical RR 0.66 (95% CI 0.42, 1.02), typical RD -0.14 (95% CI -0.28, 0.01)]. There was mild heterogeneity of treatment effect (I squared 8%) (TABLE 01.09).

Two trials comprising 158 survivors reported effect on neuromotor delay in survivors assessed on the PDI using the BSID (Gunn 1998; Shankaran 2005). Meta-analysis demonstrated no significant difference in mean PDI in the hypothermic groups [WMD 0.76 (95% CI -5.15, 6.68)] (TABLE 01.10).

Developmental delay in survivors assessed (Table 01.11-01.13):

Four trials reported developmental delay or intellectual impairment (Gunn 1998; Eicher 2005; Gluckman 2005; Shankaran 2005). There was a total of 319 survivors, of whom 100 had developmental delay on MDI more than 2 SD below the mean using the BSID. Meta-analysis of the four trials failed to show a statistically significant effect in the hypothermia groups [typical RR 0.74 (95% CI 0.53, 1.02), typical RD -0.10 (95% CI -0.20, 0.01)]. Meta-analysis of the three high quality trials (Gunn 1998; Gluckman 2005; Shankaran 2005) also failed to show a statistically significant effect in cooled infants [RR 0.76 (95% CI 0.54, 1.06), RD -0.09 (95% CI -0.20, 0.02)] (TABLE 01.11).

Meta-analysis of the two trials that used selective head cooling with mild systemic hypothermia (Gunn 1998; Gluckman 2005) failed to show a statistically significant effect [typical RR 0.86 (95% CI 0.54, 1.36), typical RD -0.05 (95% CI -0.19, 0.10)]. Meta-analysis of the two trials that used whole body cooling (Eicher 2005; Shankaran 2005) demonstrated a reduction in developmental delay on MDI in the hypothermia groups that was of borderline statistical significance [typical RR 0.64 (95% CI 0.41, 1.00), typical RD -0.14 (95% CI -0.28, 0.00)] (TABLE 01.12).

Two trials reported the effect of hypothermia on mental development in 158 survivors assessed on MDI using the BSID (Gunn 1998; Shankaran 2005). Meta-analysis demonstrated no significant difference in mean MDI in the hypothermic groups [WMD 1.93 (95% CI -4.16, 8.03)] (TABLE 01.13).

Blindness in survivors assessed (Table 01.14):

Four trials reported effect of hypothermia on this visual outcome (Gunn 1998; Eicher 2005; Gluckman 2005; Shankaran 2005). There was a total of 328 survivors, of whom 35 were legally blind. Meta-analysis of the four trials showed no significant effect of hypothermia on the visual outcome of blindness [typical RR 0.57 (95% CI 0.30, 1.08), typical RD -0.06 (95% CI -0.13, 0.01)].

Sensorineural hearing loss requiring amplification (Table 01.15):

Four studies reported effect on this auditory outcome (Gunn 1998; Eicher 2005; Gluckman 2005; Shankaran 2005). There was a total of 314 survivors, of whom 17 had sensorineural hearing loss requiring amplification. Meta-analysis showed no significant effect of hypothermia on aided sensorineural hearing loss [typical RR 0.93 (95% CI 0.37, 2.34), typical RD 0.00 (95% CI -0.06, 0.05)].

Cardiovascular adverse effects (Table 01.16-01.18):

Five trials reported effect on heart rate (Gunn 1998; Akisu 2003; Eicher 2005; Gluckman 2005; Shankaran 2005). There was a total of 552 infants, of whom 26 had a sinus bradycardia below 80/minute. Meta-analysis of the five trials demonstrated significantly increased sinus bradycardia in hypothermia groups [typical RR 5.96 (95% CI 2.15, 16.49), typical RD 0.07 (95% CI 0.04, 0.11)] (TABLE 01.16).

Five trials reported the effect of hypothermia on the need for blood pressure support with inotropes (Gunn 1998; ICE 2002; Shankaran 2002; Gluckman 2005; Shankaran 2005). There was a total of 505 infants, of whom 266 required inotrope support for hypotension. Meta-analysis of the five trials demonstrated an increase in hypotension treated with inotropes in hypothermia groups that was of borderline significance [typical RR 1.17 (95% CI 1.00, 1.38), typical RD 0.08 (0.00, 0.17)] (TABLE 01.17).

Six trials reported effect of hypothermia on cardiac arrhythmia requiring medical intervention and/or cessation of cooling (Gunn 1998; ICE 2002; Akisu 2003; Eicher 2005; Gluckman 2005; Shankaran 2005). There was a total of 569 infants, of whom 2 had an arrhythmia requiring medical intervention. Meta-analysis of the six trials failed to demonstrate a significant effect of hypothermia on arrhythmia requiring medical treatment in hypothermic groups [typical RR 1.04 (95% CI 0.07, 16.39), typical RD 0.00 (-0.02, 0.02)] (TABLE 01.18).

Haematological adverse effects (Table 01.19-0.22):

Three trials reported the effect of hypothermia on anaemia requiring blood transfusion (Gunn 1998; Eicher 2005; Gluckman 2005). There was a total of 322 infants, of whom 39 were transfused for anaemia. Meta-analysis of the three trials failed to show significant effect of hypothermia on anaemia requiring blood transfusion [typical RR 1.16 (95% CI 0.67, 2.04), typical RD 0.02 (95% CI -0.05, 0.09)] (TABLE 01.19).

Two trials reported the effect of hypothermia on white cell count (Gunn 1998; Gluckman 2005). There was a total of 254 infants, of whom 6 had leukopaenia with a white cell count below 5 x 10^9/L. Meta-analysis of the two trials failed to show significant effect of hypothermia on the incidence of leukopaenia [typical RR 0.97 (95% CI 0.22, 4.33), typical RD 0.00 (95% CI -0.04, 0.04)] (TABLE 01.20).

Four trials reported the effect of hypothermia on platelet count (Gunn 1998; Eicher 2005; Gluckman 2005; Shankaran 2005). There was a total of 531 infants, of whom 124 were thrombocytopaenic with platelet count below 150 x 10^9/L. Meta-analysis of the four trials showed statistically significantly increased thrombocytopaenia in the hypothermic groups [typical RR 1.55 (95% CI 1.14, 2.11), typical RD 0.09 (95% CI 0.03, 0.15)] (TABLE 01.21).

Four trials reported the effect of hypothermia on coagulopathy resulting in major thrombosis or haemorrhage (Gunn 1998; ICE 2002; Gluckman 2005; Shankaran 2005). There was a total of 486 infants, of whom 14 had severe coagulopathy. Meta-analysis of the four trials failed to show significant effect on severe coagulopathy in cooled infants [typical RR 0.83 (95% CI 0.31, 2.24), typical RD -0.01 (95% CI -0.03, 0.02)] (TABLE 01.22).

Metabolic adverse effects (Table 01.23-0.24):

Four trials reported the effect of hypothermia on glucose homeostasis (Gunn 1998, Akisu 2003; Gluckman 2005; Shankaran 2005). There was a total of 490 infants, of whom 73 were hypoglycaemic with a blood glucose below 2.6 mmol/L. Meta-analysis of the four trials failed to show significant hypoglycaemia in hypothermic groups [typical RR 0.83 (95% CI 0.54, 1.27), typical RD -0.03 (95% CI -0.09, 0.03)] (TABLE 01.23).

Three trials reported the effect of hypothermia on serum potassium (Gunn 1998; Eicher 2005; Gluckman 2005). There was a total of 323 infants, of whom 175 had hypokalaemia with a serum potassium below 3.5 mmol/L. Meta-analysis of the three trials showed no statistically significant difference in the incidence of hypokalaemia in cooled infants [typical RR 1.03 (95% CI 0.85, 1.25), typical RD 0.02 (95% CI -0.09, 0.12)] (TABLE 01.24).

Renal impairment (Table 01.25):

Five trials reported the effect of hypothermia on urine output (Gunn 1998; ICE 2002; Shankaran 2002; Gluckman 2005; Shankaran 2005). There was a total of 505 infants, of whom 147 had oliguria with urine output below 1 mL/kg/hour. Meta-analysis of the five trials showed no statistically significant difference in rate of oliguria in cooled infants [typical RR 0.81 (95% CI 0.59, 1.12), typical RD -0.05 (95% CI -0.12, 0.03)].

Sepsis (Table 01.26):

Five trials reported the effect of hypothermia on sepsis (Gunn 1998; Akisu 2003; Eicher 2005; Gluckman 2005; Shankaran 2005). There were a total of 552 infants, of whom 28 had culture proven sepsis. Meta-analysis of the five trials failed to show a significant effect of hypothermia on sepsis [typical RR 0.86 (95% CI 0.42, 1.76), typical RD -0.01 (-0.04, 0.03)].

Short-term neurological outcomes (Table 01.27):

Five trials reported the effect of hypothermia on clinically recognized seizures (Gunn 1998; ICE 2002; Shankaran 2002; Akisu 2003; Gluckman 2005). There were a total of 322 infants, of whom 220 had clinically recognized seizures. Meta-analysis of five trials failed to show a significant effect of therapeutic hypothermia on the incidence of clinically recognized seizures [typical RR 0.96 (95% CI 0.84, 1.10), typical RD -0.03 (95% CI -0.12, 0.07)]. Other short-term neurological outcomes have not been reported, including MRI, standardised neurological assessment and days to full sucking feeds.

In summary, there was a borderline significant negative effect of hypothermia on the need for inotrope support and a significant increase in thrombocytopaenia with a platelet count below 150 x 10^9/L. There was no significant effect of hypothermia on other short term adverse outcomes or on neurological status as defined by the incidence of clinically recognized seizures in the first three days of life. Analysis of many secondary outcomes planned for this review were unable to be performed because they were not reported in the included trials. Many planned subgroup analyses

on the basis of gestation, timing of commencement of cooling, as well as the degree and duration of cooling and rewarming were still unable to be performed because of lack of eligible data.

THERAPEUTIC HYPOTHERMIA VS. STANDARD CARE (INFANTS WITH SEVERE ENCEPHALOPATHY) (COMPARISON 02)

Death or major disability in survivors assessed (Table 02.01):
Three trials reported the effect of hypothermia on this composite outcome (Gunn 1998; Gluckman 2005; Shankaran 2005). There was a total of 153 infants with severe encephalopathy, of whom 122 died or survived with major neurodevelopmental disability. Meta-analysis of the three trials found a significant reduction in death or major neurodevelopmental disability in survivors [typical RR 0.80 (95% CI 0.68, 0.94), typical RD -0.18 (95% CI -0.31, -0.05), NNT 6 (95% CI 3, 20)].

Mortality (Table 02.02):
Three trials reported the effect of hypothermia on mortality in infants with severe encephalopathy (Gunn 1998; Gluckman 2005; Shankaran 2005). There was a total of 153 infants with severe encephalopathy, of whom 82 died. One trial (Gluckman 2005) found a significant reduction in the cooled group. Meta-analysis of the three trials found a significant reduction in mortality in infants with severe encephalopathy [typical RR 0.72 (95% CI 0.56, 0.94), typical RD -0.20 (95% CI -0.35, -0.04), NNT 5 (95% CI 3, 25)].

Major disability in survivors assessed (Table 02.03):
Three trials reported the effect of hypothermia on neurodevelopmental disability in survivors assessed (Gunn 1998, Gluckman 2005; Shankaran 2005). There was no significant effect of cooling on disability in the 62 survivors who had severe encephalopathy [typical RR 0.69 (95% CI 0.42, 1.13); typical RD -0.19 (95% CI -0.44, 0.07)].

THERAPEUTIC HYPOTHERMIA VS. STANDARD CARE (INFANTS WITH MODERATE ENCEPHALOPATHY) (COMPARISON 03)

Death or major disability in survivors assessed (Table 03.01):
Three trials reported the effect of hypothermia on this composite outcome (Gunn 1998; Gluckman 2005; Shankaran 2005). There was a total of 278 infants with moderate encephalopathy, of whom 124 died or survived with major neurodevelopmental disability. Meta-analysis of the three trials found a reduction in death or major neurodevelopmental disability in survivors that was of borderline statistical significance [typical RR 0.76 (95% CI 0.58, 1.00), typical RD -0.12 (95% CI -0.23, 0.00)].

Mortality (Table 03.02):
Three trials reported the effect of hypothermia on mortality in infants with moderate encephalopathy (Gunn 1998; Gluckman 2005; Shankaran 2005). There was a total of 278 infants with moderate encephalopathy, of whom 52 died. Meta-analysis of the three trials failed to show a significant effect on mortality in cooled infants with moderate encephalopathy [typical RR 0.79 (95% CI 0.49, 1.29), typical RD -0.04 (95% CI -0.14, 0.05)].

Major disability in survivors assessed (Table 03.03):
Three trials reported the effect of hypothermia in infants with moderate encephalopathy on neurodevelopmental disability in survivors assessed (Gunn 1998; Gluckman 2005; Shankaran 2005). There were 226 survivors with moderate encephalopathy, of whom 72 had major neurodevelopmental disability. Meta-analysis of the three trials did not demonstrate any significant effect on disability among survivors who had moderate encephalopathy [typical RR 0.71 (95% CI 0.48, 1.05); typical RD -0.11 (95% CI -0.23, 0.01)].

DISCUSSION

This systematic review demonstrates that therapeutic hypothermia for term newborn infants with moderate or severe hypoxic ischaemic encephalopathy results in a reduction in the composite outcome of mortality or long-term neurodevelopmental disability to 18 months of age. This result is both statistically significant and clinically important, with a relative risk reduction of 24%, absolute risk reduction of 15% and NNT of 7. To prevent one death or major disability, one would need to treat as many as 14 infants or as few as four infants. This reduction in death or major disability remains significant in the subgroup analysis for severe encephalopathy (NNT 6, as many as 20 infants or as few as three infants), and is of borderline significance for moderate encephalopathy. In the overall analysis, the effects on each component contributing to the composite outcome (death, major neurodevelopmental disability in survivors) are also statistically significant and clinically important. These results are consistent across the four trials that measured the effect on death or major disability (I squared 0%). Overall, the methodology of the included studies is strong. This is particularly true of the two largest studies (Gluckman 2005; Shankaran 2005) that contributed most of the weight to the pooled analysis.

An important outcome of this review is that cooling decreases mortality, without increasing major neurodevelopmental disability in survivors. Among all treated infants, there is a significant reduction in mortality (analysis 01.03) with a statistically insignificant trend towards a decrease in major disability (analysis 01.04). The upper limit on the RD confidence interval shows that the most pessimistic view would be that any increase in major disability among a population of similar babies treated with hypothermia is unlikely to be more than 2%. In addition, major neurodevelopmental disability is significantly reduced in survivors (analysis 01.05). Therefore, cooling reduces mortality and if an infant survives, also decreases his/her chance of major disability.

Several limitations of the available evidence should be noted. By clinical necessity, the caretakers could not be blinded to the intervention. Even so, in each of the four trials that assessed the effect of cooling on major neurodevelopmental disability, assessors of

neurodevelopment were blinded to treatment group assignment. The effect of treatment group on mortality could be biased by the unblinded intervention if it resulted in fewer decisions by caretakers to withdraw intensive care in cooled babies. However, the finding that major neurodevelopmental disability was not increased in survivors who had been cooled does not support this speculation.

In the overall analyses, the number of infants studied is substantial; the estimates of treatment effect on the primary outcome, death or major neurodevelopmental disability, and on each component of this composite outcome, were reasonably precise. However, these estimates of treatment effect were less precise in subgroup analyses based on degree of encephalopathy, method of cooling, and quality of follow-up. The better method of cooling may remain uncertain until selective head cooling and whole body cooling are directly compared in clinical trials.

Reporting of many of the secondary outcomes specified in our original protocol is not adequate to assess adverse outcomes or safety. More cooled infants had significant thrombocytopaenia. The increased treatment of hypotension with inotropes in cooled infants was of borderline significance.

Cautious application of the results of this meta-analysis is recommended. Trials contributing participants to this meta-analysis were conducted within strict protocols and often at centres of excellence with considerable experience in therapeutic hypothermia.

There are at least three ongoing randomised controlled trials of whole body cooling in term infants with HIE (n = 672) (ICE; nnn-Hypothermia; TOBY) and one awaiting assessment (n = 157) (Shao 2006). The results of this review are based on 638 infants, fewer than half the number of patients known to have been randomized into eligible trials. Incorporation of the results of these trials comprising an additional 829 infants into future updates of this review could alter the present results and conclusions.

AUTHORS' CONCLUSIONS

Implications for practice

There is evidence from the eight randomised controlled trials (n = 638) included in this systematic review that therapeutic hypothermia is beneficial to term newborns with hypoxic ischaemic encephalopathy. Death or major disability, mortality and in neurodevelopmental disability in survivors are all reduced. Importantly, mortality is reduced without increasing major disability in survivors. While there is also some evidence of harm from therapeutic hypothermia, increased thrombocytopaenia and hypotension, the benefits of cooling on survival and neurodevelopment outweigh these short-term adverse effects.

It is important to note that this review comprises an analysis based on less than half of all infants currently known to be randomised into eligible trials of cooling. Careful follow-up of all infants from another four ongoing randomised trials (n = 829) and incorporation of data will clarify the effectiveness and safety of cooling. This additional data could potentially alter the results and modify these conclusions.

Implications for research

Further well designed and executed studies with appropriate power are required to determine the most appropriate method of providing therapeutic hypothermia. These studies should compare whole body with selective head cooling with mild systemic hypothermia, and evaluate simpler methods of cooling, earlier initiation of cooling, the most appropriate method and duration of rewarming and hypothermia combined with adjunctive therapies.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Akisu 2003

Methods	Single center RCT in Turkey. Blinding of randomisation: Unclear, stated by computer generated protocol number and method of concealment not specified. Blinding of intervention: Not possible. Blinding of outcome measurement: Unclear if outcome assessors blinded to treatment allocation. Follow-up: complete to discharge.
Participants	21 term infants with peripartum asphyxia [5 minute Apgar score below 6, with acidosis on cord or arterial blood shortly after delivery (pH < 7.1 or base deficit > 10mmol/L) and encephalopathy] without congenital abnormality (metabolic, malformations, chromosomal, congenital infection)or transitory drug depression.
Interventions	Hypothermia: Temperature lowered in 11 infants by cooling cap for 72 hours (left external auditory canal temperature lowered to 33-33.5C and rectal temperature maintained at 36-36.5C by servomechanism of radiant warmer). Standard therapy: 10 infants had rectal temperature maintained at 36-36.5C by servomechanism of radiant warmer.
Outcomes	Primary outcome: Platelet-activating factor in CSF. Secondary outcomes included adverse effects of hypothermia (bradycardia, arrhythmia, hypotension, renal impairment, hypoglycaemia, sepsis, thrombocytopaenia)and short-term outcome to discharge from hospital (mortality, length of hospital stay, seizures, abnormal EEG, abnormal cranial ultrasound and CT scan).
Notes	Age at initiation of cooling included (1.9 hours), but not age at randomisation for infants allocated to standard care. 7 non-randomised control term infants without asphyxia not included in review. Not stated if death followed decision to withdraw care.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Eicher 2005

Methods	Multicentred RCT in US. Blinding of randomisation: Adequate, with web-based centralized online blocked randomization. Blinding of intervention: Not possible. Blinding of outcome measurement: Caregivers not blinded to treatment assignment, but assessors of neurodevelopment at 12 months were. Follow-up: Assessment of short-term outcomes nearly complete (62/65), but incomplete 12 month assessment (53/65 = 81%).
Participants	Includes 65 infants >=35 weeks gestation, >2000 grams birth weight, who were <=6 hours of age with >= one clinical sign of a hypoxic-ischaemic insult [cord gas <=7.0 or base deficit >=13, initial infant gas pH < 7.1, Apgar score <=5 at 10 minutes, continued resuscitation after 5 minutes, fetal bradycardia lasting >= 15 minutes, or postnatal hypoxic ischaemic event with oxygen desaturation <70% or arterial oxygen tension < 35 mmHg for 20 minutes with evidence of ischaemia (chest compressions, hypotension, haemorrhage)] and two features of neonatal encephalopathy (posturing, seizures, autonomic dysfunction, or abnormalities of tone, reflexes or state of consciousness). Infants excluded with sepsis at birth (2 infants allocated to standard care), maternal chorioamnionitis, birth weight or head circumference <10th centile for gestational age, or congenital abnormalities.
Interventions	Hypothermia: Temperature lowered in 32 infants by application of ice to head and body for up to 2 hours and then maintained at 32.5-33.5C (rectal) on a servo-controlled cooling blanket for 48 hours. Control infants: 33 had rectal temperature maintained at 36.5-37.5C by servo-controlled radiant warmer.
Outcomes	Efficacy and safety outcomes published in 2 consecutive reports: death or 12 month neurodevelopmental outcome (Bayley MDI and PDI , CAT/CLAMS or Vineland assessments)and short-term adverse effects of cooling (coagulopathy, cardiac arrhthymias, persistent metabolic acidosis, sepsis/pneumonia within the first 7 days of life, hypokalemia, necrotizing enterocolitis, skin injury, extension of intracranial hemorrhage, persistent pulmonary hypertension of the newborn, and treatment with ECMO).
Notes	Randomised at 3.1 (standard care)/3.4 (hypothermia)hours. Rewarmed by 0.5C per hour after 48 hours. Considered to be lower quality study as only 12 month neuromotor outcome reported. In addition, follow up was incomplete (81%) and only composite outcome of death or severe neuromotor impairment was reported. 3 infants were excluded after randomisation, with no data available. Denominators are 31 for both groups as reported by authors. Of 24 deaths, 18 followed withdrawal of support (9 cooled, 9 standard care). Additional information provided by authors for age at randomisation, all short-term adverse effects, and neurodevelopmental outcome at 12 months (but not according to apriori definition as per review).

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Gluckman 2005

Methods	Multi-centred international RCT. Blinding of randomization: Adequate, with block randomisation by pregenerated computer numbers in opaque sealed envelopes stratified by participating centre. Blinding of intervention: Not possible, with care givers aware of treatment allocation. Blinding of outcome measurement: Uncertainty about masking of short-term outcome assessors, but assessors of 18 month neurodevelopmental outcome masked to treatment group assignment. Follow up: 18 month follow-up in 218/234 (93%).
Participants	234 infants born at >=36 weeks gestation WITH clinical evidence of peripartum hypoxia-ischaemia [Apgar score <=5 at 10 minutes, continued need for resuscitation at 10 minutes, or severe acidosis (pH <7 or base deficit >=16 in cord blood or arterial/venous blood within 60 minutes of birth)] AND moderate or severe encephalopathy (Sarnat criteria) or clinical seizures AND moderate or severely abnormal background or seizures on amplitude integrated electroencephalography. Excluded infants were older than 5.5 hours at randomisation, or had received prophylactic anticonvulsants, or had major congenital abnormalities, or had head trauma, or had severe growth restriction (<1800 grams birth weight), or were considered too critically unwell to benefit from intensive care, or equipment was unavailable, or were planned to participate in other trials.
Interventions	Hypothermia (n=116): head cooling by cooling cap (Olympic Medical Cool Care System) on a radiant warmer servo-controlled to infant's abdominal skin temperature adjusted to maintain rectal temperature at 34-35C for 72 hours. Control treatment (n=118): radiant warmer servo-controlled to infant's abdominal skin temperature adjusted to maintain rectal temperature at 36.8-37.2C.
Outcomes	Primary: combined frequency of mortality and severe neurodevelopmental disability in survivors at 18 months of age (Gross motor function 3-5; MDI <70 or bilateral cortical visual impairment). Secondary: adverse events in first 7 days of life including mortality, arrhythmia, hypotension, coagulopathy, abnormal renal function, hyponatraemia, hypokalaemia, bone marrow depression, abnormal liver function, metabolic acidosis.
Notes	Randomised at 4.6 hours. Rewarmed at no more than 0.5C per hour. Sponsored by Olympic Medical who funded study, supplied all equipment including amplitude integrated EEG monitors and provided administrative support. Scientific advisory committee responsible for other aspects of design, data analysis and publication. Later report of primary outcome by severity of encephalopathy at randomisation. Not stated if deaths followed withdrawal of care. Additional information provided by authors on short-term morbidity (prolonged QT interval, hypotension treated with inotropes, anaemia, leukopaenia, thrombocytopaenia, oliguria), short-term neurological outcomes (severity of HIE, seizures, anticonvulsant therapy) and long-term neurodevelopmental outcome (according to severity of HIE, cerebral palsy, BSID PDI and MDI, confirmation of major neurodevelopmental disability in 23 cooled and 31 control infants).

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Gunn 1998

Methods	Single centred RCT in New Zealand. Blinding of randomisation: Adequate, with randomisation by sequential computer generated numbers in opaque sealed envelopes. Blinding of intervention: Not possible. Blinding of outcome measurement: Uncertainty as to whether outcome assessors blinded to treatment allocation for both short and some long-term outcomes, but 18 month psychological assessment was blinded. Follow-up: Assessment complete for short-term outcomes and long-term follow-up.
Participants	Includes infants randomised in the report of Gunn 1998, and additional infants randomised in the reports of Battin 2001 and Battin 2003, ie 31 term infants with perinatal asphyxia (5 minute Apgar score <=6 AND cord/first arterial pH <=7.09 AND encephalopathy)without major congenital abnormality.
Interventions	Hypothermia: Temperature lowered in 18 infants by cooling cap for 72 hours. Sequential randomisation of rectal temperature to 36.0-36.5C (n=6), then to 35.5-35.9C (n=6), then to 34.5-35.4C (n=6). Control infants: 13 infants had rectal temperature maintained 36.8-37.2C with servo controlled radiant warmer.
Outcomes	Acute adverse effects of hypothermia/complications of asphyxia (seizures, hypoglycaemia, acidosis, hypotension, sinus bradycardia, arrhythmia, persistent pulmonary hypertension, sepsis, thrombocytopaenia, renal impairment, hyponatraemia, hypokalaemia), 18 month mortality and neurodevelopmental disability on Bayley MDI and PDI.
Notes	40 infants reported, with 31 randomised. Non randomised infants (7 cooled to 34-35C, 2 controls) not included in review. Randomised at 3.8 hours (standard care)/ 4.4 hours (hypothermia)after birth. Not stated if deaths followed withdrawal of care. Additional data provided from author for short-term outcomes

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

ICE 2002

Methods	Multicentred pilot study in Australia. Blinding of randomisation: Adequate, with randomisation by sequential computer generated numbers in opaque sealed envelopes, stratified by centre. Blinding of intervention: Not possible with caregivers not blinded to treatment assignment. Blinding of outcome measurement: Assessors of short-term outcomes not blinded. Follow-up: Complete to hospital discharge.
Participants	17 infants >=35 weeks with moderate or severe encephalopathy AND intrapartum hypoxia-ischemia (two of: Apgar score <=5 at 10 minutes, ongoing resuscitation with the need for ventilation at 10 minutes, cord or arterial blood gas within one hour of birth with pH < 7.1 and/or base deficit in excess of 12). Infants with obvious or suspected congenital abnormalities, or who weighed <2000 grams, or who required >80% FiO2 or were 'in extremis' with death imminent were excluded.

ICE 2002 (*Continued*)

Interventions	7 infants cooled by being exposed to the ambient environment (turning radiant warmer off) with Hot/Cold gel packs at 10C as required to maintain rectal temperature at 33.5-34.5C for 72 hours. The 10 standard care infants rectal temperature was maintained at 36.5-37.5C.
Outcomes	Primary outcome was the feasibility of method of cooling. Secondary outcomes were the adverse effects, including mortality, severity of encephalopathy, seizures, hypotension, arrhythmias, coagulopathy, renal impairment, hepatic dysfunction.
Notes	Enrolled and randomised at 3.9 hours. Rewarming by 0.5C every 2 hours. Four deaths all followed decisions to withdraw support.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Lin 2006

Methods	Single centre study in China. Blinding of randomization: Inadequate, quasi-randomised (alternate day allocation according to odd or even day of admission). Blinding of intervention: Not possible. Blinding of outcome measurement: Unable to assess. Follow-up incomplete: Analysis not intention to treat, and followed to 10 days of age.
Participants	62 consecutive term infants with peripartum hypoxia-ischaemia (Apgar <6 at 5 minutes with first postnatal arterial pH <7.10 or base deficit >15) and clinical encephalopathy quasi-randomised within 6 hours of birth. Infants with major congenital abnormalities and severe hypoxia were excluded.
Interventions	32 infants cooled by cooling cap device shielded under radiant warmer with output to maintain rectal temperature at 34-35C for 72 hours. The 30 standard care infants had intermittent measurement of rectal temperature - target temperature not stated. All infants received prophylactic phenobarbitone (loading and maintenance)and dopamine (5 mcg/kg/min) throughout 72 hour study period.
Outcomes	Mortality, neuroimaging (CT scan) and neurobehavioural assessment.
Notes	Only trial to rewarm spontaneously at room temperature. Enrolled at 3.6 (hypothermia)/3.8 (standard care) hours. Four deaths all followed withdrawal of care.

Risk of bias

Item	Authors' judgement	Description

Lin 2006 (*Continued*)

Allocation concealment?	No	C - Inadequate

Shankaran 2002

Methods	Multicentred RCT in NICHD centres in US. Blinding of randomisation: Adequate, with centralised randomisation generated by random, permuted block algorithm with block sizes of 2 and 4 and stratified by centre. Blinding of intervention: Not possible, with care givers not blinded to treatment assignment. Blinding of outcome measurement: Uncertainty as to whether outcome assessors blinded to treatment allocation for short-term outcomes. Follow-up: complete to hospital discharge.
Participants	19 term infants less than 6 hours of age with peripartum asphyxia [either (a) Blood gas within one hour of birth with pH <=7.0 or BE >=-16 OR (b) if no blood gas or if pH 7.01-7.15 or BE 10-15.9 then acute perinatal event (late or variable decelerations resulting in caesarean section, cord prolapse, placental abruption, uterine rupture, maternal trauma or maternal respiratory arrest)] AND seizures or moderate/severe encephalopathy.
Interventions	Hypothermia: 9 cooled to 34.5C (oesophageal)for 72 hours with servo controlled cooling blanket. Control: 10 infants had abdominal skin temperature servo controlled to 36.5 C via radiant warmer.
Outcomes	Adverse effects of hypothermia (hypotension requiring inotrope, persistent pulmonary hypertension, renal failure, hepatic dysfunction), including mortality. In addition length of stay and discharge neurological status (gavage feeding, abnormal examination, anticonvulsants for seizures, abnormal MRI).
Notes	Randomised at mean of 4.1 hours after birth. 3 of 5 deaths followed withdrawal of care.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Shankaran 2005

Methods	Multi-centred randomised controlled trial within NICHD network in the US. Blinding of randomization: Adequate with centralised randomisation by telephone by data-coordinating centre, stratified by centre and generated by random, permuted block algorithm. Blinding of intervention: Not possible. Blinding of outcome measurement: Uncertain if short-term outcome assessors blinded to treatment allocation, but all neurologic and development examiners were. Follow-up: complete 18-22 month follow up in 205/208 (98.6%).
Participants	208 infants >=36weeks gestation less than 6 hours of age with either (a) pH <=7.0 or base deficit >=16mmol/L on cord blood or blood gas within one hour of birth OR (b) if no blood gas or if pH 7.01-7.15mmol/L or base deficit 10-15.9 then additional criteria required: acute perinatal event (late or variable decelerations,

Shankaran 2005 (*Continued*)

	cord prolapse, cord rupture, uterine rupture, maternal trauma, haemorrhage or cardiorespiratory arrest) AND either a 10 minute Apgar score <=5 or assisted ventilation initiated at birth and continued for at least 10 minutes AND encephalopathy (on standardized neurologic examination by a certified examiner) or seizures. Excluded infants were unable to be enrolled by 6 hours of age, had major congenital abnormalities or growth restriction (birth weight <=1800 grams), had consent refused by parent or neonatologist, or who were moribund.
Interventions	102 infants were placed on a precooled infant blanket (Blanketrol II Hyper-Hypothermia System, Cincinnati Sub-Zero) servo-controlled to oesophageal temperature of 33-34C for 72 hours. 106 infants received standard care with skin temperature servo-controlled to abdominal skin temperature 36.5-37C. All infants had abdominal and oesophageal temperature monitoring and were nursed on a radiant warmer.
Outcomes	Primary: death or moderate/ severe disability at 18-22 months according to Gross Motor Function Classification System, Bayley MDI and PDI, aided hearing loss or presence of persistent seizures (Moderate disability - BSID MDI 70-84 and at least one of: GMFCS 2, hearing impaired without amplification or persistent seizure disorder. Severe disability - BSID MDI <70, GMFCS 3-5, aided hearing loss or blindness). Secondary outcomes included adverse events during 72 hour intervention (cardiac arrhythmia, persistent acidosis, major thrombosis or bleeding, skin changes, death) and to hospital discharge (hypotension, PPHN, renal impairment, hepatic dysfunction, sepsis, hypoglycaemia, hypokalaemia, death, length of stay, feeding status and anticonvulsants at discharge).
Notes	Rewarming: 0.5C per hour. Randomisation at mean 4.3 hours of age. Reported primary outcome by severity of encephalopathy at randomisation. Of 62 deaths, 39 followed withdrawal of care (12/24 cooled, 27/38 standard care). Additional information provided by authors on short-term adverse effects (hypotension treated with inotropes, oliguria), death according to severity of HIE, long-term neurodevelopment (BSID PDI and MDI).

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Characteristics of excluded studies *[ordered by study ID]*

Azzopardi 2000	Case series (without controls)
Compagnoni 2002	Retrospective cohort study with historical controls
Debillon 2003	Case series (without controls)

(*Continued*)

Horn 2006	Case series reported from a pilot RCT that was discontinued when it became evident that modifications to the cooling technique were required
Kilani 2002	Retrospective cohort study with historical controls
Lista 2004	Retrospective cohort study with historical controls
Simbruner 1999	Retrospective cohort study with historical controls
Thoresen 2000	Case series (without controls)
Zhou 2002	Method of allocation not able to be determined, although described as 'random assignment'. No predefined outcomes for this review were reported.

Characteristics of ongoing studies *[ordered by study ID]*

ICE

Trial name or title	Infant Cooling Evaluation Trial (ICE): A randomised controlled trial of the effect of whole body cooling on the outcome of term infants with hypoxic ischaemic encephalopathy.
Methods	
Participants	Infants >=35 weeks with moderate or severe encephalopathy AND intrapartum hypoxia-ischemia (2 of: Apgar score <=5 at 10 minutes, need for ventilation at 10 minutes, cord or neonatal blood gas within one hour of birth with pH < 7.1 and/or base deficit in excess of 12).
Interventions	Hypothermia to 33-34 degrees celsius (rectal) by exposure to ambient environment (turning radiant warmer off) and Hot/Cold packs as required for 72 hours. Control infants temperature 36.7-37.3 C (rectal).
Outcomes	Primary: survival free of major neurodevelopmental disability at 2 years
Starting date	February 2001
Contact information	sue.jacobs@rwh.org.au
Notes	Sample size: 300 218 infants randomized when recruitment stopped on July 27 2007.

nnn-Hypothermia

Trial name or title	Induced systemic hypothermia in asphyxiated newborn infants
Methods	

nnn-Hypothermia (*Continued*)

Participants	Infants admitted to neo.nEuro.network centres >= 36 weeks gestation with severe birth asphyxia (one of: Apgar score <=5 at 10 minutes, ventilation at 10 minutes, ph< 7 or base deficit >= 16 within 60 minutes of birth) AND moderate to severe encephalopathy AND abnormal background or seizures on amplitude integrated EEG.
Interventions	Hypothermia: rectal temperature to 33-34 degrees celsius for 72 hours using a cooling mattress. Control: rectal temperature 37 degrees celsius.
Outcomes	Primary: survival at 18-21 months postnatal age free of severe neurodevelopmental handicap.
Starting date	March 2001
Contact information	georg.simbruner@i-med.ac.at
Notes	Sample size: 150 129 infants randomized when recruitment stopped on April 30 2006.

TOBY

Trial name or title	TOBY: Whole body hypothermia for the treatment of perinatal asphyxial encephalopathy
Methods	
Participants	Infants >= 36 weeks gestation with intrapartum asphyxia (one of: Apgar score <=5 at 10 minutes, ventilation at 10 minutes, ph< 7 or base deficit >= 16 within 60 minutes of birth) AND moderate to severe encephalopathy AND abnormal background or seizures on amplitude integrated EEG.
Interventions	Hypothermia: rectal temperature 33-34 degrees celsius for 72 hours using a cooling mattress. Control: rectal temperature 37 +/- 0.2 degrees celsius.
Outcomes	Primary: combined rate of mortality and severe neurodevelopmental impairment at 18 months.
Starting date	November 2002
Contact information	natal asphyxial encephalopathy Methods
Notes	Sample size: 236. This was later increased to 'around 400' to ensure adequate power for longer term outcomes, including IQ. 325 infants were enrolled when recruitment ended on November 30 2006.

DATA AND ANALYSES

Comparison 1. Therapeutic hypothermia versus standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or major disability in survivors assessed, by quality of follow-up	4	506	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.65, 0.89]
1.1 High quality follow-up at 18-22 months	3	454	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.67, 0.93]
1.2 Lower quality follow-up at 12 months	1	52	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.41, 0.92]
2 Death or major disability in survivors assessed, by method of cooling	4	506	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.65, 0.89]
2.1 Selective head cooling with mild systemic hypothermia	2	249	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.69, 1.05]
2.2 Whole body cooling	2	257	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.55, 0.86]
3 Mortality, by method of cooling	8	638	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.58, 0.94]
3.1 Selective head cooling with mild systemic hypothermia	4	332	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.59, 1.16]
3.2 Whole body cooling	4	306	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.47, 0.93]
4 Major neurodevelopmental disability, by quality of follow-up	4	506	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.57, 1.09]
4.1 High quality follow-up at 18-22 months	3	454	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.59, 1.16]
4.2 Lower quality follow-up at 12 months	1	52	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.18, 1.59]
5 Major neurodevelopmental disability in survivors assessed, by quality of follow-up	4	336	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.51, 0.92]
5.1 High quality follow-up at 18-22 months	3	308	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.53, 0.99]
5.2 Lower quality follow-up at 12 months	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.14, 0.97]
6 Major neurodevelopmental disability in survivors assessed, by method of cooling	4	336	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.51, 0.92]
6.1 Selective head cooling with mild systemic hypothermia	2	165	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.51, 1.17]
6.2 Whole body cooling	2	171	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.40, 0.92]
7 Cerebral palsy in survivors assessed, by method of cooling	3	306	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.52, 1.05]

7.1 Selective head cooling with mild systemic hypothermia	2	165	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.52, 1.22]
7.2 Whole body cooling	1	141	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.36, 1.18]
8 Neuromotor delay (BSID PDI more than 2 SD below mean) in survivors assessed, by quality of follow-up	4	311	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.53, 1.00]
8.1 High quality follow-up at 18-22 months	3	283	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.56, 1.11]
8.2 Lower quality follow-up at 12 months	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.14, 0.97]
9 Neuromotor delay (BSID PDI more than 2 SD below mean) in survivors assessed, by method of cooling	4	311	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.53, 1.00]
9.1 Selective head cooling with mild systemic hypothermia	2	147	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.51, 1.29]
9.2 Whole body cooling	2	164	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.42, 1.02]
10 Neuromotor development (BSID PDI) in survivors assessed	2	158	Mean Difference (IV, Fixed, 95% CI)	0.76 [-5.15, 6.68]
11 Developmental delay (BSID MDI more than 2 SD below mean) in survivors assessed, by quality of follow-up	4	319	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.53, 1.02]
11.1 High quality follow-up at 18-22 months	3	290	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.54, 1.06]
11.2 Lower quality follow-up at 12 months	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.19, 1.68]
12 Developmental delay (BSID MDI more than 2 SD below mean) in survivors assessed, by method of cooling	4	319	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.53, 1.02]
12.1 Systemic head cooling with mild systemic hypothermia	2	153	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.54, 1.36]
12.2 Whole body cooling	2	166	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.41, 1.00]
13 Mental development (BSID MDI) in survivors assessed	2	158	Mean Difference (IV, Fixed, 95% CI)	1.93 [-4.16, 8.03]
14 Blindness in survivors assessed, by method of cooling	4	328	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.30, 1.08]
14.1 Selective head cooling with mild systemic hypothermia	2	161	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.23, 1.37]
14.2 Whole body cooling	2	167	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.22, 1.43]
15 Deafness in survivors assessed, by method of cooling	4	314	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.37, 2.34]
15.1 Selective head cooling with mild systemic hypothermia	2	144	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.36, 5.72]
15.2 Whole body cooling	2	170	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.18, 2.31]

16 Sinus bradycardia	5	552	Risk Ratio (M-H, Fixed, 95% CI)	5.96 [2.15, 16.49]
17 Hypotension requiring inotropic support	5	505	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [1.00, 1.38]
18 Arrhythmia requiring medical treatment	6	569	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.07, 16.39]
19 Anaemia requirning transfusion	3	322	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.67, 2.04]
20 Leukopaenia	2	254	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.22, 4.33]
21 Thrombocytopaenia	4	531	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [1.14, 2.11]
22 Coagulopathy resulting in major thrombosis or haemorrhage	4	486	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.31, 2.24]
23 Hypoglycaemia	4	490	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.54, 1.27]
24 Hypokalaemia	3	323	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.85, 1.25]
25 Oliguria	5	505	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.59, 1.12]
26 Sepsis	5	552	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.42, 1.76]
27 Seizures	5	322	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.84, 1.10]

Comparison 2. Therapeutic hypothermia versus standard care in infants with severe encephalopathy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or major disability in survivors assessed	3	153	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.68, 0.94]
2 Mortality	3	153	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.56, 0.94]
3 Major disability in survivors assessed	3	62	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.42, 1.13]

Comparison 3. Therapeutic hypothermia versus standard care in infants with moderate encephalopathy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or major disability in survivors assessed	3	278	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.58, 1.00]
2 Mortality	3	278	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.49, 1.29]
3 Major disability in survivors assessed	3	226	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.48, 1.05]

Analysis 1.1. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 1 Death or major disability in survivors assessed, by quality of follow-up.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 1 Death or major disability in survivors assessed, by quality of follow-up

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 High quality follow-up at 18-22 months					
Gunn 1998	7/18	4/13		2.9 %	1.26 [0.46, 3.44]
Gluckman 2005	59/108	73/110		44.5 %	0.82 [0.66, 1.02]
Shankaran 2005	45/102	64/103		39.2 %	0.71 [0.54, 0.93]
Subtotal (95% CI)	**228**	**226**		**86.6 %**	**0.79 [0.67, 0.93]**
Total events: 111 (Hypothermia), 141 (Standard care)					
Heterogeneity: Chi² = 1.60, df = 2 (P = 0.45); I² =0.0%					
Test for overall effect: Z = 2.82 (P = 0.0048)					
2 Lower quality follow-up at 12 months					
Eicher 2005	14/27	21/25		13.4 %	0.62 [0.41, 0.92]
Subtotal (95% CI)	**27**	**25**		**13.4 %**	**0.62 [0.41, 0.92]**
Total events: 14 (Hypothermia), 21 (Standard care)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.35 (P = 0.019)					
Total (95% CI)	**255**	**251**		**100.0 %**	**0.76 [0.65, 0.89]**
Total events: 125 (Hypothermia), 162 (Standard care)					
Heterogeneity: Chi² = 2.80, df = 3 (P = 0.42); I² =0.0%					
Test for overall effect: Z = 3.42 (P = 0.00063)					

Analysis 1.2. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 2 Death or major disability in survivors assessed, by method of cooling.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 2 Death or major disability in survivors assessed, by method of cooling

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Selective head cooling with mild systemic hypothermia					
Gunn 1998	7/18	4/13		2.9 %	1.26 [0.46, 3.44]
Gluckman 2005	59/108	73/110		44.5 %	0.82 [0.66, 1.02]
Subtotal (95% CI)	**126**	**123**		**47.4 %**	**0.85 [0.69, 1.05]**
Total events: 66 (Hypothermia), 77 (Standard care)					
Heterogeneity: Chi² = 0.69, df = 1 (P = 0.41); I² =0.0%					
Test for overall effect: Z = 1.49 (P = 0.14)					
2 Whole body cooling					
Eicher 2005	14/27	21/25		13.4 %	0.62 [0.41, 0.92]
Shankaran 2005	45/102	64/103		39.2 %	0.71 [0.54, 0.93]
Subtotal (95% CI)	**129**	**128**		**52.6 %**	**0.69 [0.55, 0.86]**
Total events: 59 (Hypothermia), 85 (Standard care)					
Heterogeneity: Chi² = 0.33, df = 1 (P = 0.57); I² =0.0%					
Test for overall effect: Z = 3.30 (P = 0.00096)					
Total (95% CI)	**255**	**251**		**100.0 %**	**0.76 [0.65, 0.89]**
Total events: 125 (Hypothermia), 162 (Standard care)					
Heterogeneity: Chi² = 2.80, df = 3 (P = 0.42); I² =0.0%					
Test for overall effect: Z = 3.42 (P = 0.00063)					

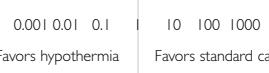
Analysis 1.3. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 3 Mortality, by method of cooling.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 3 Mortality, by method of cooling

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Selective head cooling with mild systemic hypothermia					
Gunn 1998	3/18	3/13		3.3 %	0.72 [0.17, 3.03]
Akisu 2003	0/11	2/10		2.4 %	0.18 [0.01, 3.41]
Gluckman 2005	36/108	42/110		39.0 %	0.87 [0.61, 1.25]
Lin 2006	2/32	2/30		1.9 %	0.94 [0.14, 6.24]
Subtotal (95% CI)	**169**	**163**		**46.7 %**	**0.83 [0.59, 1.16]**
Total events: 41 (Hypothermia), 49 (Standard care)					
Heterogeneity: Chi^2 = 1.16, df = 3 (P = 0.76); I^2 =0.0%					
Test for overall effect: Z = 1.08 (P = 0.28)					
2 Whole body cooling					
ICE 2002	1/7	3/10		2.3 %	0.48 [0.06, 3.69]
Shankaran 2002	2/9	3/10		2.7 %	0.74 [0.16, 3.48]
Eicher 2005	10/32	14/33		12.9 %	0.74 [0.38, 1.41]
Shankaran 2005	24/102	38/103		35.4 %	0.64 [0.41, 0.98]
Subtotal (95% CI)	**150**	**156**		**53.3 %**	**0.66 [0.47, 0.93]**
Total events: 37 (Hypothermia), 58 (Standard care)					
Heterogeneity: Chi^2 = 0.25, df = 3 (P = 0.97); I^2 =0.0%					
Test for overall effect: Z = 2.36 (P = 0.018)					
Total (95% CI)	**319**	**319**		**100.0 %**	**0.74 [0.58, 0.94]**
Total events: 78 (Hypothermia), 107 (Standard care)					
Heterogeneity: Chi^2 = 2.40, df = 7 (P = 0.93); I^2 =0.0%					
Test for overall effect: Z = 2.45 (P = 0.014)					



Analysis 1.4. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 4 Major neurodevelopmental disability, by quality of follow-up.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 4 Major neurodevelopmental disability, by quality of follow-up

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 High quality follow-up at 18-22 months					
Gunn 1998	4/18	1/13		1.8 %	2.89 [0.36, 22.94]
Gluckman 2005	23/108	31/110		47.2 %	0.76 [0.47, 1.21]
Shankaran 2005	21/102	26/103		39.8 %	0.82 [0.49, 1.35]
Subtotal (95% CI)	**228**	**226**		**88.8 %**	**0.83 [0.59, 1.16]**
Total events: 48 (Hypothermia), 58 (Standard care)					
Heterogeneity: Chi² = 1.54, df = 2 (P = 0.46); I² =0.0%					
Test for overall effect: Z = 1.11 (P = 0.27)					
2 Lower quality follow-up at 12 months					
Eicher 2005	4/27	7/25		11.2 %	0.53 [0.18, 1.59]
Subtotal (95% CI)	**27**	**25**		**11.2 %**	**0.53 [0.18, 1.59]**
Total events: 4 (Hypothermia), 7 (Standard care)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.13 (P = 0.26)					
Total (95% CI)	**255**	**251**		**100.0 %**	**0.79 [0.57, 1.09]**
Total events: 52 (Hypothermia), 65 (Standard care)					
Heterogeneity: Chi² = 2.07, df = 3 (P = 0.56); I² =0.0%					
Test for overall effect: Z = 1.42 (P = 0.16)					

Analysis 1.5. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 5 Major neurodevelopmental disability in survivors assessed, by quality of follow-up.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 5 Major neurodevelopmental disability in survivors assessed, by quality of follow-up

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 High quality follow-up at 18-22 months					
Gunn 1998	4/15	1/10		1.7 %	2.67 [0.35, 20.51]
Gluckman 2005	23/72	31/68		45.6 %	0.70 [0.46, 1.07]
Shankaran 2005	21/78	26/65		40.5 %	0.67 [0.42, 1.08]
Subtotal (95% CI)	**165**	**143**		**87.8 %**	**0.73 [0.53, 0.99]**
Total events: 48 (Hypothermia), 58 (Standard care)					
Heterogeneity: Chi² = 1.69, df = 2 (P = 0.43); I² =0.0%					
Test for overall effect: Z = 2.01 (P = 0.044)					
2 Lower quality follow-up at 12 months					
Eicher 2005	4/17	7/11		12.2 %	0.37 [0.14, 0.97]
Subtotal (95% CI)	**17**	**11**		**12.2 %**	**0.37 [0.14, 0.97]**
Total events: 4 (Hypothermia), 7 (Standard care)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.02 (P = 0.044)					
Total (95% CI)	**182**	**154**		**100.0 %**	**0.68 [0.51, 0.92]**
Total events: 52 (Hypothermia), 65 (Standard care)					
Heterogeneity: Chi² = 3.28, df = 3 (P = 0.35); I² =9%					
Test for overall effect: Z = 2.54 (P = 0.011)					

Analysis 1.6. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 6 Major neurodevelopmental disability in survivors assessed, by method of cooling.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 6 Major neurodevelopmental disability in survivors assessed, by method of cooling

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Selective head cooling with mild systemic hypothermia					
Gunn 1998	4/15	1/10		1.7 %	2.67 [0.35, 20.51]
Gluckman 2005	23/72	31/68		45.6 %	0.70 [0.46, 1.07]
Subtotal (95% CI)	**87**	**78**		**47.3 %**	**0.77 [0.51, 1.17]**
Total events: 27 (Hypothermia), 32 (Standard care)					
Heterogeneity: Chi² = 1.62, df = 1 (P = 0.20); I² =38%					
Test for overall effect: Z = 1.22 (P = 0.22)					
2 Whole body cooling					
Eicher 2005	4/17	7/11		12.2 %	0.37 [0.14, 0.97]
Shankaran 2005	21/78	26/65		40.5 %	0.67 [0.42, 1.08]
Subtotal (95% CI)	**95**	**76**		**52.7 %**	**0.60 [0.40, 0.92]**
Total events: 25 (Hypothermia), 33 (Standard care)					
Heterogeneity: Chi² = 1.19, df = 1 (P = 0.27); I² =16%					
Test for overall effect: Z = 2.35 (P = 0.019)					
Total (95% CI)	**182**	**154**		**100.0 %**	**0.68 [0.51, 0.92]**
Total events: 52 (Hypothermia), 65 (Standard care)					
Heterogeneity: Chi² = 3.28, df = 3 (P = 0.35); I² =9%					
Test for overall effect: Z = 2.54 (P = 0.011)					

Analysis 1.7. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 7 Cerebral palsy in survivors assessed, by method of cooling.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 7 Cerebral palsy in survivors assessed, by method of cooling

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Selective head cooling with mild systemic hypothermia					
Gunn 1998	3/15	1/10		2.3 %	2.00 [0.24, 16.61]
Gluckman 2005	23/72	29/68		57.6 %	0.75 [0.48, 1.16]
Subtotal (95% CI)	**87**	**78**		**59.9 %**	**0.80 [0.52, 1.22]**
Total events: 26 (Hypothermia), 30 (Standard care)					
Heterogeneity: Chi² = 0.80, df = 1 (P = 0.37); I² =0.0%					
Test for overall effect: Z = 1.04 (P = 0.30)					
2 Whole body cooling					
Shankaran 2005	15/77	19/64		40.1 %	0.66 [0.36, 1.18]
Subtotal (95% CI)	**77**	**64**		**40.1 %**	**0.66 [0.36, 1.18]**
Total events: 15 (Hypothermia), 19 (Standard care)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.40 (P = 0.16)					
Total (95% CI)	**164**	**142**		**100.0 %**	**0.74 [0.52, 1.05]**
Total events: 41 (Hypothermia), 49 (Standard care)					
Heterogeneity: Chi² = 1.01, df = 2 (P = 0.60); I² =0.0%					
Test for overall effect: Z = 1.70 (P = 0.089)					

Analysis 1.8. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 8 Neuromotor delay (BSID PDI more than 2 SD below mean) in survivors assessed, by quality of follow-up.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 8 Neuromotor delay (BSID PDI more than 2 SD below mean) in survivors assessed, by quality of follow-up

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 High quality follow-up at 18-22 months					
Gunn 1998	3/12	1/10		1.9 %	2.50 [0.31, 20.45]
Gluckman 2005	21/69	23/56		43.1 %	0.74 [0.46, 1.19]
Shankaran 2005	20/74	22/62		40.6 %	0.76 [0.46, 1.26]
Subtotal (95% CI)	**155**	**128**		**85.6 %**	**0.79 [0.56, 1.11]**
Total events: 44 (Hypothermia), 46 (Standard care)					
Heterogeneity: Chi^2 = 1.24, df = 2 (P = 0.54); I^2 =0.0%					
Test for overall effect: Z = 1.37 (P = 0.17)					
2 Lower quality follow-up at 12 months					
Eicher 2005	4/17	7/11		14.4 %	0.37 [0.14, 0.97]
Subtotal (95% CI)	**17**	**11**		**14.4 %**	**0.37 [0.14, 0.97]**
Total events: 4 (Hypothermia), 7 (Standard care)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.02 (P = 0.044)					
Total (95% CI)	**172**	**139**		**100.0 %**	**0.73 [0.53, 1.00]**
Total events: 48 (Hypothermia), 53 (Standard care)					
Heterogeneity: Chi^2 = 3.25, df = 3 (P = 0.35); I^2 =8%					
Test for overall effect: Z = 1.95 (P = 0.051)					

Analysis 1.9. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 9 Neuromotor delay (BSID PDI more than 2 SD below mean) in survivors assessed, by method of cooling.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 9 Neuromotor delay (BSID PDI more than 2 SD below mean) in survivors assessed, by method of cooling

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Selective head cooling with mild systemic hypothermia					
Gunn 1998	3/12	1/10		1.9 %	2.50 [0.31, 20.45]
Gluckman 2005	21/69	23/56		43.1 %	0.74 [0.46, 1.19]
Subtotal (95% CI)	**81**	**66**		**44.9 %**	**0.81 [0.51, 1.29]**
Total events: 24 (Hypothermia), 24 (Standard care)					
Heterogeneity: Chi² = 1.24, df = 1 (P = 0.26); I² =20%					
Test for overall effect: Z = 0.88 (P = 0.38)					
2 Whole body cooling					
Eicher 2005	4/17	7/11		14.4 %	0.37 [0.14, 0.97]
Shankaran 2005	20/74	22/62		40.6 %	0.76 [0.46, 1.26]
Subtotal (95% CI)	**91**	**73**		**55.1 %**	**0.66 [0.42, 1.02]**
Total events: 24 (Hypothermia), 29 (Standard care)					
Heterogeneity: Chi² = 1.69, df = 1 (P = 0.19); I² =41%					
Test for overall effect: Z = 1.85 (P = 0.064)					
Total (95% CI)	**172**	**139**		**100.0 %**	**0.73 [0.53, 1.00]**
Total events: 48 (Hypothermia), 53 (Standard care)					
Heterogeneity: Chi² = 3.25, df = 3 (P = 0.35); I² =8%					
Test for overall effect: Z = 1.95 (P = 0.051)					

Analysis 1.10. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 10 Neuromotor development (BSID PDI) in survivors assessed.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 10 Neuromotor development (BSID PDI) in survivors assessed

Study or subgroup	Hypothermia N	Mean(SD)	Standard care N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Gunn 1998	12	90.8 (15.1)	10	97.6 (7.3)		37.5 %	-6.80 [-16.47, 2.87]
Shankaran 2005	74	83.6 (21.8)	62	78.3 (22.5)		62.5 %	5.30 [-2.19, 12.79]
Total (95% CI)	**86**		**72**			**100.0 %**	**0.76 [-5.15, 6.68]**

Heterogeneity: Chi² = 3.76, df = 1 (P = 0.05); I² =73%

Test for overall effect: Z = 0.25 (P = 0.80)

Analysis 1.11. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 11 Developmental delay (BSID MDI more than 2 SD below mean) in survivors assessed, by quality of follow-up.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 11 Developmental delay (BSID MDI more than 2 SD below mean) in survivors assessed, by quality of follow-up

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 High quality follow-up at 18-22 months					
Gunn 1998	3/13	0/9		1.0 %	5.00 [0.29, 86.43]
Gluckman 2005	21/70	24/61		43.9 %	0.76 [0.47, 1.23]
Shankaran 2005	19/75	24/62		45.0 %	0.65 [0.40, 1.08]
Subtotal (95% CI)	**158**	**132**		**90.0 %**	**0.76 [0.54, 1.06]**
Total events: 43 (Hypothermia), 48 (Standard care)					
Heterogeneity: Chi² = 2.01, df = 2 (P = 0.37); I² =0%					
Test for overall effect: Z = 1.62 (P = 0.10)					
2 Lower quality follow-up at 12 months					
Eicher 2005	4/17	5/12		10.0 %	0.56 [0.19, 1.68]
Subtotal (95% CI)	**17**	**12**		**10.0 %**	**0.56 [0.19, 1.68]**

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Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 4 (Hypothermia), 5 (Standard care)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.03 (P = 0.30)					
Total (95% CI)	**175**	**144**		**100.0 %**	**0.74 [0.53, 1.02]**
Total events: 47 (Hypothermia), 53 (Standard care)					
Heterogeneity: Chi² = 2.20, df = 3 (P = 0.53); I² =0.0%					
Test for overall effect: Z = 1.86 (P = 0.064)					

Analysis 1.12. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 12 Developmental delay (BSID MDI more than 2 SD below mean) in survivors assessed, by method of cooling.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 12 Developmental delay (BSID MDI more than 2 SD below mean) in survivors assessed, by method of cooling

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Systemic head cooling with mild systemic hypothermia					
Gunn 1998	3/13	0/9		1.0 %	5.00 [0.29, 86.43]
Gluckman 2005	21/70	24/61		43.9 %	0.76 [0.47, 1.23]
Subtotal (95% CI)	**83**	**70**		**44.9 %**	**0.86 [0.54, 1.36]**
Total events: 24 (Hypothermia), 24 (Standard care)					
Heterogeneity: Chi² = 1.70, df = 1 (P = 0.19); I² =41%					
Test for overall effect: Z = 0.65 (P = 0.51)					
2 Whole body cooling					
Eicher 2005	4/17	5/12		10.0 %	0.56 [0.19, 1.68]
Shankaran 2005	19/75	24/62		45.0 %	0.65 [0.40, 1.08]
Subtotal (95% CI)	**92**	**74**		**55.1 %**	**0.64 [0.41, 1.00]**
Total events: 23 (Hypothermia), 29 (Standard care)					
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² =0.0%					
Test for overall effect: Z = 1.94 (P = 0.052)					
Total (95% CI)	**175**	**144**		**100.0 %**	**0.74 [0.53, 1.02]**
Total events: 47 (Hypothermia), 53 (Standard care)					
Heterogeneity: Chi² = 2.20, df = 3 (P = 0.53); I² =0.0%					
Test for overall effect: Z = 1.86 (P = 0.064)					

Analysis 1.13. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 13 Mental development (BSID MDI) in survivors assessed.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 13 Mental development (BSID MDI) in survivors assessed

Study or subgroup	Hypothermia N	Mean(SD)	Standard care N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Gunn 1998	13	82.8 (19.2)	8	93.1 (12.6)		20.0 %	-10.30 [-23.91, 3.31]
Shankaran 2005	75	80.2 (20.2)	62	75.2 (20.3)		80.0 %	5.00 [-1.81, 11.81]
Total (95% CI)	**88**		**70**			**100.0 %**	**1.93 [-4.16, 8.03]**

Heterogeneity: Chi^2 = 3.88, df = 1 (P = 0.05); I^2 =74%

Test for overall effect: Z = 0.62 (P = 0.53)

Analysis 1.14. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 14 Blindness in survivors assessed, by method of cooling.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 14 Blindness in survivors assessed, by method of cooling

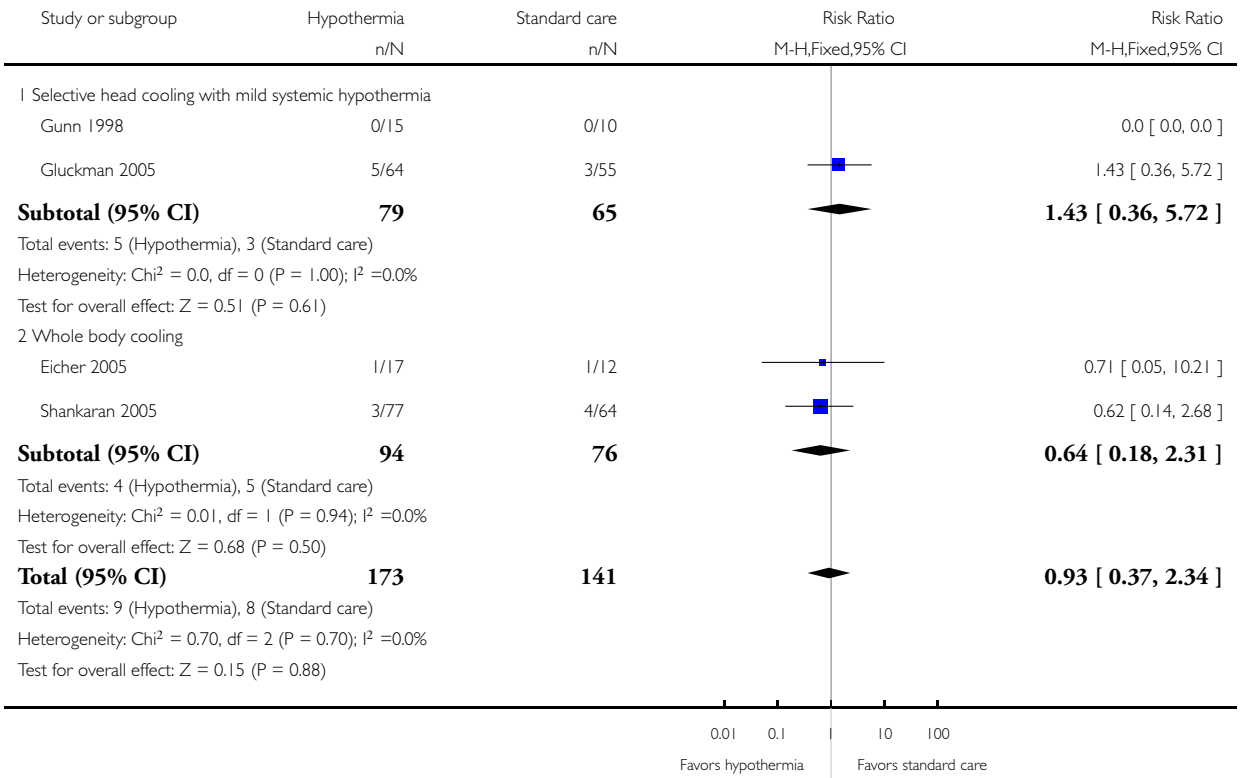
Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Selective head cooling with mild systemic hypothermia				
Gunn 1998	0/15	0/10		0.0 [0.0, 0.0]
Gluckman 2005	7/72	11/64		0.57 [0.23, 1.37]
Subtotal (95% CI)	**87**	**74**		**0.57 [0.23, 1.37]**
Total events: 7 (Hypothermia), 11 (Standard care)				
Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 1.26 (P = 0.21)				
2 Whole body cooling				
Eicher 2005	2/17	1/12		1.41 [0.14, 13.86]
Shankaran 2005	5/75	9/63		0.47 [0.16, 1.32]
Subtotal (95% CI)	**92**	**75**		**0.57 [0.22, 1.43]**
Total events: 7 (Hypothermia), 10 (Standard care)				
Heterogeneity: Chi² = 0.75, df = 1 (P = 0.39); I² =0.0%				
Test for overall effect: Z = 1.20 (P = 0.23)				
Total (95% CI)	**179**	**149**		**0.57 [0.30, 1.08]**
Total events: 14 (Hypothermia), 21 (Standard care)				
Heterogeneity: Chi² = 0.75, df = 2 (P = 0.69); I² =0.0%				
Test for overall effect: Z = 1.74 (P = 0.082)				

Analysis 1.15. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 15 Deafness in survivors assessed, by method of cooling.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 15 Deafness in survivors assessed, by method of cooling



Analysis 1.16. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 16 Sinus bradycardia.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 16 Sinus bradycardia

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Gunn 1998	1/18	0/13		2.21 [0.10, 50.32]
Akisu 2003	0/11	0/10		0.0 [0.0, 0.0]
Eicher 2005	11/31	2/31		5.50 [1.33, 22.80]
Gluckman 2005	10/112	1/118		10.54 [1.37, 80.97]
Shankaran 2005	1/102	0/106		3.12 [0.13, 75.63]
Total (95% CI)	**274**	**278**		**5.96 [2.15, 16.49]**

Total events: 23 (Hypothermia), 3 (Standard care)

Heterogeneity: $Chi^2 = 0.86$, df = 3 (P = 0.84); $I^2 = 0.0\%$

Test for overall effect: Z = 3.43 (P = 0.00059)

Analysis 1.17. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 17 Hypotension requiring inotropic support.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 17 Hypotension requiring inotropic support

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gunn 1998	3/18	0/13		0.5 %	5.16 [0.29, 92.04]
ICE 2002	3/7	5/10		3.4 %	0.86 [0.30, 2.46]
Shankaran 2002	5/9	3/10		2.3 %	1.85 [0.61, 5.63]
Gluckman 2005	74/112	65/118		51.5 %	1.20 [0.97, 1.48]
Shankaran 2005	55/102	53/106		42.3 %	1.08 [0.83, 1.40]
Total (95% CI)	**248**	**257**		**100.0 %**	**1.17 [1.00, 1.38]**

Total events: 140 (Hypothermia), 126 (Standard care)

Heterogeneity: Chi^2 = 2.43, df = 4 (P = 0.66); I^2 =0.0%

Test for overall effect: Z = 1.91 (P = 0.056)

Analysis 1.18. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 18 Arrhythmia requiring medical treatment.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 18 Arrhythmia requiring medical treatment

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Gunn 1998	0/18	0/13		0.0 [0.0, 0.0]
ICE 2002	0/7	0/10		0.0 [0.0, 0.0]
Akisu 2003	0/11	0/10		0.0 [0.0, 0.0]
Eicher 2005	0/31	0/31		0.0 [0.0, 0.0]
Gluckman 2005	0/112	0/118		0.0 [0.0, 0.0]
Shankaran 2005	1/102	1/106		1.04 [0.07, 16.39]
Total (95% CI)	**281**	**288**		**1.04 [0.07, 16.39]**

Total events: 1 (Hypothermia), 1 (Standard care)

Heterogeneity: $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 0.03 (P = 0.98)

Analysis 1.19. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 19 Anaemia requirning transfusion.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 19 Anaemia requirning transfusion

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gunn 1998	2/18	0/13		3.2 %	3.68 [0.19, 70.87]
Eicher 2005	14/31	8/31		43.8 %	1.75 [0.86, 3.57]
Gluckman 2005	5/111	10/118		53.1 %	0.53 [0.19, 1.51]
Total (95% CI)	**160**	**162**		**100.0 %**	**1.16 [0.67, 2.04]**

Total events: 21 (Hypothermia), 18 (Standard care)

Heterogeneity: $Chi^2 = 4.02$, df = 2 (P = 0.13); $I^2 = 50\%$

Test for overall effect: Z = 0.53 (P = 0.59)

Analysis 1.20. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 20 Leukopaenia.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 20 Leukopaenia

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gunn 1998	1/18	0/13		16.7 %	2.21 [0.10, 50.32]
Gluckman 2005	2/107	3/116		83.3 %	0.72 [0.12, 4.24]
Total (95% CI)	**125**	**129**		**100.0 %**	**0.97 [0.22, 4.33]**

Total events: 3 (Hypothermia), 3 (Standard care)

Heterogeneity: Chi² = 0.37, df = 1 (P = 0.54); I² =0.0%

Test for overall effect: Z = 0.04 (P = 0.97)

Analysis 1.21. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 21 Thrombocytopaenia.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 21 Thrombocytopaenia

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gunn 1998	7/18	2/13		5.2 %	2.53 [0.62, 10.25]
Eicher 2005	20/31	12/31		26.9 %	1.67 [1.00, 2.79]
Gluckman 2005	39/112	29/118		63.4 %	1.42 [0.94, 2.12]
Shankaran 2005	3/102	2/106		4.4 %	1.56 [0.27, 9.14]
Total (95% CI)	**263**	**268**		**100.0 %**	**1.55 [1.14, 2.11]**

Total events: 69 (Hypothermia), 45 (Standard care)

Heterogeneity: Chi² = 0.73, df = 3 (P = 0.87); I² =0.0%

Test for overall effect: Z = 2.77 (P = 0.0057)

Analysis 1.22. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 22 Coagulopathy resulting in major thrombosis or haemorrhage.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 22 Coagulopathy resulting in major thrombosis or haemorrhage

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gunn 1998	2/18	0/13		7.0 %	3.68 [0.19, 70.87]
ICE 2002	1/7	4/10		39.8 %	0.36 [0.05, 2.55]
Gluckman 2005	0/112	2/118		29.5 %	0.21 [0.01, 4.34]
Shankaran 2005	3/102	2/106		23.7 %	1.56 [0.27, 9.14]
Total (95% CI)	**239**	**247**		**100.0 %**	**0.83 [0.31, 2.24]**

Total events: 6 (Hypothermia), 8 (Standard care)

Heterogeneity: Chi^2 = 2.96, df = 3 (P = 0.40); I^2 =0.0%

Test for overall effect: Z = 0.37 (P = 0.71)

Analysis 1.23. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 23 Hypoglycaemia.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 23 Hypoglycaemia

Study or subgroup	Hypothermia n/N	Standard cafre n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gunn 1998	5/18	2/13		5.9 %	1.81 [0.41, 7.90]
Akisu 2003	2/11	2/10		5.3 %	0.91 [0.16, 5.30]
Gluckman 2005	14/112	20/118		49.2 %	0.74 [0.39, 1.39]
Shankaran 2005	12/102	16/106		39.6 %	0.78 [0.39, 1.57]
Total (95% CI)	**243**	**247**		**100.0 %**	**0.83 [0.54, 1.27]**

Total events: 33 (Hypothermia), 40 (Standard cafre)

Heterogeneity: Chi^2 = 1.24, df = 3 (P = 0.74); I^2 =0.0%

Test for overall effect: Z = 0.87 (P = 0.38)

Analysis 1.24. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 24 Hypokalaemia.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 24 Hypokalaemia

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gunn 1998	8/18	5/13		6.8 %	1.16 [0.49, 2.73]
Eicher 2005	9/31	9/31		10.5 %	1.00 [0.46, 2.18]
Gluckman 2005	71/112	73/118		82.8 %	1.02 [0.84, 1.25]
Total (95% CI)	**161**	**162**		**100.0 %**	**1.03 [0.85, 1.25]**

Total events: 88 (Hypothermia), 87 (Standard care)

Heterogeneity: Chi^2 = 0.08, df = 2 (P = 0.96); I^2 =0.0%

Test for overall effect: Z = 0.31 (P = 0.76)

Analysis 1.25. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 25 Oliguria.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 25 Oliguria

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Gunn 1998	18/18	13/13		0.0 [0.0, 0.0]
ICE 2002	3/7	5/10		0.86 [0.30, 2.46]
Shankaran 2002	3/9	5/10		0.67 [0.22, 2.03]
Gluckman 2005	24/112	32/118		0.79 [0.50, 1.25]
Shankaran 2005	20/102	24/106		0.87 [0.51, 1.47]
Total (95% CI)	**248**	**257**		**0.81 [0.59, 1.12]**

Total events: 68 (Hypothermia), 79 (Standard care)

Heterogeneity: $Chi^2 = 0.20$, df = 3 (P = 0.98); $I^2 = 0.0\%$

Test for overall effect: Z = 1.27 (P = 0.20)

Analysis 1.26. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 26 Sepsis.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 26 Sepsis

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gunn 1998	1/18	1/13		7.7 %	0.72 [0.05, 10.52]
Akisu 2003	1/11	2/10		13.9 %	0.45 [0.05, 4.28]
Eicher 2005	3/31	3/31		19.9 %	1.00 [0.22, 4.58]
Gluckman 2005	3/112	3/118		19.4 %	1.05 [0.22, 5.11]
Shankaran 2005	5/102	6/106		39.1 %	0.87 [0.27, 2.75]
Total (95% CI)	**274**	**278**		**100.0 %**	**0.86 [0.42, 1.76]**

Total events: 13 (Hypothermia), 15 (Standard care)

Heterogeneity: $Chi^2 = 0.43$, df = 4 (P = 0.98); $I^2 = 0.0\%$

Test for overall effect: Z = 0.41 (P = 0.68)

Analysis 1.27. Comparison 1 Therapeutic hypothermia versus standard care, Outcome 27 Seizures.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care

Outcome: 27 Seizures

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gunn 1998	10/18	4/13		4.2 %	1.81 [0.72, 4.50]
ICE 2002	5/7	8/10		5.9 %	0.89 [0.51, 1.57]
Shankaran 2002	3/9	4/10		3.4 %	0.83 [0.25, 2.76]
Akisu 2003	0/11	3/10		3.3 %	0.13 [0.01, 2.26]
Gluckman 2005	89/116	94/118		83.3 %	0.96 [0.84, 1.10]
Total (95% CI)	**161**	**161**		**100.0 %**	**0.96 [0.84, 1.10]**

Total events: 107 (Hypothermia), 113 (Standard care)

Heterogeneity: Chi^2 = 3.83, df = 4 (P = 0.43); I^2 =0.0%

Test for overall effect: Z = 0.54 (P = 0.59)

Analysis 2.1. Comparison 2 Therapeutic hypothermia versus standard care in infants with severe encephalopathy, Outcome 1 Death or major disability in survivors assessed.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 2 Therapeutic hypothermia versus standard care in infants with severe encephalopathy

Outcome: 1 Death or major disability in survivors assessed

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gunn 1998	2/3	3/3		5.2 %	0.71 [0.31, 1.66]
Gluckman 2005	28/40	32/35		50.3 %	0.77 [0.61, 0.96]
Shankaran 2005	23/32	34/40		44.5 %	0.85 [0.66, 1.09]
Total (95% CI)	**75**	**78**		**100.0 %**	**0.80 [0.68, 0.94]**

Total events: 53 (Hypothermia), 69 (Standard care)

Heterogeneity: Chi^2 = 0.40, df = 2 (P = 0.82); I^2 =0.0%

Test for overall effect: Z = 2.65 (P = 0.0080)

Analysis 2.2. Comparison 2 Therapeutic hypothermia versus standard care in infants with severe encephalopathy, Outcome 2 Mortality.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 2 Therapeutic hypothermia versus standard care in infants with severe encephalopathy

Outcome: 2 Mortality

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gunn 1998	2/3	3/3		6.5 %	0.71 [0.31, 1.66]
Gluckman 2005	21/40	27/35		53.7 %	0.68 [0.48, 0.96]
Shankaran 2005	15/32	24/40		39.8 %	0.78 [0.50, 1.22]
Total (95% CI)	**75**	**78**		**100.0 %**	**0.72 [0.56, 0.94]**

Total events: 38 (Hypothermia), 54 (Standard care)

Heterogeneity: Chi^2 = 0.23, df = 2 (P = 0.89); I^2 =0.0%

Test for overall effect: Z = 2.41 (P = 0.016)

Analysis 2.3. Comparison 2 Therapeutic hypothermia versus standard care in infants with severe encephalopathy, Outcome 3 Major disability in survivors assessed.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 2 Therapeutic hypothermia versus standard care in infants with severe encephalopathy

Outcome: 3 Major disability in survivors assessed

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Gunn 1998	0/1	0/1		0.0 [0.0, 0.0]
Gluckman 2005	7/19	5/8		0.59 [0.27, 1.31]
Shankaran 2005	8/17	10/16		0.75 [0.40, 1.42]
Total (95% CI)	**37**	**25**		**0.69 [0.42, 1.13]**

Total events: 15 (Hypothermia), 15 (Standard care)

Heterogeneity: Chi^2 = 0.22, df = 1 (P = 0.64); I^2 =0.0%

Test for overall effect: Z = 1.49 (P = 0.14)

Analysis 3.1. Comparison 3 Therapeutic hypothermia versus standard care in infants with moderate encephalopathy, Outcome 1 Death or major disability in survivors assessed.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 3 Therapeutic hypothermia versus standard care in infants with moderate encephalopathy

Outcome: 1 Death or major disability in survivors assessed

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gunn 1998	4/10	1/5		1.9 %	2.00 [0.30, 13.51]
Gluckman 2005	28/62	39/69		53.0 %	0.80 [0.57, 1.13]
Shankaran 2005	22/69	30/63		45.1 %	0.67 [0.43, 1.03]
Total (95% CI)	**141**	**137**		**100.0 %**	**0.76 [0.58, 1.00]**

Total events: 54 (Hypothermia), 70 (Standard care)

Heterogeneity: Chi^2 = 1.40, df = 2 (P = 0.50); I^2 =0.0%

Test for overall effect: Z = 1.98 (P = 0.048)

Analysis 3.2. Comparison 3 Therapeutic hypothermia versus standard care in infants with moderate encephalopathy, Outcome 2 Mortality.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 3 Therapeutic hypothermia versus standard care in infants with moderate encephalopathy

Outcome: 2 Mortality

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gunn 1998	1/10	0/5		2.2 %	1.64 [0.08, 34.28]
Gluckman 2005	13/62	15/69		48.2 %	0.96 [0.50, 1.86]
Shankaran 2005	9/69	14/63		49.6 %	0.59 [0.27, 1.26]
Total (95% CI)	**141**	**137**		**100.0 %**	**0.79 [0.49, 1.29]**

Total events: 23 (Hypothermia), 29 (Standard care)

Heterogeneity: Chi^2 = 1.15, df = 2 (P = 0.56); I^2 =0.0%

Test for overall effect: Z = 0.94 (P = 0.35)

Analysis 3.3. Comparison 3 Therapeutic hypothermia versus standard care in infants with moderate encephalopathy, Outcome 3 Major disability in survivors assessed.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 3 Therapeutic hypothermia versus standard care in infants with moderate encephalopathy

Outcome: 3 Major disability in survivors assessed

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gunn 1998	3/9	1/5		3.1 %	1.67 [0.23, 12.09]
Gluckman 2005	15/49	24/54		54.7 %	0.69 [0.41, 1.15]
Shankaran 2005	13/60	16/49		42.2 %	0.66 [0.35, 1.24]
Total (95% CI)	**118**	**108**		**100.0 %**	**0.71 [0.48, 1.05]**

Total events: 31 (Hypothermia), 41 (Standard care)

Heterogeneity: Chi^2 = 0.77, df = 2 (P = 0.68); I^2 =0.0%

Test for overall effect: Z = 1.73 (P = 0.083)

WHAT'S NEW

Last assessed as up-to-date: 27 June 2007.

21 May 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 2001

Review first published: Issue 4, 2003

28 June 2007	New search has been performed	This review updates the existing review of 'Cooling for newborns with hypoxic ischaemic encephalopathy' that was published in the Cochrane Library (Cochrane Database of Systematic Reviews), Issue 4, 2003 (Jacobs 2003). Since the first version of this review, it has become apparent that not all control infants randomised to 'normothermia' had their temperature in the normal range. Therefore, 'normothermia' has been renamed 'standard care' in this updated review. Six additional randomised controlled trials and 587 additional infants were included in the review (8 trials and 638 total infants); a further 4 studies were excluded. We are awaiting further information or publication of one completed randomised trial comprising 157 infants. Long-term follow-up from 3 ongoing trials is awaited, all having completed or stopped recruitment. These additional 829 infants will be incorporated into future updates of this review, and could change the results and overturn the conclusions of this review. The evidence for therapeutic hypothermia has changed significantly since the 2003 review, which concluded that there was a lack of evidence that therapeutic hypothermia was either beneficial or harmful to newborns with hypoxic ischaemic encephalopathy and that cooling should only be performed in the context of randomised controlled trials. This 2007 update concludes that there is evidence that therapeutic hypothermia is beneficial to term newborns with hypoxic ischaemic encephalopathy, and that cooling decreases death, without increasing major disability in survivors. The benefits of cooling on survival and neurodevelopment outweigh the short-term adverse effects.
28 June 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Sue Jacobs: responsible for all aspects of review - search, data abstraction, entry and analysis; manuscript and editing of review

Rod Hunt: data abstraction and reviewed manuscript

William Tarnow-Mordi: reviewed manuscript

Terrie Inder: reviewed manuscript

Peter Davis: data abstraction and entry, manuscript preparation

DECLARATIONS OF INTEREST

Dr Sue Jacobs is the Principal Investigator for one of the ongoing randomised controlled trials, the Infant Cooling Evaluation (ICE) trial.

SOURCES OF SUPPORT

Internal sources

- Neonatal Services, Royal Women's Hospital, Melbourne, Australia.
- Departments of Pediatrics, Neurology and Radiology, St Louis Childrens Hospital, University of Washington, USA.
- Westmead Hospital, Sydney, Australia.
- Department of Obstetrics and Gynaecology, University of Melbourne, Australia.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Asphyxia Neonatorum [*complications]; Developmental Disabilities [*prevention & control]; Hypothermia, Induced [adverse effects; *methods]; Hypoxia-Ischemia, Brain [mortality; *therapy]; Infant, Newborn; Randomized Controlled Trials as Topic

MeSH check words

Humans