

Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial

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Summary

Background Cerebral hypothermia can improve outcome of experimental perinatal hypoxia-ischaemia. We did a multicentre randomised controlled trial to find out if delayed head cooling can improve neurodevelopmental outcome in babies with neonatal encephalopathy.

Methods 234 term infants with moderate to severe neonatal encephalopathy and abnormal amplitude integrated electroencephalography (aEEG) were randomly assigned to either head cooling for 72 h, within 6 h of birth, with rectal temperature maintained at 34–35°C (n=116), or conventional care (n=118). Primary outcome was death or severe disability at 18 months. Analysis was by intention to treat. We examined in two predefined subgroup analyses the effect of hypothermia in babies with the most severe aEEG changes before randomisation—ie, severe loss of background amplitude, and seizures—and those with less severe changes.

Findings In 16 babies, follow-up data were not available. Thus in 218 infants (93%), 73/110 (66%) allocated conventional care and 59/108 (55%) assigned head cooling died or had severe disability at 18 months (odds ratio 0·61; 95% CI 0·34–1·09, p=0·1). After adjustment for the severity of aEEG changes with a logistic regression model, the odds ratio for hypothermia treatment was 0·57 (0·32–1·01, p=0·05). No difference was noted in the frequency of clinically important complications. Predefined subgroup analysis suggested that head cooling had no effect in infants with the most severe aEEG changes (n=46, 1·8; 0·49–6·4, p=0·51), but was beneficial in infants with less severe aEEG changes (n= 172, 0·42; 0·22–0·80, p=0·009).

Interpretation These data suggest that although induced head cooling is not protective in a mixed population of infants with neonatal encephalopathy, it could safely improve survival without severe neurodevelopmental disability in infants with less severe aEEG changes.

Introduction

Hypoxic-ischaemic encephalopathy is an important cause of acute neurological injury at birth, occurring in about one to two babies per 1000 term livebirths.¹ No specific clinical intervention has been shown to alter outcome. Experiments have shown that a reduction in brain temperature of 2–5°C applied after perinatal hypoxia-ischaemia can improve neuropathological,^{2–6} cerebral energetic,^{7,8} electrophysiological,^{1,2} and functional outcomes.^{5,9}

The neuroprotective effects of experimental cooling are dependent on both a sufficient duration of cooling and on the timing of initiation of cooling.¹ Extended cooling for 24–72 h, started as late as 6 h after injury, has been associated with persistent protection.^{3,5,8–10} However, there is rapid loss of effect as treatment delay is increased,¹ and cooling does not seem to be protective if started after the onset of delayed seizures.^{1,11} Furthermore, hypothermia seems to be less protective in those with the most severe cerebral injuries than in those with less severe injuries.^{5,8,11} These issues could restrict the application of hypothermia to neonatal encephalopathy, in which there is much variation both in the apparent timing of the insult and in the severity.

Nevertheless, early induction of moderate hypothermia in adult patients after cardiac arrest improves neurological recovery,^{12,13} and moderate hypothermia is generally safe in an intensive-care setting.^{14–18}

Our aim was to investigate whether 72 h of selective head cooling with mild systemic hypothermia,^{14,17} started within 6 h of birth, improves neurodevelopmental outcome at 18 months in infants with moderate or severe neonatal encephalopathy.

Methods

This study was done in 25 perinatal centres in accordance with a trial design registered with the US Food and Drug Administration under the investigational device exemption/premarket approval programme. The institutional review board of every centre approved the protocol, and written informed consent was obtained from parents before randomisation.

Patients

From July, 1999, to January, 2002, we recruited infants born at 36 weeks or longer gestation with acute encephalopathy, with a stepwise protocol consisting of clinical evidence of exposure to perinatal hypoxia-

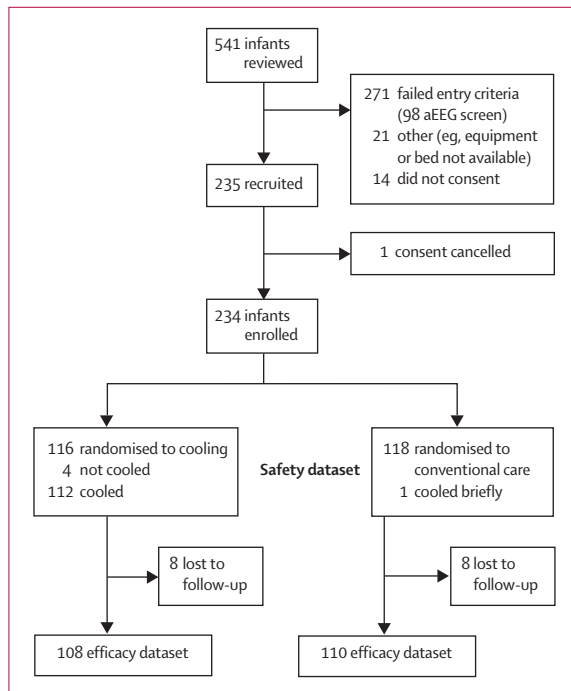


Figure 1: Trial profile

ischaemia, an abnormal neurological examination, and an abnormal aEEG (amplitude integrated electroencephalography) recording.

	Cooled (n=116)	Control (n=118)
Gestational age (weeks)	38.9 (1.6)	39.1 (1.4)
Birthweight (g)	3399 (663)	3504 (625)
Head circumference (cm)	34.6 (1.8)	35.0 (1.9)
Girls (%)	52 (45%)	60 (51%)
Emergency caesarean section (%)	80 (69%)	75 (64%)
5 min Apgar score (n=229)		
0-3	88 (77%)	77 (68%)
4-6	25 (22%)	31 (27%)
7-10	2 (2%)	6 (5%)
10 min Apgar score (n=166)		
0-3	21 (70%)	12 (55%)
4-6	5 (17%)	6 (27%)
7-10	4 (13%)	4 (18%)
Blood gas within 60 min of birth (mean=21 min)		
pH (93 cooled, 100 control)	6.9 (0.2)	6.9 (0.2)
PCO ₂ (mm Hg, 85 cooled, 95 control)	63 (14-223)	81 (17-227)
Base deficit (mmol/L, 78 cooled, 92 control)	21.0 (32.0-3.6)	20.4 (35.2-3.9)
Pre-randomisation aEEG		
Normal/mildly abnormal*	7 (6%)	9 (8%)
Moderately abnormal	63 (54%)	76 (64%)
Severely abnormal	42 (36%)	32 (27%)
Seizures present	68 (59%)	75 (64%)
Age at randomisation, h	4.8 (2.6-6.0)	4.7 (2.1-6.1)

* All patients with normal or mildly abnormal aEEG background amplitude before randomisation had seizures. Data are mean (SD), number of patients (%), or median (range)

Table 1: Baseline characteristics

Clinical inclusion criteria were: an Apgar score of 5 or less at 10 min after birth; a continued need for resuscitation, including endotracheal or mask ventilation at 10 min after birth; or severe acidosis, defined as pH less than 7.00 or a base deficit of 16 mmol/L or more in an umbilical cord blood sample or an arterial or venous blood sample obtained within 60 min of birth. Eligible infants were then assessed for evidence of moderate or severe encephalopathy by a certified examiner according to criteria modified from Sarnat and Sarnat,¹⁹ including lethargy, stupor, or coma, with one or more of hypotonia, abnormal reflexes (including oculomotor or pupillary abnormalities), an absent or weak suck, or clinical evidence of seizures.

We used aEEG recordings to improve the specificity of case selection,^{20,21} to control for severity of injury,²⁰ and to allow subgroup analysis to test the hypothesis that hypothermia is not protective in infants with the most severe abnormalities on aEEG before randomisation. Certified investigators did at least 20 min of aEEG recordings (Lectromed, Letchworth, UK) in infants who satisfied the above entry criteria. The aEEG was done at any time after 1 h of age, except within 30 min of intravenous anticonvulsant treatment, provided the results were available within 5.5 h. We selected infants for randomisation if they had a background aEEG voltage that was moderately abnormal (upper margin >10 μV and lower margin <5 μV) or severely abnormal (upper margin <10 μV), seizures identified by a sudden increase in voltage accompanied by narrowing of the band of aEEG activity followed by a brief period of suppression, or both.²⁰

Exclusion criteria were: infants older than 5.5 h of age at the time of randomisation; prophylactic administration of high-dose anticonvulsants; major congenital abnormalities; head trauma causing major intracranial haemorrhage; severe growth restriction, with birthweight less than 1800 g; head circumference less than mean-2 SD for gestation if birthweight and length greater than mean-2 SD; infants judged critically ill and unlikely to benefit from neonatal intensive care by the attending neonatologist; unavailability of essential equipment; and planned concurrent participation in other experimental treatments.

Procedures

We randomly assigned infants either head cooling and mild systemic hypothermia or control treatment of conventional care. We stratified randomisation by centre in a randomised block design with a block size of six. Randomisation codes for every centre were pregenerated by computer and supplied in numbered, sealed opaque envelopes. Masking could not be achieved because of the nature of the intervention. Assignment was subsequently verified against the centrally held list.

For infants randomly assigned head cooling, we fitted a cooling cap (Olympic Medical Cool Care System,

Olympic Medical, Seattle, WA, USA) around the head for 72 h.^{14,17,22} The system consisted of a small thermostatically controlled cooling unit and a pump that circulated water through the cap. The initial water temperature was set between 8°C and 12°C. All infants were nursed under a radiant overhead heater, which was servo-controlled to the infant's abdominal skin temperature and adjusted to maintain the rectal temperature at 34–35°C. Adjustments were made to the cooling cap water temperature to stay within these limits. At the start of hypothermia, the overhead heater was turned off for 20–30 min to accelerate cooling, then turned back on once the rectal temperature had fallen to 35·5°C.

We obtained blood cultures and full blood counts from all infants before treatment started, with investigation and treatment for infection as clinically indicated. Seizures were diagnosed clinically and managed with a loading dose of 20 mg/kg of phenobarbital. Subsequent treatment was according to the local standard of care. We did not feed study infants during cooling; feeding after rewarming was at the discretion of the attending clinician who directed all other aspects of clinical care. At the end of the 72 h cooling period, the infants were slowly rewarmed at no more than 0·5°C/h until their temperature was within normal temperature range (ie, 36·5–37·5°C). Cooling was discontinued sooner than 72 h if the parents withdrew consent or if the attending neonatologist thought it was necessary for clinical reasons (eg, need for extracorporeal membrane oxygenation).

Infants randomly assigned to the non-cooled group (control) were cared for under an overhead radiant heater, which was servo-controlled to the infant's abdominal skin temperature to maintain the rectal temperature at 36·8–37·2°C. They received standard clinical care for their centre by the attending neonatologist.

We undertook physiological recordings and laboratory tests according to a standard protocol. Heart rate, pulse oximetry, and rectal, abdominal skin, fontanel, and nasopharyngeal temperatures were monitored continuously (Olympic Medical Cool Care System). We did electrocardiography if bradycardia of less than 80 bpm or arrhythmia was seen, and we calculated the QT interval.

We defined three major adverse events: (1) major cardiac arrhythmia (ie, arrhythmia other than sinus arrhythmia or bigeminy); (2) major venous thrombosis (ie, thrombosis of a major vessel not related to an infusion line); and (3) severe hypotension despite full support (ie, hypotension despite repeated administration of volume and maximum tolerated inotrope support—eg, intravenous dopamine infusions at ≥ 20 $\mu\text{g}/\text{kg}$ per min).

We defined potential postnatal complications or adverse events in the first 7 days of life as follows: hypotension (ie, mean arterial blood pressure < 40 mm Hg); and coagulopathy (ie, clinical bleeding with abnormal clotting

	Cooled (n=112)	Control (n=118)	Fisher's exact p value
Major adverse events			
Major cardiac arrhythmia	0	0	..
Major venous thrombosis	0	2 (2%)	0·50
Severe hypotension despite full support	3 (3%)	3 (3%)	1·00
Unanticipated serious adverse event*	1 (1%)	0	0·49
Postnatal complications			
Minor cardiac arrhythmia†	10 (9%)	1 (1%)	0·004
Hypotension	62 (55%)	61 (52%)	0·60
Coagulopathy	21 (19%)	17 (14%)	0·38
Prolonged coagulation times	56 (50%)	50 (42%)	0·29
Abnormal renal function	73 (65%)	83 (70%)	0·48
Hyponatraemia	49 (44%)	46 (39%)	0·50
Hypokalaemia	71 (63%)	73 (62%)	0·89
Platelet count $< 100\,000$ per μL	36 (32%)	26 (22%)	0·10
Raised liver enzymes concentrations	42 (38%)	62 (53%)	0·02
Metabolic acidosis	22 (20%)	27 (23%)	0·63
Respiratory distress	94 (84%)	92 (78%)	0·31
Systemic infection	3 (3%)	3 (3%)	1·00
Haemococoncentration	3 (3%)	1 (1%)	0·36
Hypoglycaemia	14 (13%)	20 (17%)	0·36
Hypocalcaemia	49 (44%)	51 (43%)	1·00
Difficulties in temperature control	36 (32%)	27 (23%)	0·14
Clinically diagnosed seizures	93 (80%)	96 (81%)	1·00
Major causes of death			
(more than one diagnosis possible)			
Encephalopathy	33 (92%)	39 (93%)	..
Persistent pulmonary hypertension	4 (11%)	4 (10%)	..
Sepsis (proven)	2 (5%)	1 (2%)	..
Renal failure	4 (11%)	2 (5%)	..
Intractable hypotension	4 (11%)	5 (12%)	..
Other	6 (17%)	10 (24%)	..

*Skin breakdown and local haemorrhage under cap in a baby who died of other causes. †Almost all cases represent sinus bradycardia. The control had sinus tachycardia. Data are number of patients (%).

Table 2: Major adverse events and postnatal complications

studies consistent with disseminated intravascular coagulation or hepatic coagulopathy). We also included: abnormal renal function (ie, urine output $< 0\cdot5$ mL/kg per h for more than 24 h after birth or maximum serum creatinine $> 0\cdot09$ mmol/L); hyponatraemia (ie, plasma sodium < 130 mmol/L); hypokalaemia (ie, plasma

	Cooling	Control	Odds ratio (95% CI)	p value
Died or severe disability at 18 months				
Died	59/108 (55%)	73/110 (66%)	0·61 (0·34–1·09)	0·10
Severe neuromotor disability	36/108 (33%)	42/110 (38%)	0·81 (0·47–1·41)	0·48
Bayley MDI < 70	14/72 (19%)	21/68 (31%)	0·54 (0·25–1·17)	0·12
Bayley MDI < 70	21/70 (30%)	24/61 (39%)	0·66 (0·32–1·36)	0·27
Bilateral cortical visual impairment	7/72 (10%)	11/64 (17%)	0·52 (0·19–1·39)	0·22
Secondary outcomes				
Multi-organ dysfunction	97/116 (84%)	95/118 (81%)	1·24 (0·64–2·40)	0·61
Multiple disabilities	15/70 (21%)	20/65 (31%)	0·61 (0·29–1·32)	0·24
Bayley PDI < 70	21/69 (30%)	23/56 (41%)	0·63 (0·30–1·31)	0·26
Bilateral sensorineural Hearing loss	5/64 (8%)	3/55 (6%)	1·47 (0·37–5·84)	0·72
Epilepsy	11/72 (15%)	11/67 (16%)	0·92 (0·38–2·24)	1·00
Continuous BSID II scores, median (range)				
Bayley MDI §	84·5 (49–116)	77·0 (49–121)		0·11
Bayley PDI	87·0 (49–127)	79·5 (49–125)		0·06

†Nine surviving patients did not have Bayley MDI scores at 18 months; four of the nine were also missing bilateral cortical visual impairment data. However, all nine had unfavourable primary outcome due to GMF ≥ 3 (GMF=5 for eight of the nine and GMF=4 for the other one). §Incidences compared by Fisher's exact test. Continuous BSID II scores compared by Cox regression analysis including baseline aEEG parameters. Data are number of patients (%) unless otherwise stated.

Table 3: Primary and secondary outcomes and components

	Outcome		p value	Odds ratio	(95% CI)
	Favourable, number (%)	Unfavourable, number (%)			
Treatment (unadjusted)			0.1	0.61	(0.34–1.09)
Treatment: cooled vs control			0.05	0.57	(0.32–1.01)
aEEG background: severely abnormal vs moderately abnormal*			0.01	2.37	(1.23–4.54)
Severe	19 (27%)	52 (73%)			
Moderate	60 (45%)	72 (55%)			
Normal/mild	7 (47%)	8 (53%)			
Seizure by aEEG: no vs yes			0.01	0.46	(0.25–0.83)
No	42 (51%)	41 (49%)			
Yes	44 (33%)	91 (67%)			
Age at randomisation (h)			0.90	1.02	(0.73–1.43)

*Infants with normal or mildly abnormal background intensity all had seizures and were included with moderate abnormality for analysis. Event rates for treatment are given in table 3.

Table 4: Primary outcome logistic regression results (n=218)

potassium <3.5 mmol/L); bone marrow depression (ie, platelet count $<100\,000$ per μL); raised liver enzyme concentrations (ie, aspartate transaminase >200 IU/L, alanine transaminase >100 IU/L); and metabolic acidosis after entry into study (ie, arterial pH <7.34 or base deficit >4 mmol/L). Other definitions included: respiratory distress, such as need for ventilatory support, mechanical ventilation, or continuous positive airway pressure or extracorporeal membrane oxygenation; systemic infection (ie, positive microbial cultures such as blood, cerebrospinal fluid, or urine cultures, taken after randomisation); haemoconcentration, increase of haematocrit (packed cell volume) by 20% or more, not associated with transfusions); hypoglycaemia (ie, blood glucose <2.6 mmol/L); hypocalcaemia (ie, plasma calcium <2 mmol/L, adjusted for albumin concentrations, or <1.0 mmol/L ionised calcium); difficulties in

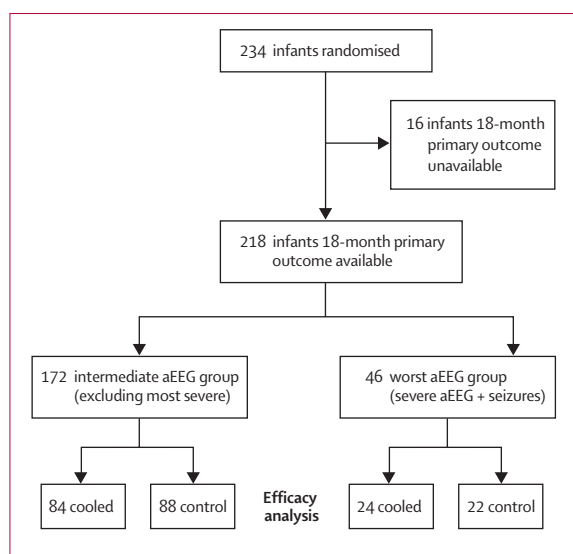


Figure 2: Subgroup analysis

temperature control (ie, rectal temperature $<33.5^{\circ}\text{C}$ or $>37.5^{\circ}\text{C}$ for more than an hour); and evidence of breakdown of skin due to pressure of the cooling cap.

At 18 months of age infants had a neurological examination, a visual and auditory assessment by certified staff, and a neurodevelopmental assessment by a developmental psychologist with the Bayley II scales (BSID II). Those who assessed neurodevelopmental outcome were masked to the treatment group.²¹ Gross motor function (GMF) classification levels 3–5 (non-ambulant, sits with support applied to lower back, or infants who have limited or no self mobility) were used to denote severe neuromotor disability.²⁴

Statistical analysis

Study power was based on an estimated poor outcome in controls of 70%.²⁰ At a two-sided 0.05 significance level, a total of 188 patients was needed for an 80% chance of detecting a relative 30% decrease in frequency (ie, 70% vs 49%). Based on an estimated 20% loss to follow-up, we needed 235 patients. The primary outcome was the combined frequency of mortality and severe neurodevelopmental disability in survivors at 18 months of age. We defined severe neurodevelopmental disability as GMF level 3–5, Bayley mental developmental index (MDI) less than 70, or bilateral cortical visual impairment. Secondary outcomes were: multiorgan dysfunction (adverse events in three or more organ systems); Bayley psychomotor development index score less than 70; bilateral sensorineural hearing loss more than 40 dB; epilepsy (recurrent seizures beyond the neonatal period, requiring anticonvulsant treatment); and multiple disabilities, ie, the presence of any two of the following—GMF 3 or more, MDI less than 70, epilepsy, cortical visual impairment, or sensorineural hearing loss.

We analysed the primary outcome according to the intention-to-treat principle using two group binomial comparisons (Fisher's exact test) and logistic regression incorporating the aEEG variables (severity of background suppression and presence of seizures) and age at randomisation. Two-sided p values less than 0.05 were regarded as significant. To examine the effect of severity of injury, as indicated by aEEG changes, on cooling efficacy we used a logistic regression model with treatment/subgroup interaction terms. Since this model indicated an interaction between effect and severity of aEEG, analyses were subsequently done in patients with the most severe aEEG changes (severely abnormal aEEG background plus seizures) and then separately in an intermediate group excluding patients with the most severe aEEG changes. Because BSID scores were truncated at a score of 49, we compared continuous BSID II scores by Cox regression incorporating the aEEG variables. For the subgroup analysis, since the tests for the two groups were done separately, p values less than 0.025 were needed for significance. For the

safety analysis, because of the large number of comparisons, two-sided p values less than 0.01 were needed for significance.

An independent data safety and monitoring board monitored adverse events, including mortality, at 25%, 50%, and 75% of study completion, but not neurodevelopmental outcomes.

Role of the funding source

This study was funded by Olympic Medical (Seattle, WA, USA). The sponsor supported the study financially, provided administrative support to the sites, supplied the aEEG monitors and the cooling devices, and monitored initial data recording and accuracy. The study was designed by, and all data interpretation was the responsibility of, the scientific advisory committee, who had full access to all the data in the study and had final responsibility for the decision to submit the report for publication. Drug and Device Development (Redmond, WA, USA) entered and held the data and did all analyses under the instructions of the scientific advisory committee.

Results

Figure 1 shows the trial profile. 234 infants were randomly allocated cooling (n=116) or control treatment (n=118). The prerandomisation aEEG recordings had moderate to severe suppressed background in 105 (91%) cooled and 108 (92%) control infants, with seizures occurring in more than half the infants in both groups (table 1). The age of the infants at randomisation and the numbers of recruitment and protocol violations at study entry (14 cooled vs 13 controls) were closely similar for both groups.

Rectal temperature fell to the target range of 34–35°C within the first 2 h of cooling and resolved without overheating during rewarming. Mean plasma glucose concentrations were raised between 4 h and 24 h compared with controls (7.6 mmol/L, [SD 4.4] vs 5.4 mmol/L, [3.1], at 4 h, $p<0.0001$) and resolved spontaneously. There was a significant fall in the mean heart rate during cooling compared with controls (114 bpm, [15], vs 145 bpm, [18], $p<0.0001$). Scalp oedema occurred in 32 cooled and one control infant ($p<0.0001$) and resolved rapidly in all babies before or shortly after the end of cooling. No cases of ventricular arrhythmia were reported and no increase in the frequency of adverse events (table 2) was noted. Most deaths occurred in the first week after birth; 15 cooled and 19 control infants died during the 76 h monitoring period and 12 cooled and 7 control infants died in the next 4 days.

Primary and secondary outcome data at 18 months were available for 218 (93%) infants (table 3); eight were lost to follow-up from each group (figure 1). Of 108 cooled infants, about half had an unfavourable primary outcome compared with two-thirds of control infants

	Cooled	Control	p value
Intermediate aEEG group, n=172			
Died or severe disability at 18 months	40 (48%)	58 (66%)	0.02
Died	24 (29%)	34 (39%)	0.20
Severe neuromotor disability	7 (12%)	15 (28%)	0.03
Bayley MDI† <70	15 (25%)	20 (40%)	0.15
Bilateral cortical visual impairment	4 (7%)	7 (14%)	0.34
Secondary outcomes			
Multiple disabilities	8 (14%)	14 (28%)	0.10
Bayley PDI <70	14 (24%)	18 (39%)	0.13
Bilateral sensorineural hearing loss	3 (6%)	1 (2%)	0.63
Epilepsy	8 (13%)	8 (15%)	0.79
Continuous BSID II scores (median, range)			
Bayley MDI	85 (49–116)	77.0 (49–119)	0.04
Bayley PDI	89.5 (49–127)	84.5 (49–125)	0.047
Severe aEEG group, n=46			
Died or severe disability at 18 months	19 (79%)	15 (68%)	0.51
Died	12 (50%)	8 (36%)	0.39
Severe neuromotor disability	7 (58%)	6 (43%)	0.70
Bayley MDI‡ <70	6 (55%)	4 (36%)	0.67
Bilateral cortical visual impairment	3 (25%)	4 (31%)	1.00
Secondary outcomes			
Multiple disabilities	7 (58%)	6 (43%)	0.70
Bayley PDI <70	7 (64%)	5 (50%)	0.67
Bilateral sensorineural hearing loss	2 (22%)	2 (17%)	1.00
Epilepsy	3 (25%)	3 (21%)	1.00

Incidences were compared by Fishers exact test. The continuous BSID II scores were compared by Cox regression analysis including baseline aEEG parameters. †Five surviving patients did not have Bayley MDI scores at 18 months; three of the five were also missing bilateral cortical visual impairment data: all five had unfavourable primary outcomes with GMF=5. ‡Four surviving patients did not have Bayley MDI scores at 18 months; one of the four was also missing bilateral cortical visual impairment data. However, all four had unfavourable primary outcome with GMF=5 in three cases and GMF=4 in the fourth case. Data are number of patients (%) unless otherwise stated.

Table 5: Primary and secondary outcomes for the intermediate aEEG group and for the severe aEEG group

(table 3). Logistic regression analysis, controlling for baseline aEEG amplitude, presence of seizures, and age at randomisation, indicated a possible effect of hypothermia (table 4). The background aEEG amplitude and the presence of seizures at enrolment were independently associated with unfavourable outcome. Post-hoc analysis (not shown) showed no effect of site on outcome.

Figure 2 shows the subgroup analysis profile. In the prespecified logistic regression model, an interaction was recorded between severity of aEEG changes and treatment ($p=0.075$). In infants with the most severe baseline aEEG changes (n=46), with severe suppression of background activity and seizures, no effect of hypothermia was noted on outcome (odds ratio 1.8, 95% CI 0.49–6.4, $p=0.51$, table 5). By contrast, in the remaining 172 infants outcome was more favourable in cooled infants than in controls (odds ratio 0.47; 95% CI 0.26–0.87, $p=0.021$, table 5). The number needed to treat was six (95% CI 3–27). Logistic regression analysis, with aEEG variables controlled for, lent support to a protective effect of hypothermia (0.42; 0.22–0.80, $p=0.009$).

Discussion

Although head cooling with mild systemic hypothermia started within 6 h of birth was of some benefit in a mixed population of infants with moderate to severe

encephalopathy, the effect was not significant. These results lend support to our a-priori hypothesis that hypothermia would not be protective in infants with the most severe aEEG abnormalities before randomisation, although there were few infants in this group.

Previous data on the effectiveness of hypothermia in newborn babies are scarce.¹ Cooling can be induced either by lowering the temperature of the whole body with a cooling blanket,^{18,25} or by head cooling with mild systemic hypothermia.²² A small controlled trial of head cooling reported slightly improved neurodevelopmental outcome²² and a study of whole body cooling reported significant improvement compared with historical controls.²⁵ In view of the clinical and statistical significance of the effect of hypothermia in the large subgroup with less severe aEEG changes in our study, therapeutic hypothermia for neonatal encephalopathy merits further investigation.

Neonatal encephalopathy is a progressive syndrome. Immediately after birth, many infants with encephalopathy show initial transient recovery of cerebral oxidative metabolism followed by secondary deterioration with cerebral energy failure 6–15 h after birth.^{26,27} This delay offers the potential for therapeutic intervention. The severity of this secondary deterioration is closely correlated with neurodevelopmental outcome at 1 and 4 years of age,²⁷ and infants with encephalopathy who do not show initial recovery of cerebral oxidative metabolism have very poor outcomes.²⁶ Essentially, experimental hypothermia is effective only if it is started in the latent phase, before the onset of secondary deterioration.^{1,2,7}

To objectively control for this clinical and pathophysiological heterogeneity, and to exclude infants with very mild encephalopathy who would be expected to have a normal prognosis,²⁸ we introduced an additional selection criterion—the presence of an abnormal aEEG within 5·5 h of birth. The aEEG records a single channel EEG from two biparietal electrodes. Before bedside display, the signal is rectified, smoothed, and amplitude integrated. The background aEEG pattern during the first 3 h postnatally has a positive predictive value of 75% for adverse outcome.²⁰ The combination of abnormal aEEG with abnormal early neurological examination increases the positive predictive value compared with either alone.²¹

Several factors probably contributed to the overall non-significant effect of hypothermia in our study. First, more infants in the cooled group showed severely abnormal Apgar scores and background aEEG amplitude than in the control group. However, this difference, which seems to be a chance effect of randomisation, was controlled for in the logistic regression model. Second, the differential treatment effect seen in the subgroup analysis strongly suggests that heterogeneity of the study population was important, such that some infants are not treatable,

whereas others might be. Alternatively, the timing of recruitment could have reduced the effect of treatment, with only 12% of infants commencing cooling less than 4 h after birth. However, by contrast with experimental data,¹ within the fairly narrow range of recruitment times, we showed no greater improvement in those treated soonest after birth than those treated later.

The considerations noted above led to the further hypothesis that hypothermia would not be protective in infants with the most severe encephalographic changes, either because there was no time available for treatment before secondary deterioration, indicated by the onset of delayed seizures against a suppressed background,^{1,11} or because the injury was too severe.^{5,8,11} This idea is lent support by the findings of our subgroup analysis, which suggest that infants with the most severe or most advanced aEEG changes shortly after birth showed no apparent improvement with hypothermia. By contrast, in the other infants, treatment was associated with an improvement in primary outcome, with a greater than 50% reduction in severe neuromotor disability in survivors and improved continuous BSID-II scores. Although prediction of mental development in infants younger than 2 years of age by the BSID-II has limitations, it is a well standardised test and infants with scores 3 SD or more below the mean rarely improve with age.²⁹ If this finding is confirmed by further studies, then six infants selected in this way would need to be treated for every infant with improved outcome. However, this study was not powered to definitively assess subgroup effects.

There is a potential trade-off between the adverse systemic effects of cooling, which increase greatly below a core temperature of about 34°C,^{15,30} and the possibility of cerebral benefit. Clinical and experimental evidence suggests that head cooling can allow effective brain cooling to be achieved with less systemic hypothermia.^{6,14} Possibly because systemic temperature was maintained over 34°C,^{14–18} the only adverse clinical effect in our study was transient oedema under the cap. Physiological effects of cooling, which did not compromise patients' care, included sinus bradycardia,¹² and a modest transient rise in plasma glucose.¹²

In conclusion, the present results suggest that, except in the most severely encephalopathic infants, selective head cooling soon after birth could be a clinically feasible treatment to reduce the disabling neurodevelopmental sequelae of neonatal encephalopathy. In the future, trials of neonatal neuroprotection classification by aEEG might help target treatment to infants most likely to respond.

Contributors

All authors participated in study design, analysis, and manuscript preparation. P Gluckman, J Wyatt, and A Gunn provided the overview of the project; A Gunn reviewed all death and adverse event reports; D Azzopardi developed the aEEG criteria and material to train the site investigators in interpretation; and D M Ferrero and C M Robertson reviewed all the neurodevelopmental outcome data.

Conflict of interest statement

Olympic Medical provided financial grants to the University of Auckland (P Gluckman) and UCL (J Wyatt) for the CoolCap trial. Every participating trial site (not the individual site investigators) received fixed part reimbursement for every infant enrolled, covering the additional costs of the trial, including clinical time, laboratory tests, neurodevelopmental assessments, and local trial administration. D Azzopardi authored a manual of aEEG interpretation that was distributed by Olympic Medical for use in the trial. Olympic Medical loaned equipment to A Gunn, M Thoresen, A Whitelaw, and J S Wyatt for use in pilot studies preceding the trial. The University of Auckland has applied for a related patent that names A Gunn; however, A Gunn has no financial interest. R Ballard, A D Edwards, D M Ferriero, R Polin, and C M Robertson declare that they have no conflict of interest.

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