Neonatal ECMO Study of Temperature (NEST): A Randomized Controlled Trial

WHAT’S KNOWN ON THIS SUBJECT: Although providing improved survival for infants with very severe cardiorespiratory problems, the use of neonatal extracorporeal membrane oxygenation has high rates of disability in survivors. Mild hypothermia has been shown to limit brain injury in a range of patient groups, including newborns.

WHAT THIS STUDY ADDS: Infants who received extracorporeal membrane oxygenation and mild hypothermia did not show an improved neurodevelopmental outcome, and nonsignificant trends in the data suggested a small adverse effect. Use of hypothermia in other potential patient groups should be thoroughly tested.

abstract

BACKGROUND: Despite evidence to support the use of extracorporeal membrane oxygenation (ECMO) in defined groups of newborn infants, rates of impairment among survivors remain high. Therapeutic hypothermia has been shown to provide neuroprotection in mature infants exposed to perinatal asphyxia. We hypothesized that therapeutic hypothermia during ECMO would reduce the proportion of infants with brain injury, and thus later impairment.

METHODS: We conducted a randomized trial in the United Kingdom to compare ECMO with cooling (34°C for the first 48 to 72 hours) with standard ECMO (37°C). The primary outcome was the cognitive composite score of the Bayley Scales of Infant and Toddler Development, Third Edition. Prespecified secondary outcomes included death, neonatal morbidity, and other neurodevelopmental and behavioral outcomes at 2 years.

RESULTS: A total of 111 infants were entered into the study, 14 died before 2 years of age (16% who received ECMO with cooling vs 9% who received ECMO alone). Two infants were lost to follow-up, and 8 were unable to complete the full range of tests. For 45 evaluated infants who received ECMO with cooling, mean cognitive scores at 2 years were 88.0 (SD: 16.2) compared with 90.6 (SD: 13.1) for 48 infants receiving ECMO only (difference in means: −2.6; 95% confidence interval: −8.7 to 3.4). The various secondary outcomes were not significantly different between the groups, but most favored ECMO without cooling.

CONCLUSIONS: In newborn infants treated by ECMO, the use of mild hypothermia for the first 48 to 72 hours did not result in improved outcomes up to 2 years of age. Pediatrics 2013;132:e1247–e1256
Extracorporeal membrane oxygenation (ECMO) is an invasive method of life support used for newborn infants with acute respiratory failure and has been shown to lead to improved outcomes.\(^1\) Despite the availability of new therapies, such as inhaled nitric oxide and high-frequency oscillation, the majority of infants who develop the severest forms of cardiorespiratory failure still are treated with ECMO, and the number of referrals reported to the Extracorporeal Life Support Organization has remained steady since the end of the 1990s.

The Cochrane review of neonatal ECMO concludes that, compared with other forms of intervention, ECMO is the most effective form of life support for infants that fulfills the eligibility criteria, both in terms of improved survival and morbidity.\(^2\) However, childhood outcome data from the UK collaborative ECMO trial, the main trial included in the Cochrane review, indicated that despite improved outcome compared with more conventional life support, rates of impairment and disability remained high.\(^3,4\) Only 32% of the original cohort of infants allocated to ECMO in that study survived without disability at 4 years of age compared with 14% in the conventional treatment arm. The origin of these impairments may stem both from the underlying condition and from changes in cerebral perfusion that accompany the process of ECMO.\(^3,4\)

There is increasing evidence of a neuroprotective effect from mild therapeutic hypothermia in different patient groups, after a variety of cerebral insults, but particularly in infants after acute hypoxia-ischemia.\(^5,6\) We therefore set out to test the potential for hypothermia to improve the outcome of infants who received neonatal ECMO. After a series of safety and feasibility studies relating to the use of mild hypothermia during neonatal ECMO,\(^7–9\) the 4 hospitals comprising the UK national ECMO service agreed to participate in a pragmatic multicenter randomized controlled trial, the Neonatal ECMO Study of Temperature (NEST). The aim of this trial was to evaluate whether, in infants requiring ECMO, cooling to 34°C for the first 48 to 72 hours of their ECMO course led to improved health status at age 2 years.

**METHODS**

**Trial Design and Participants**

This was a 2-arm randomized controlled trial comparing outcomes for infants allocated to receive ECMO and cooling with infants allocated to receive standard (normothermic) ECMO; methods are reported in full in the published protocol.\(^10\) All participants were cared for in 1 of the 4 UK ECMO centers and included infants transferred from other hospitals across the country for care. Each infant met existing standard criteria for ECMO eligibility based on the clinical decision of the local ECMO team. Infants were excluded if they

- were referred for ECMO because of a diagnosis of congenital diaphragmatic hernia (because of an increased inherent risk of poor neurodevelopmental outcome and potentially severe underlying pulmonary hypoplasia incompatible with long-term survival);
- received ECMO post–cardiac surgery (because these infants were not part of the original underpinning study and their prognosis was likely to be heavily influenced by their primary diagnosis); or
- had received any therapeutic cooling before randomization.

Because of the life-threatening condition of the infants involved and the need to carry out long-distance transfers in a high proportion of cases, consent procedures involved a 2-stage process. Written (wherever possible) or witnessed verbal consent was taken in the first instance, and this consent was reaffirmed within the subsequent 24 to 48 hours with documentation in the infant’s medical record.

**Intervention and Clinical Management**

For participants randomly assigned to receive mild hypothermia, the process of cooling commenced immediately upon initiation of the ECMO circuit by adjustment of the heat exchanger in the circuit to achieve a core temperature of 34°C. Temperature was measured by nasopharyngeal, rectal, or urinary electronic temperature probes; and the water heater was adjusted to maintain this core temperature. All infants in this arm received a minimum of 48 hours of cooling (to allow for any infant that rapidly improved while receiving ECMO) to a maximum of 72 hours before being rewarmed over a 12-hour period, in keeping with the published neuroprotection trials.\(^5,6\) Those infants randomly assigned to the control arm of the study received conventional ECMO throughout, with a targeted body temperature of 37°C.

Apart from the temperature during the first 48 to 72 hours, all other aspects of management were identical within each ECMO center. For those successfully weaned from ECMO, referral back to their local hospital occurred when considered safe by the clinical team in the ECMO center.

As well as the routine intensive monitoring associated with ECMO, cerebral amplitude-integrated electroencephalography (aEEG) recording was attempted in all infants during the first 72 hours of ECMO. Cerebral ultrasound assessments were also performed during the infant’s stay in the ECMO center on the basis of clinical need. Most infants had left the ECMO center before they were well enough to undergo MRI scanning of their brain, local
units receiving the infants back after ECMO were encouraged to perform MRI scans, but this decision was left to their discretion.

Outcomes

The primary outcome was the cognitive score from the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III), at 2 years of age corrected for prematurity where relevant (24–27 months). All infants were assessed by the same pediatrician, who was blinded to the original allocation, in an appropriate clinical setting close to their home or at home in a few cases. Death was not included in a composite primary outcome, because our interpretation of the literature at the time the protocol was developed was that mild hypothermia was unlikely to influence mortality and hence we chose to focus on the outcome for which there was significant biological plausibility that a benefit might result. However, death was included as a secondary outcome. A number of additional psychomotor tests as well as a physical examination by the pediatrician were also carried out. Prespecified secondary outcomes were as follows:

- Death
- Neurologic optimality score
- Gross and fine motor score from the Bayley-III
- Cerebral palsy
- Gross motor function classification score
- Seizures requiring regular anticonvulsant treatment
- Visual difficulties not corrected by eyeglasses
- Hearing difficulties requiring aids
- Language-expressive and receptive scores from the Bayley-III
- Parent Report of Children’s Abilities-revised

- Infant Characteristics Questionnaire
- The Brief Infant-Toddler Social and Emotional Assessment
- Measures of growth: height, weight, and head circumference
- Rates of “no impairment” (Bayley-III cognition, language, and motor scores 85; normal neurologic examination; normal vision [including glasses]; and normal hearing without aids)

Sample Size

The sample size estimate was based on what was considered to be a clinically important difference in the Bayley-III cognitive score at 2 years’ corrected age, based on existing knowledge of ECMO survivors. Given that the primary outcome could be assessed only in survivors, the sample size estimate was inflated to allow for mortality among those who died before the age of 2 years. Assuming a mean cognitive score of 95 (SD: 15) in the control group, recruitment of 118 infants with an estimated mortality of 20% provided a realistic recruitment target (ie, 94 surviving infants) while also giving 90% power to detect a 10-point difference between the 2 arms with a 2-sided 5% level of significance.

Randomization

Assignment to a treatment group was performed by using a secure Web-based system (hosted by the National Perinatal Epidemiology Unit, Clinical Trials Unit, Oxford, UK). As soon as parental consent was obtained, the recruiting ECMO specialist logged onto a Web site and obtained the treatment allocation of ECMO only or ECMO with cooling. A deterministic minimization algorithm was used to ensure a balanced treatment allocation within center and by method of cannulation (veno-venous or veno-arterial).

Blinding

The parents, who completed self-report questionnaires at 2 years, were aware of the allocation their infant had received. It was not possible to blind the staff involved in clinical care of the infant during the time on ECMO; however, the pediatrician who performed the 2-year assessments was masked to allocation and parents were asked not to reveal this information.

Statistical Methods

Infants were analyzed in their allocated group, regardless of allocation received or deviations from the protocol. For the primary outcome analysis, the mean difference in the Bayley-III cognitive score between groups and 95% confidence interval (CI) were calculated and analyzed by using the independent 2-sample t test. An adjusted analysis was also performed, adjusting for the minimization criteria (center and method of cannulation).

Secondary outcomes were summarized with counts (percentages) for categorical variables, means (SD) for normally distributed continuous variables, or medians (interquartile or entire range, whichever was appropriate) for skewed continuous variables. The magnitude and direction of the treatment effects were assessed by calculating the relative risk (RR; 99% CI) for categorical outcomes, the mean difference (99% CI) for normally distributed continuous variables, and the median difference (99% CI) for skewed continuous variables. SD scores were calculated for growth data by using the British 1990 growth reference (revised September 1996). Prespecified subgroup analyses were performed by using a statistical test of interaction on the following outcomes: Bayley-III cognitive score, vision, hearing, and neurologic optimality score. Analyses were performed by 2 members of the NEST research team: Louise Linsell, MSc and Ed Juszczak, MSc.
The subgroups examined were as follows: initial method of cannulation (veno-arterial versus veno-venous), infant’s worst oxygenation index in the 4 hours before random assignment (<60 vs ≥60), initial aEEG pattern shown on the cerebral function monitor (normal versus abnormal), and principal clinical diagnosis leading to ECMO referral (severe cardiorespiratory failure versus other).

Oversight

The NEST protocol was approved by the Trent Multicentre Research Ethics Committee and the local research ethics committee of each participating hospital. The conduct of the study was overseen by an independent trial steering committee with advice from an independent data monitoring and ethics committee. The independent data monitoring committee met on 5 occasions and did not recommend early stopping.

RESULTS

Recruitment and Analysis Population

Between June 1, 2006, and March 31, 2010, 111 infants were recruited to the trial, of whom 55 were allocated to ECMO only and 56 were allocated to ECMO with cooling (Fig 1). We identified an additional 46 infants who were screened and not recruited for a variety of reason including parents declined, insufficient to time to seek consent (generally because of clinical deterioration), and nonavailability of staff with approval to carry out consent. We recognize that a small number of additional infants would potentially have been eligible for this trial but who, for clinical reasons, were not transferred for ECMO.

Follow-up occurred at 2 years of age and within a window of ±3 months. All assessments and neurologic examinations were performed by a single pediatric assessor. Fourteen infants died before follow-up at 2 years (12 before hospital discharge): 5 in the ECMO-only group and 9 in the ECMO-with-cooling group. This difference was not significant, and by chance, 3 deaths relating to underlying metabolic/congenital anomalies were all in the cooling arm. Pediatric assessments were performed for 95 of 97 (98%) survivors (sample size was based on 94 survivors). Two survivors in the ECMO-only group emigrated, and no data were collected after discharge, although 1 infant was known to be alive at 2 years. The baseline characteristics of all infants who were randomly assigned (n = 111) and those assessed by a pediatrician at age 2 (n = 95) were broadly similar (Table 1). Eight assessments were partially completed due to behavioral problems; however, only 2 of these infants (ECMO with cooling) were excluded from the primary analysis because in the other 6 infants the cognitive score component of the assessment was completed. Eighty-eight parent questionnaires were received: there was a response rate of 43 of 48 (90%) in the ECMO-only group and 45 of 47 (96%) in the ECMO-with-cooling group.

All 111 infants were included in the analysis wherever data were available. The numbers of infants included in the analysis of the Bayley-III cognitive composite score (primary outcome) were 48 of 55 (87%) in the ECMO-only group and 45 of 56 (80%) in the ECMO-with-cooling group.

Compliance and Clinical Outcomes Before Discharge

Two infants (ECMO-only group) recovered after trial entry and ECMO was not required, and 2 infants (ECMO-with-cooling group) died on day 2 of the ECMO run. An additional 5 infants (4 in the ECMO-only group, 1 in the ECMO-with-cooling group) did not require ECMO.
after 48 hours; hence, these infants received cooling only up until that point (Table 2). It was observed that infants allocated to ECMO with cooling received fewer inotropes on days 2 and 3 and less heparin throughout the 72-hour period than infants in the ECMO-only group. Clinical characteristics before discharge were similar in both groups, although the number of events for some conditions was low.

**Health and Neurodevelopmental Outcomes at 2 Years**

The mean Bayley-III scores for cognition (primary outcome), language, and motor skills at 2 years’ corrected age were slightly lower in the ECMO-with-cooling group; the variances were slightly greater, but the differences were not statistically significant (Table 3). The mean cognitive score in the ECMO-only group was 90.6 (SD: 13.1) compared with 88.0 (SD: 16.2) in the ECMO-with-cooling group (difference in means: 2.6 points; 95% CI: −8.7 to 3.4). After adjusting for the minimization factors,
95% CI: e1252
FIELD
difference in means was
center, and intended cannulation, the
Two infants (ECMO only) recovered after trial entry and ECMO was not required. The duration of the intervention (cooling)
died on day 2 of the ECMO run.

**TABLE 2** Clinical Outcomes of Infants Before Discharge

<table>
<thead>
<tr>
<th></th>
<th>All Randomly Assigned Infants (N = 111)</th>
<th>ECMO Only (n = 55)</th>
<th>ECMO With Cooling (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants on ECMO* , n (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Day 1</td>
<td>53 (96)</td>
<td>56 (100)</td>
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<tr>
<td>Day 2</td>
<td>53 (96)</td>
<td>54 (96)</td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>49 (88)</td>
<td>53 (95)</td>
<td></td>
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<tr>
<td>Reported sepsis, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before admission to ECMO unit</td>
<td>12 (22)</td>
<td>11 (20)</td>
<td></td>
</tr>
<tr>
<td>During stay in ECMO unit</td>
<td>6 (11)</td>
<td>8 (14)</td>
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</tr>
<tr>
<td>After stay in ECMO unit</td>
<td>11 (20)</td>
<td>7 (13)</td>
<td></td>
</tr>
<tr>
<td>Cardiac arrhythmia requiring intervention, n (%)</td>
<td>3 (5)</td>
<td>3 (5)</td>
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<tr>
<td>Pulmonary air leak, n (%)</td>
<td></td>
<td>2 (4)</td>
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<tr>
<td>Pulmonary hemorrhage, n (%)</td>
<td></td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>Necrotizing enterocolitis, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
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<tr>
<td>Renal support while receiving ECMO, n (%)</td>
<td>8 (15)</td>
<td>8 (14)</td>
<td></td>
</tr>
<tr>
<td>Jaundice requiring intervention, n (%)</td>
<td>4 (7)</td>
<td>3 (5)</td>
<td></td>
</tr>
<tr>
<td>Head ultrasound performed, n (%)</td>
<td>54 (98)</td>
<td>56 (100)</td>
<td></td>
</tr>
<tr>
<td>MRI performed, n (%)</td>
<td>17 (31)</td>
<td>19 (34)</td>
<td></td>
</tr>
<tr>
<td>Duration of hospital stay before death or discharge, median (IQR), d</td>
<td>21 (16–33)</td>
<td>22.5 (17–30.5)</td>
<td></td>
</tr>
<tr>
<td>Duration of respiratory support, median (IQR), d</td>
<td>9 (7–15)</td>
<td>10 (7–14)</td>
<td></td>
</tr>
<tr>
<td>Died before hospital discharge, n (%)</td>
<td>4 (7)</td>
<td>8 (14)</td>
<td></td>
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</tbody>
</table>

*IQR, interquartile range.

Twelve deaths occurred before hospital discharge (4 ECMO only and 8 ECMO with cooling), and 2 additional deaths were reported (1 in each arm) after discharge, so the proportion of deaths at 2 years was 5 of 55 (9%) in the ECMO-only group versus 9 of 56 (16%) in the ECMO-with-cooling group (RR: 1.77; 99% CI: 0.46–6.83). Cerebral palsy was diagnosed in 3 of 48 infants (6%) in the ECMO-only group versus 7 of 47 infants (15%) in the ECMO-with-cooling group (RR: 0.57–1.45).

Overall, this pattern of small differences favoring the ECMO-only group was consistent throughout the health and neurologic findings at 2 years, apart from growth outcomes, which favored the ECMO-with-cooling group (Table 3). The use of aEEG did not appear to be helpful in predicting outcome.

**Parent Report of Abilities and Behavior at 2 Years**

Parent-reported outcomes showed a different pattern, which tended to favor ECMO with cooling, but the differences were small and none of the differences were significant (Table 4).

**Subgroup Analyses**

There was no evidence that the effect of cooling was inconsistent across specific subgroups of infants; however, CIs were very wide due to the small numbers in each subgroup.

**Safety**

Serious adverse event reports were not different between the 2 groups: 11 were reported in the ECMO-only group (1 infant experienced 2 events) and 13 in the ECMO-with-cooling group (1 infant experienced 3 events) (Supplemental Table 5).

**DISCUSSION**

This trial indicates that therapeutic cooling during neonatal ECMO does not improve neurodevelopmental outcome at age 2 years. The trial was relatively small because it was based on realistic but nonetheless somewhat speculative estimates of the size of improvement that might result from the use of cooling. However, there is no suggestion in these results of a trend toward improved outcome that the trial was too small to demonstrate; if anything, the opposite is true.

Was the intervention adequate? Whereas we planned in the protocol that infants in the cooling arm could receive cooling for a minimum of 48 hours, the vast majority of those recruited completed 72 hours of cooling. Seventy-two hours of cooling has been shown to be effective in providing neuroprotection in infants exposed to significant perinatal asphyxia. From a technical perspective, cooling on ECMO proved to be easy to achieve by use of the circuit and was not associated with an increase in complications. It could be argued that longer cooling or cooling to a lower temperature might have been more effective, but the trend in the results presented here of a worse outcome with cooling must at least raise a strong note of caution before considering the use of such approaches.10

Was this the wrong study population? By excluding infants with diaphragmatic hernia and those receiving ECMO for postoperative cardiac support we...
<table>
<thead>
<tr>
<th></th>
<th>ECMO Only (n = 48)</th>
<th>ECMO With Cooling (n = 47)</th>
<th>RR (99% CI) Unless Otherwise Specified (Mean Difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surviving infants assessed at 2 years (n = 95)</strong></td>
<td></td>
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<tr>
<td>Bayley-III Scales of Infant and Toddler Development</td>
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<tr>
<td>Cognitive composite score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD (primary outcome)</td>
<td>90.6 ± 13.1</td>
<td>88.0 ± 16.2</td>
<td>−2.6 (−8.7 to 3.4)*</td>
</tr>
<tr>
<td>Unknown, n</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Language composite score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>96.3 ± 17.2</td>
<td>95.5 ± 22.3</td>
<td>−0.8 (−12.0 to 10.4)</td>
</tr>
<tr>
<td>Unknown, n</td>
<td>4</td>
<td>4</td>
<td></td>
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<tr>
<td>Motor composite score</td>
<td></td>
<td></td>
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<tr>
<td>Mean ± SD</td>
<td>96.2 ± 14.4</td>
<td>89.9 ± 16.0</td>
<td>−6.3 (−14.7 to 2.0)</td>
</tr>
<tr>
<td>Unknown, n</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Death before 2 years (whole sample), n (%)</strong></td>
<td>5/55 (9)</td>
<td>9/56 (16)</td>
<td>1.77 (0.46 to 6.83)</td>
</tr>
<tr>
<td>Neurologic optimality score (maximum of 78)</td>
<td></td>
<td></td>
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<tr>
<td>Median score (IQR)</td>
<td>77 (75–77)</td>
<td>77 (75–78)</td>
<td></td>
</tr>
<tr>
<td>Optimal (≥74), n (%)</td>
<td>40 (63)</td>
<td>38 (61)</td>
<td>1 (referent)</td>
</tr>
<tr>
<td>Suboptimal (&lt;74), n (%)</td>
<td>8 (17)</td>
<td>9 (19)</td>
<td>1.15 (0.37 to 3.07)</td>
</tr>
<tr>
<td>Cerebral palsy, n (%)</td>
<td>3 (6)</td>
<td>7 (15)</td>
<td>2.38 (0.44 to 13.0)</td>
</tr>
<tr>
<td>Spastic bilateral</td>
<td>0</td>
<td>3</td>
<td></td>
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<tr>
<td>Hemiplegia</td>
<td>1</td>
<td>3</td>
<td></td>
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<tr>
<td>Dyskinetic</td>
<td>1</td>
<td>0</td>
<td></td>
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<tr>
<td>Nonclassified</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Gross Motor Function Classification Scale, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cerebral palsy</td>
<td>45 (94)</td>
<td>40 (85)</td>
<td>1 (referent)</td>
</tr>
<tr>
<td>Level 1–2</td>
<td>2 (4)</td>
<td>5 (8)</td>
<td>2.38 (0.44 to 13.0)</td>
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<tr>
<td>Level 3–5</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td></td>
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<tr>
<td>Seizures requiring anticonvulsant treatment, n (%)</td>
<td>0 (0)</td>
<td>5 (11)</td>
<td></td>
</tr>
<tr>
<td>Usual vision (with glasses if worn), n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Normal or near normal</td>
<td>48 (100)</td>
<td>44 (94)</td>
<td>1 (referent)</td>
</tr>
<tr>
<td>Impaired but useful</td>
<td>0 (0)</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>Sees light/gross movement only</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>No useful vision (blind)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
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<tr>
<td>Usual hearing (with aids if worn), n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal or near normal</td>
<td>48 (100)</td>
<td>43 (91)</td>
<td>1 (referent)</td>
</tr>
<tr>
<td>Hearing loss corrected by aids</td>
<td>0 (0)</td>
<td>3 (6)</td>
<td></td>
</tr>
<tr>
<td>Some hearing (loss not corrected</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>No useful hearing even with aids</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Functioning within the normal range: Bayley cognitive, language, and motor scores ≥85, Gross Motor Function Classification Scale = 0, and normal vision (including glasses) and normal hearing (without aids), n (%)</td>
<td>28 (64)</td>
<td>27 (53)</td>
<td>0.99 (0.65 to 1.50)</td>
</tr>
<tr>
<td>Unknown, n</td>
<td>4</td>
<td>4</td>
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<tr>
<td>All surviving infants not lost to follow-up (n = 95)</td>
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<tr>
<td>Growth SDSb</td>
<td></td>
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<tr>
<td>Weight SDS, mean ± SD</td>
<td>−0.12 ± 1.39</td>
<td>0.33 ± 1.19</td>
<td>0.45 (−0.08 to 0.98)</td>
</tr>
<tr>
<td>Unknown, n</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Height SDS, mean ± SD</td>
<td>−0.42 ± 1.29</td>
<td>0.07 ± 1.21</td>
<td>0.48 (−0.03 to 0.99)</td>
</tr>
<tr>
<td>Unknown, n</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Head circumference SDS, mean ± SD</td>
<td>−1.23 ± 1.34</td>
<td>−1.11 ± 1.92</td>
<td>0.11 (−0.57 to 0.78)</td>
</tr>
<tr>
<td>Unknown, n</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Feeding difficulties, n (%)</td>
<td>4 (8)</td>
<td>4 (9)</td>
<td>1.02 (0.18 to 5.84)</td>
</tr>
<tr>
<td>Head function, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal head control</td>
<td>48 (100)</td>
<td>46 (98)</td>
<td>1 (referent)</td>
</tr>
<tr>
<td>Abnormal head control</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Poor head control</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>No head control</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Trunk function, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No apparent problem</td>
<td>46 (96)</td>
<td>43 (91)</td>
<td>1 (referent)</td>
</tr>
<tr>
<td>Sits unsupported, less secure</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td>2.04 (0.23 to 17.8)</td>
</tr>
<tr>
<td>Cannot sit unless supported</td>
<td>0 (0)</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>Difficult to place in sitting position</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Lower limb function, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
recruited infants to the trial who form the core group of most ECMO programs around the world. In addition, infants of this type were shown previously to be at risk of poor neurodevelopmental outcome, and indeed those previous findings have been mirrored in this study, with the mean cognitive score for both groups being 90.

In developing this study we felt that there was strong empirical evidence that cooling infants who received ECMO might result in improved outcomes. The fact that such improvements did not result suggests that at least some of our judgments in this regard were misplaced. There was no suggestion in the data that an increase in complications related to cooling masked an underlying positive effect, such as that seen in trials of cooling in infants who had suffered intrapartum asphyxia. It was, of course, in animal models of intrapartum asphyxia that the underpinning research regarding the neuroprotective effects of cooling in newborns were first assessed and established. It may be that the nature of the insult in infants who receive ECMO (ie, it takes place over a relatively prolonged period) is such that damage cannot be prevented by the use of cooling for a period during the insult, albeit at what is likely to be the time of maximum physiologic disruption. Existing data certainly suggest that it is the underlying condition and or the associated physiologic changes rather than the use of ECMO that results in an increased risk of long-term neurodevelopmental impairment.

In terms of the wider implication of this study, it seems clear that the use of cooling for neuroprotection during ECMO (it is sometimes used to reduce oxygen consumption) is to be avoided. However, the results of this study also highlight the potential dangers of extrapolating existing research findings from 1 group to another without appropriate testing. For example, the current trend to use mild cooling to treat intrapartum asphyxia in infants who do not meet the entry criteria of the original trials may well be unwise because the same response cannot be assumed, as we found here. Conversely, a potential role for mild cooling for a period after neonatal cardiac surgery as a means of improving long-term outcomes in these infants remains untested, and the results of this study are of no direct relevance.

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The NEST study group collaborators/investigators: Dr David Field, Denis Azzopardi, Dr Peter Brocklehurst, Dr Frances Cowan, Dr David Edwards, and Mr Richard Firmin. Data Monitoring Committee members: Diana Elbourne (Chair), Dr Richard Cooke, Dr Linda Franck, Dr Henry Halliday, Dr Duncan Macrae, and Dr Neil Marlow. Trial Steering Committee members: Dr Andrew Wilkinson (Chair), Ms Pauline Fellows, Dr Mary Montgomery, Ms Farrah Pradhan, Dr Claire Snowdon, and Dr Marianne Thoresen. National Perinatal Epidemiology Unit Coordinating Centre: Ms Denise Jennings, Mr Ed Juszczak, Ms Ursula Bowler, Ms Sarah

TABLE 3 Continued

<table>
<thead>
<tr>
<th>Walks fluently</th>
<th>ECMO Only (n = 48)</th>
<th>ECMO With Cooling (n = 47)</th>
<th>RR (99% CI) Unless Otherwise Specified (Mean Difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gait functional but nonfluent</td>
<td>45 (94)</td>
<td>41 (87)</td>
<td>1 (referent)</td>
</tr>
<tr>
<td>Reduced mobility restricts lifestyle</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>2.04 (0.36 to 11.7)</td>
</tr>
<tr>
<td>No independent walking</td>
<td>2 (4)</td>
<td>4 (8)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Upper limb function, n (%)</th>
<th>ECMO Only (n = 48)</th>
<th>ECMO With Cooling (n = 47)</th>
<th>RR (99% CI) Unless Otherwise Specified (Mean Difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No apparent problem</td>
<td>45 (94)</td>
<td>42 (89)</td>
<td>1 (referent)</td>
</tr>
<tr>
<td>Some difficulty but feeds self</td>
<td>2 (4)</td>
<td>3 (6)</td>
<td>1.70 (0.28 to 10.4)</td>
</tr>
<tr>
<td>Unable to feed self</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>Contractures present</td>
<td>1 (2)</td>
<td>4 (8)</td>
<td>4.09 (0.24 to 69.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Usual communication, n (%)</th>
<th>ECMO Only (n = 48)</th>
<th>ECMO With Cooling (n = 47)</th>
<th>RR (99% CI) Unless Otherwise Specified (Mean Difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uses speech</td>
<td>39 (81)</td>
<td>36 (77)</td>
<td>1 (referent)</td>
</tr>
<tr>
<td>Speech plus other formal method</td>
<td>4 (8)</td>
<td>2 (4)</td>
<td>1.25 (0.45 to 3.50)</td>
</tr>
<tr>
<td>Formal systematized method only</td>
<td>2 (4)</td>
<td>3 (6)</td>
<td></td>
</tr>
<tr>
<td>No communication</td>
<td>3 (6)</td>
<td>6 (13)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall disability from any cause, n (%)</th>
<th>ECMO Only (n = 48)</th>
<th>ECMO With Cooling (n = 47)</th>
<th>RR (99% CI) Unless Otherwise Specified (Mean Difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No disability</td>
<td>38 (79)</td>
<td>32 (68)</td>
<td>1 (referent)</td>
</tr>
<tr>
<td>Impairment without disability</td>
<td>7 (15)</td>
<td>10 (21)</td>
<td>1.53 (0.62 to 3.80)</td>
</tr>
<tr>
<td>Mild disability</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Moderate disability</td>
<td>2 (4)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Severe disability</td>
<td>1 (2)</td>
<td>3 (6)</td>
<td></td>
</tr>
</tbody>
</table>

SDS, SD score.
a 95% CI for primary outcome.
Ayers, Mr Andy King, Dr Maggie Redshaw, and Ms Louise Linsell. Recruiting centers (n = number recruited per centre): Glenfield Hospital (59) (Mr Giles Peek, Ms Anne-Marie Hill, Ms Gail Faulkner, Dr Hitesh Pandya, Dr Marie Horan, Dr Chris Harvey); Great Ormond Street Hospital (21) (Dr Aparna Hoskote, Dr Allan Goldman, Ms Liz Smith, Ms Maura O’Callaghan, Ms Helen Boardman); Freeman Hospital (10) (Dr Jane Cassidy, Dr Jon Smith, Ms Caroline McPherson, Dr Alan Fenton, Dr Janet Berrington); and the Royal Hospital for Sick Children Glasgow (21) (Dr Judith Simpson, Mr Carl Davis, Ms Morag Liddell, Ms Gillian Wylie). Follow-up was carried out by Dr Andrew T.M. Chew and supervised by Dr Frances Cowan. The cranial ultrasound and MRI interpreter was Dr Frances Cowan. The Cerebral Function Monitoring interpreter was Dr Denis Azzopardi. The writing committee consisted of Dr David Field, Mr Ed Juszczak, Ms Louise Linsell, Dr Denis Azzopardi, Dr Frances Cowan, Dr Neil Marlow, and Dr David Edwards.

We especially thank the parents who agreed to let their children take part in the NEST study and to the funders who made it possible.

TABLE 4 Parent Report of Abilities and Behavior of Infant at 2 Years

<table>
<thead>
<tr>
<th></th>
<th>Surviving Infants Assessed at 2 Years (n = 95)</th>
<th>ECMO Only (n = 48)</th>
<th>ECMO With Cooling (n = 47)</th>
<th>Mean Difference (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PARCA-R</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent-report composite score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD score</td>
<td>84.3 ± 35.8</td>
<td>87.4 ± 44.1</td>
<td>3.1 (−14.3 to 20.4)</td>
<td></td>
</tr>
<tr>
<td>Unknown, n</td>
<td>5</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nonverbal Cognition Scale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD score</td>
<td>25.4 ± 4.6</td>
<td>24.2 ± 7.7</td>
<td>−1.2 (−3.9 to 1.5)</td>
<td></td>
</tr>
<tr>
<td>Unknown, n</td>
<td>5</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Linguistic Skills Scale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD score</td>
<td>58.9 ± 32.7</td>
<td>62.2 ± 39.7</td>
<td>3.3 (−12.3 to 18.9)</td>
<td></td>
</tr>
<tr>
<td>Unknown, n</td>
<td>5</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ICQIC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fussy/difficult/demanding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD score</td>
<td>53.7 ± 11.7</td>
<td>51.7 ± 13.5</td>
<td>−1.9 (−7.4 to 3.5)</td>
<td></td>
</tr>
<tr>
<td>Unknown, n</td>
<td>6</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadaptable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD score</td>
<td>14.2 ± 4.9</td>
<td>15.2 ± 4.9</td>
<td>0.9 (−1.2 to 3.1)</td>
<td></td>
</tr>
<tr>
<td>Unknown, n</td>
<td>7</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD score</td>
<td>26.0 ± 4.8</td>
<td>25.7 ± 5.2</td>
<td>−0.4 (−2.5 to 1.8)</td>
<td></td>
</tr>
<tr>
<td>Unknown, n</td>
<td>5</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unsociable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD score</td>
<td>11.3 ± 3.6</td>
<td>11.3 ± 3.9</td>
<td>−0.05 (−1.7 to 1.6)</td>
<td></td>
</tr>
<tr>
<td>Unknown, n</td>
<td>5</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BITSEAC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Problem subtotal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD score</td>
<td>10.6 ± 7.1</td>
<td>11.9 ± 8.6</td>
<td>1.3 (−2.0 to 4.6)</td>
<td></td>
</tr>
<tr>
<td>Possible problem (&gt;25th percentile), n (%)</td>
<td>13 (30)</td>
<td>11 (24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown, n</td>
<td>5</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Competence subtotal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD score</td>
<td>16.8 ± 3.0</td>
<td>161 ± 3.9</td>
<td>−0.7 (−2.1 to 0.6)</td>
<td></td>
</tr>
<tr>
<td>Possible delay (&lt;5th percentile), n (%)</td>
<td>10 (23)</td>
<td>16 (35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown, n</td>
<td>5</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


a The PARCA-R composite score (range: 0–158) is the sum of the Nonverbal Cognition Scale (range: 0–54) and the Linguistic Skills Scale (range: 0–124). A higher score indicates better performance.

b The 4 domains of the ICQ have the following range of values: fussy/difficult/demanding (range: 16–112), unadaptable (range: 5–35), persistent (range: 6–42), and unsociable (range: 5–35). A higher score indicates less desirable characteristics.

c A higher score for the BITSEA Problem subtotal (range: 0–62) indicates more problems. A higher score for the BITSEA Competence subtotal (range: 0–24) indicates greater competence.

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