Active Versus Passive Cooling During Neonatal Transport

WHAT'S KNOWN ON THIS SUBJECT: Cooling infants with hypoxic-ischemic encephalopathy shortly after birth improves survival and neurodevelopmental outcome. The optimal way to cool infants during transfer to regional NICUs is unclear.

WHAT THIS STUDY ADDS: Data from a regional neonatal transfer team, using first passive and subsequently active cooling for these infants, suggest that active cooling results in improved thermal control and a reduction in stabilization time.

BACKGROUND AND OBJECTIVE: Therapeutic hypothermia is now the standard of care for hypoxic-ischemic encephalopathy. Treatment should be started early, and it is often necessary to transfer the infant to a regional NICU for ongoing care. There are no large studies reporting outcomes from infants cooled passively compared with active (servo-controlled) cooling during transfer. Our goal was to review data from a regional transport service, comparing both methods of cooling.

METHODS: This was a retrospective observational study of 143 infants referred to a regional NICU for ongoing therapeutic hypothermia. Of the 134 infants transferred, the first 64 were cooled passively, and 70 were subsequently cooled after purchase of a servo-controlled mattress. Key outcome measures were time to arrival at the regional unit, temperature at referral and arrival at the regional unit, and temperature stability during transfer.

RESULTS: The age cooling was started was significantly shorter in the actively cooled group (46 [0–352] minutes vs 120 [0–502] minutes; *P* < .01). The median (range) stabilization time (153 [60–385] minutes vs 133 [45–505] minutes; *P* = .04) and age at arrival at the regional unit (504 [191–924] minutes vs 452 [225–1265] minutes; *P* = .01) were significantly shorter in the actively cooled group. Only 39% of infants passively cooled were within the target temperature range at arrival to the regional unit compared with 100% actively cooled.

CONCLUSIONS: Servo-controlled active cooling has been shown to improve temperature stability and is associated with a reduction in transfer time. *Pediatrics* 2013;132:841–846

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KEY WORDS
hypothermia, hypoxic-ischemic encephalopathy, neonatal, transport medicine

ABBREVIATIONS
ANTS—Acute Neonatal Transfer Service
HIE—hypoxic-ischemic encephalopathy
NTS—Neonatal Transport Service
TOBY—Total Body Hypothermia trial

Dr Chaudhary collated and analyzed the data, and drafted the initial manuscript; Dr Farrer conceptualized and designed the study, collected the data, and reviewed and revised the manuscript; Dr Broster collected the data, and reviewed and revised the manuscript; Ms McRitchie collated and analyzed the data and reviewed the manuscript; Dr Austin analyzed the data and redrafted the manuscript, and all authors approved the final manuscript as submitted.

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Therapeutic hypothermia has been shown to improve survival and neuro-developmental outcome. In the United Kingdom, both the National Institute for Health and Clinical Excellence and the British Association of Perinatal Medicine issued guidance on the provision of therapeutic hypothermia for infants with HIE. The recommendation was that “this procedure should only be carried out in units experienced in the care of severely ill neonates, by staff that have been specifically trained in the use of therapeutic hypothermia.” In the United Kingdom, this recommendation has been interpreted as the large-network NICUs.

All the major clinical trials randomized infants with intention to intervention by 6 hours of age. Experimental studies have shown that the benefit of cooling is maximal the sooner it is commenced, and the Total Body Hypothermia (TOBY) trial showed a trend to improved outcome in infants cooled within 4 hours of delivery. There is limited evidence regarding the efficacy of cooling started beyond 12 hours of age. Therefore, current evidence would suggest that the sooner cooling is commenced, the more likely it is to be beneficial.

Given that infants with HIE are born in all delivery settings, to minimize delay in initiating treatment, cooling should be commenced at the place of birth and continued during transfer to the regional NICU. In the East of England, the Acute Neonatal Transfer Service (ANTS) first transferred infants for therapeutic hypothermia to 1 of the 3 network NICUs in June 2009. In October 2009, the service began operating 24 hours, at which time cooling became the standard of care throughout the region. In April 2010, a quality improvement project, funded by a grant from the Health Foundation, was created to develop a coordinated service for neonatal neuroprotection in the region. A large proportion of the project involved providing education and training to health care professionals in all the hospitals in the unit. The project team worked closely with ANTS in developing integrated care pathways for identification, stabilization, and transfer of infants undergoing therapeutic hypothermia. Infants were initially stabilized and transferred by using passive cooling methods. In January 2011, ANTS acquired a servo-controlled cooling mattress to actively cool infants during stabilization and subsequent transfer to the network NICU.

The aim of this retrospective observational study was to compare the effectiveness of passive and active cooling during transfer. The key outcome measurements were: time to target temperature, stabilization time, and temperature stability during transfer. Target temperature range was defined as 33.0°C to 34.0°C.

METHODS

Infants, Units, Eligibility Criteria, and Passive Cooling

All newborn infants referred to ANTS for cooling between June 2009 and May 2012 were included in the current study. The ANTS team covers all of the East of England, which consists of 18 hospitals, including 3 network NICUs that provide a cooling service. Infants were assessed for eligibility according to the regional guidelines, developed from the UK TOBY cooling register. This protocol required that infants have evidence of a perinatal hypoxic-ischemic insult (Apgar score <5 at 10 minutes or continued need for active resuscitation at 10 minutes or acidosis within 60 minutes of birth with a pH <7.00 and/or base deficit ≥16 mmol/L) and ongoing or evolving encephalopathy (altered state of consciousness, abnormal tone and abnormal primitive reflexes, or presence of clinical seizures). The TOBY study found that the effect of cooling did not significantly vary according to the severity of abnormality on amplitude-integrated electroencephalography; therefore, this monitoring was not required before commencing cooling. If the infants met the criteria for therapeutic hypothermia, then passive cooling was commenced according to the regional care pathway (Fig 1), including core (rectal) temperature monitoring.

Data Collection

ANTS routinely collect basic demographic and operational data for all referred infants, including timing of referral, dispatch from base, arrival and departure from the referring hospital (stabilization time), and arrival at the destination hospital. For all infants referred for cooling, the following data were also routinely collected for audit purposes: age at which passive cooling started, initial rectal temperature, rectal temperature when ANTS arrived (as well as 15-minute rectal temperature measurements until arrival at the destination hospital), and time to target temperature.

Data Analysis

Infants were divided into 2 groups (passive and active) according to the method of cooling used during stabilization and transfer by the ANTS team. For each group, differences were assessed by using Student’s t test (normal distribution) or the Mann-Whitney U test (skewed distribution). Data were analyzed by using Prism 6 (GraphPad Software, San Diego, CA). A P value <.05 was considered significant for all statistical analysis.
FIGURE 1
Page from the regional care pathway for the diagnosis and initial management of HIE. A temperature chart, devised for local units with the aim of achieving controlled cooling with the use of passive methods, is depicted.
**RESULTS**

A total of 143 eligible infants were referred to the ANTS team between June 2009 and May 2012. Of the 143 referrals, 134 were transferred to 1 of the 3 network NICUs for ongoing therapeutic hypothermia. Of the 9 who were not transferred by ANTS, 2 were too sick to move and died at the local unit, and 7 were transferred into London by the London neonatal transport service (NTS) because the ANTS team was busy with other emergency transfers. Between June 2009 and March 2011, a total of 64 infants were transferred and cooled by passive means, through the whole stabilization and transfer period. From March 2011 to May 2012, the 70 infants transferred were passively cooled until the ANTS team arrived, and the infants were then placed on a Tecotherm (Inspiration Healthcare Ltd, Leicester, United Kingdom) servo-controlled cooling mattress until they reached the referral unit (actively cooled).

There was no difference in gender, gestational age, or degree of acidosis at referral between the passively cooled and actively cooled groups (Table 1). The transfer times are shown in Table 2. There were no significant differences between the 2 groups in age at referral, dispatch time, or journey time to the regional NICU; however, both the stabilization time and age at arrival at the network NICU were significantly shorter in the actively cooled group \((P = .04\) and .01, respectively).

Cooling was started either before or shortly after referral to the ANTS team. The median (range) age cooling was started in the passive group was 120 (0–502) minutes, significantly longer than in the active cooling group (46 [0–352] minutes; \(P < .01\)). Forty-seven infants (73%) in the passive group and all 70 infants in the active group achieved target temperature before admission to the network NICU. In those who did reach target temperature, there was no significant difference in the time taken to achieve target temperature: a median (range) of 185 (15–451) minutes in the passive group versus 180 (0–430) minutes in the active group \((P = .95)\).

Figure 2 shows the mean temperature of infants in the active and passive groups at the following time points: (1) on arrival by ANTS at the referring unit; (2) on departure from the referring unit; and (3) on arrival at the network NICU. There was a significant difference between the temperature on arrival at the referring unit and the temperature on departure from the referring unit for both groups \((P = .006\) for both passive and active groups) but no difference between departure from the referring unit and arrival to the network NICU \((P = .75\) and .07 for passive and active groups, respectively). However, the number of infants outside the target temperature range (33°C–34°C) was significantly greater in the passive group, with 27% of infants not achieving target temperature and 34% of infants overcooled \((P = .02\), Fisher’s exact test).

**DISCUSSION**

In this observational study, we found that servo-controlled active cooling on transfer improved temperature stability, decreased the incidence of overcooling, and reduced stabilization and transfer time. All infants enrolled into the clinical trials of therapeutic hypothermia were cooled within 6 hours of life, and experimental evidence has shown a lack of benefit with delayed cooling. In the East of England, 2 of the 3 network NICUs participated in the TOBY trial and continued to cool infants who fulfilled the TOBY cooling criteria beyond the end of the trial. In October 2009, the third network NICU also started cooling infants, which coincided with the introduction of 24-hour cover from the ANTS. The 2 groups, passive and active, are separated temporally, with the passive group consisting of infants cooled throughout the region between June 2009 and March 2011 and the active group consisting of infants cooled throughout the region between March 2011 and May 2012.

After publication of the National Institute for Health and Clinical Excellence guidance on therapeutic hypothermia, a regional project commenced in 2010 to develop a coordinated service for cooling infants. One of the key objectives of this project was to engage all health care professionals in the region and provide training and support for

| TABLE 1 Gestational Age, Gender, and Degree of Acidosis in the Passive and Active Groups |
|-----------------------------------------------|-------------------------------|-------------------------|
| Variable                                      | Passive (n = 64)              | Active (n = 70)         | \(P\)               |
| Gestational age, mean ± SD, wk                | 39.5 ± 2.0                    | 39.7 ± 1.7             | .25                 |
| Male gender                                   | 32                            | 37                      | .17                 |
| First pH, mean ± SD                           | 7.04 ± 0.21                   | 7.06 ± 0.21            | .52                 |
| First Base Excess, mean ± SD                  | −16.7 ± 7.8                   | −15.7 ± 6.3            | .45                 |

| TABLE 2 Age at Referral, Dispatch Time From ANTS Base, Stabilization Time, and Age at Arrival to the Regional Unit in the Passive and Active Groups |
|-----------------------------------------------|-------------------------------|-------------------------|
| Variable                                      | Passive (n = 64)              | Active (n = 70)         | \(P\)               |
| Age at referral, min                         | 104 (23–485)                  | 93 (32–358)            | .24                 |
| Dispatch time, min                           | 62 (2–300)                    | 55 (4–630)             | .29                 |
| Stabilization time, min                      | 153 (60–385)                  | 135 (45–505)           | .04                 |
| Age at arrival at cooling cot, min           | 504 (191–924)                 | 452 (225–1265)         | .01                 |
| Journey time, min                            | 72.5 (30–160)                 | 70 (25–105)            | .08                 |

Data are presented as median (range).
the identification and initiation of therapeutic hypothermia. The aim of the training program was to improve the identification and early management of infants with HIE; it was achieved by developing guidelines and specific care pathways, outreach teaching in each of the 18 hospitals in the region, and a series of regional seminars. Between May 2010 and May 2012, there was a total of 64 visits, and 675 staff were trained (229 doctors, 352 nurses, and 94 students). At the start of the project, none of the hospitals apart from the 3 regional NICUs monitored core (rectal) temperature. By May 2012, all the hospitals monitored rectal temperature in infants identified for cooling. The results of this training and support explain why the age cooling commenced was significantly earlier in the later (active) group compared with the earlier (passive) group. There was no difference between the 2 groups in the distances traveled; therefore, the earlier arrival at the cooling cot in the active group is due to the reduced stabilization time. This reduction in stabilization time is likely due to the reduced need for intervention to stabilize the temperature once the servo-controlled mattress is placed on the infant. For those infants who achieved target temperature, there was no difference in time to target temperature; however, in the passive group, only 73% of infants reached target temperature. More significant were the 22 infants who were overcooled. Asphyxiated infants have more temperature instability than healthy term infants.10 Our experience of infants who were overcooled during transfer was that it was very difficult to get them back within target range, and if they did warm up, they would often “overshoot.” There is currently no consensus on how best to manage infants requiring therapeutic hypothermia during transfer. Kendall et al11 published experiences regarding transfer of 39 infants in and around London. All infants were passively cooled according to a standardized protocol (identical to the protocol used by our ANTS team in the passive group). In their study, 33% of infants were outside target temperature range on arrival at the cooling center, including 11% overcooled infants. There are significant differences, however, between the London NTS and ANTS in terms of geographical distance and number of cooling centers (8 in London and 3 in the East of England). This difference is reflected in the journey time of the NTS between 30 and 90 minutes, compared with ANTS (25–160 minutes). Fairchild et al,12 from Virginia, reported

FIGURE 2
Box plot for temperature measurement at time of arrival of the transfer team (ANTS) at the referring unit, departure of ANTS from the referring unit, and arrival of ANTS at the regional cooling unit. The area between the lines shows the target temperature range of 33°C to 34°C; the percentages reflect those infants within the range at arrival at the regional unit (significant difference between the temperature on arrival at the referring unit and the temperature from the referring unit [*] and arrival at cooling unit [+], P = .006).
their 4-year experience of therapeutic hypothermia during transfer to a single NICU. Of 40 infants cooled, 35 were cooled on transfer using “active” but not servo-controlled methods (cool packs in the incubator). According to their report, 34% of infants had a rectal temperature <32°C on arrival at the cooling center. This risk of hypothermia from passive cooling on transfer was further highlighted by Hallberg et al., reporting on their experience in Stockholm, Sweden. Of the 18 infants cooled on transfer, 6 had a temperature <33°C on arrival. The largest study to date comes from O’Reilly et al. in Bristol, United Kingdom. In this report, 46 infants were cooled on transfer: 10 passively, 17 actively using cooling adjuncts, and 19 actively, by using a servo-controlled cooling system. As with our study, O’Reilly et al found that a significant number of infants passively cooled, or actively cooled with adjuncts, had temperatures outside the therapeutic range. In contrast, 84% of infants actively cooled by using a servo-controlled system had temperatures in-range on arrival at the cooling center.

All published trials to date, including the current study, are limited by the fact that they are retrospective uncontrolled studies. As cooling has moved from clinical research to standard of care, there is a natural learning curve from both the referring units and the transfer teams, which is likely to improve thermal management regardless of means. Our study is the largest to date, and it demonstrates that a coordinated regional approach to training improves early identification, and the use of regional guidelines improves compliance with monitoring of core (rectal) temperature. Consistently maintaining infants within the therapeutic temperature range was only possible by using a servo-controlled system. This approach was also found to reduce the stabilization time and hence time to arrival at the cooling center, which is a key objective of any transfer team.

**CONCLUSIONS**

To effectively manage infants requiring therapeutic hypothermia, it is important that initiation of cooling is not delayed and that cooling commences in the local referring unit. Servo-controlled active cooling has been shown to improve temperature stability within the therapeutic range throughout transfer with a reduction in transfer time. Transfer teams operating over medium to large distances should seriously consider this approach.

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