Temperature Control During Therapeutic Hypothermia for Newborn Encephalopathy Using Different Blanketrol Devices

Abbot R. Laptook,¹ Howard Kilbride,² Edward Shepherd,³ Scott A. McDonald,⁴
Seetha Shankaran,⁵ William Truog,² Abhik Das,⁴ Rosemary D. Higgins,⁶
and the Optimizing Cooling Sub-Committee⁶

Therapeutic hypothermia improves the survival and neurodevelopmental outcome of infants with newborn encephalopathy of a hypoxic-ischemic origin. The NICHD Neonatal Research Network (NRN) Whole Body Cooling trial used the Cincinnati Sub-Zero Blanketrol II to achieve therapeutic hypothermia. The Blanketrol III is now available and provides additional cooling modes that may result in better temperature control. This report is a retrospective comparison of infants undergoing hypothermia using two different cooling modes of the Blanketrol device. Infants from the NRN trial were cooled with the Blanketrol II using the Automatic control mode (B2 cohort) and were compared with infants from two new NRN centers that adopted the NRN protocol and used the Blanketrol III in a gradient mode (B3 cohort). The primary outcome was the percent time the esophageal temperature stayed between 33°C and 34°C (target 33.5°C) during maintenance of hypothermia. Cohorts had similar birth weight, gestational age, and level of encephalopathy at the initiation of therapy. Baseline esophageal temperature differed between groups (36.6°C ± 1.0°C for B2 vs. 33.9°C ± 1.2°C for B3, $p < 0.0001$) reflecting the practice of passive cooling during transport prior to initiation of active device cooling in the B3 cohort. This difference prevented comparison of temperatures during induction of hypothermia. During maintenance of hypothermia the mean and standard deviation of the percent time between 33°C and 34°C was similar for B2 compared to B3 cohorts (94.8% ± 0.1% vs. 95.8% ± 0.1%, respectively). Both the automatic and gradient control modes of the Blanketrol devices appear comparable in maintaining esophageal temperature within the target range during maintenance of therapeutic hypothermia.

Introduction

ENCEPHALOPATHY IN LATE preterm and term newborns is a serious condition stemming from multiple different etiologies and can be associated with a poor outcome including cerebral palsy, neurodevelopmental impairments, and neurosensory deficits when assessed as late as 30 months (Miller *et al.*, 2004; Pierrat *et al.*, 2005). In the subset of newborn encephalopathy attributed to hypoxia-ischemia, outcome has been tracked over longer intervals and poor outcomes persist even at school age (Robertson *et al.*, 1989). The clinical management of hypoxic-ischemic encephalopathy has traditionally been limited to intensive supportive

care whereby organ system dysfunction was supported, biochemical abnormalities were corrected, and seizures were treated when present. Over recent years management has changed with the demonstration of benefit associated with therapeutic hypothermia among multiple clinical trials. Meta-analysis of eight randomized clinical trials involving 1344 participants indicate that therapeutic hypothermia initiated at less than 6 hours of age in newborns with moderate or severe encephalopathy is associated with a reduction in death or major disability at 18 months of age (relative risk 0.75, 95% confidence intervals, 0.68, 0.83) (Jacobs *et al.*, 2013).

Therapeutic hypothermia is being disseminated throughout the neonatal community with more widespread penetration in

¹Department of Pediatrics, Women & Infants Hospital of Rhode Island, Alpert Medical School of Brown University, Providence, Rhode Island.

²Children's Mercy Hospital, Kansas City, Missouri.

³Nationwide Children's Hospital, Columbus, Ohio.

⁴Statistics and Epidemiology Unit, RTI International, Research Triangle Park, North Carolina.

⁵Wayne State University, Detroit, Michigan.

⁶NICHD Neonatal Research Network, Bethesda, Maryland.

some countries compared to others (Azzopardi *et al.*, 2012; Iwata *et al.*, 2012). Both head and body cooling are used, both are effective and there are no clear data that one mode of cooling is superior to the other. Irrespective of the mode of cooling, temperature control is important. Wide fluctuations in temperature above and below a target temperature may limit the effectiveness of therapeutic hypothermia; elevated temperatures may provide less neuroprotection and lower temperatures may pose a greater risk of adverse events.

A number of different commercial devices are available for providing therapeutic hypothermia. In the National Institute of Child Health and Development (NICHD) Neonatal Research Network (NRN) whole body cooling trial, the Blanketrol II (Cincinnati Sub-Zero [CSZ], Cincinnati, OH) was used in the Automatic Control mode and the esophageal temperature was the site controlled (Shankaran *et al.*, 2005). Unexpectedly, decreases in esophageal temperature of more than 1.5°C below the target temperature of 33.5°C occurred in some infants. These observations prompted a detailed review of the temperature profile of infants undergoing body cooling (Shankaran *et al.*, 2012). During the maintenance phase, 10 of 101 infants had esophageal temperatures of <32.0°C for 3.2±3.1 hours (mean±standard deviation, range 0.3–8.0 hours). Since completion of the NICHD whole body cooling trial there have been modifications to the Blanketrol devices to achieve better temperature control during therapeutic hypothermia. The Blanketrol II has been replaced by the Blanketrol III and the latter has additional automatic control modes designed to limit the magnitude of the difference between the esophageal and circulating water temperature (gradient modes) and in turn decrease fluctuations in temperature above and below the target temperature.

Following completion of the NICHD whole body cooling trial, two centers of the NRN started providing therapeutic hypothermia as a part of routine clinical care and used the newer Automatic Control modes available on the Blanketrol III. Data from the two centers using the Blanketrol III allowed a comparison of the temperature profile of infants undergoing therapeutic hypothermia with the Blanketrol II data from the NICHD whole body cooling trial. This comparison tested the hypotheses that the Blanketrol III provides more precise temperature control during therapeutic hypothermia as characterized by less variability in temperature during the maintenance phase of cooling (primary outcome), and less overshoot during induction with a shorter time to equilibration of esophageal temperature at the target temperature (secondary outcome).

Methods

This is a retrospective comparison of two cohorts of infants undergoing therapeutic hypothermia with different modes of cooling using the CSZ Blanketrol device. One cohort ($n=101$) included infants undergoing hypothermia from the NICHD whole body cooling trial, enrolled between 2000 and 2003, and cooled using the automatic control mode of the Blanketrol II (B2 cohort) (Shankaran *et al.*, 2005). The second cohort ($n=110$) consisted of infants born between 2008 and 2010 and provided whole body cooling at Children's Mercy Hospital (Kansas City, MO, $n=57$) and Nationwide Children's Hospital (Columbus, OH, $n=53$) using the Gra-

dient 10C mode or the Gradient Variable mode of the Blanketrol III (B3 cohort). These two centers adopted and implemented the NICHD hypothermia regimen including eligibility criteria, use of the Blanketrol device, and frequency of recording temperatures. Both cohorts had temperature probes positioned in the lower third of the esophagus and an esophageal temperature (Tes) of 33.5°C was the target temperature.

The Blanketrol device functions as follows: in the Automatic Control mode the Tes is compared to the target temperature by the unit's microprocessor; if the infant's Tes is lower than the target temperature, the device heats the circulating water to the highest allowable water temperature (42°C) to elevate the infant's Tes. If the infant's Tes exceeds the target temperature, the device cools the circulating water to the lowest allowable water temperature (4°C) until the Tes is decreased to the target temperature. When the Tes reaches the target temperature the unit continues to circulate the water without heating or cooling. If the Tes falls below or increases above the target temperature, the device resumes heating or cooling, respectively. In the NICHD randomized trial, the Automatic Control mode was used with two blankets attached to the device; one for the infant to lie on (25×33-inches) and a larger blanket (25×64-inches) suspended nearby. Preliminary work using newborn piglets performed prior to the NICHD whole body cooling trial indicated that circulating water through two blankets simultaneously reduced the magnitude of the swings in temperature above and below the target temperature compared to using a single blanket (Shankaran *et al.*, 2002).

In the Gradient 10C mode the device monitors the infant's Tes and limits the maximum difference between the circulating water temperature and Tes to 10°C above or below the Tes; this is designed to minimize the swings in Tes, which may occur if the circulating water temperature is changing by large increments. Similar to the Automatic Control mode, when the Tes reaches the target temperature the unit continues to circulate the water without heating or cooling, respectively. The Gradient Variable mode functions similarly to the Gradient 10C mode except that the user inputs a specific gradient offset value for the difference between the water temperature and Tes. This provides flexibility in determining the extent of difference in the water temperature and Tes. The Gradient 10C and Gradient Variable modes were used with a single blanket (25×33-inches) positioned under the infant.

Demographic information included birth weight and gestational age. Inclusion in the analyses of these studies required documentation of moderate or severe encephalopathy since this was a criteria of the NICHD whole body cooling trial (Shankaran *et al.*, 2005). Comparisons between cohorts were performed for baseline data and temperatures during induction and maintenance of hypothermia. Baseline represents assessments when the infant was placed on the blanket. The induction period was defined as following initial placement of the infant on the cooling blanket and continued through the initial overshoot below the target temperature ending when Tes returned to within 0.1°C of 33.5°C, the target temperature. The maintenance period extended from completion of induction until the initiation of rewarming after 72 hours of hypothermia. The primary outcome was the percent time Tes was in the target range (33°C–34°C). Cohorts were compared

using mean and standard deviations, 95% confidence intervals of the mean, median, and interquartile ranges. Mean values during maintenance were determined using a longitudinal, repeated measures regression model. Similar modeling was used to compare the temperature gradient between Tes and the blanket water. The proportion of infants with Tes above 34°C and below 33°C was compared with a Fisher's exact test. A secondary outcome was the temperature achieved during induction of hypothermia.

Results

In the B2 cohort, there were 102 infants randomized to hypothermia but one infant did not receive the intervention. Of the remaining 101 infants, 1 met inclusion criteria due to seizures and a neurological examination was not performed on this infant. Thus, 100 infants assessed to be moderate or severely encephalopathic constituted the B2 cohort. In the B3 cohort, 110 patients were eligible but 20 were excluded due to missing neurologic exams ($n=6$) or presence of mild encephalopathy ($n=14$). Ninety infants with moderate or severe encephalopathy made up the B3 cohort.

Infant characteristics along with baseline data at the initiation of cooling are listed in Table 1. Infants in the two cohorts were similar in birth weight, gestational age, Apgar scores at 5 and 10 minutes, acid-base status, and level of encephalopathy. Apgar scores at 1 minute differed between cohorts. The B3 cohort was all out-born infants reflecting that these two hospitals do not have delivery services. Missing data were more common in the B3 cohort (see numbers for each variable, Table 1). During the NICHD trial, infants were maintained normothermic and if randomized to hypothermia were placed on a precooled blanket. Following the trial some centers, including the two centers contributing patients to the B3 cohort, implemented cooling during transport. As a result, the mean baseline temperatures were lower for skin and esophageal sites and higher for blanket water among B3 in-

fants. There were 55 infants in the B3 cohort with a baseline esophageal temperature <35°C; six had baseline temperatures <32.5°C (lowest value 29.7°C), six had baseline temperatures between 32.5°C and 32.9°C, 23 had baseline temperatures between 33°C and 33.9°C, and 20 had baseline temperatures between 34°C and 34.9°C. There were 12 infants with baseline esophageal temperatures above 35°C and 23 infants had missing baseline temperature. All infants in the B2 cohort were placed on precooled blankets in the Automatic Control mode and 79% of B3 cohort was placed on blankets with the Gradient 10C mode and the remainder was placed on the Gradient Variable mode.

Table 2 and Figure 1 provide data during induction of hypothermia. In view of the wide range of temperatures among the B3 cohort, data for induction are presented for all 90 infants, and three subgroups of B3 infants (Baseline Tes <35°C, Tes $\geq$ 35°C, and infants without a baseline temperature). Due to the differences in baseline temperature, statistical comparisons were not performed during induction. Induction using the automatic control mode in the B2 group was characterized by a rapid fall in Tes to initially surpass the target temperature of 33.5°C in less than an hour. This was followed by an overshoot of Tes reaching a maximum deviation to 32.1°C by 1.4 hours of induction. Tes then increased to reach equilibration within 3.2 hours of the initiation of induction. For B3 infants the maximum Tes deviation <33.5°C was less (32.7°C) and occurred in a shorter interval of time (1.1 hours). The overall time to reach equilibration was almost half that noted with the B2 cohort (1.8 hours). Given the differences in the temperature profile, B2 infants had a greater number of Tes <33°C and Tes <32°C during induction. Of note, three infants of the B3 cohort who were missing a baseline temperature ($n=23$, Table 2) accounted for much of the variability in the cooling profile of the overall B3 cohort. Reasons for the excessively long time to equilibration cannot be determined with the available data. Recalculation of the time to equilibration for

TABLE 1. BASELINE DATA

	B2 (n = 100)		B3 (n = 90)		p-Value
Birth weight (g)	n = 100	3381 $\pm$ 621	n = 90	3307 $\pm$ 656	0.86
Gestational age (weeks)	n = 100	39.0 $\pm$ 1.6	n = 90	38.5 $\pm$ 1.8	0.08
Apgar score					
1 minute	n = 99	1 (0–1)	n = 89	1 (0–2)	0.01 ^a
5 minute	n = 99	3 (1–4)	n = 89	3 (1–4)	0.33
10 minute	n = 93	4 (3–5)	n = 83	4 (3–6)	0.26
Blood gas–cord or in 1st hour					
pH	n = 71	6.87 $\pm$ 0.19	n = 83	6.91 $\pm$ 0.18	0.87
Base deficit	n = 61	18.4 $\pm$ 6.7	n = 60	21 $\pm$ 6.82	0.09
Out-born (%)	n = 100	46%	n = 90	100%	<0.0001
Level of HIE	n = 100		n = 90		0.43
Moderate	—	69%	—	74%	
Severe	—	31%	—	26%	
Postnatal age at initiation of cooling (hour)	n = 100	5.00 $\pm$ 1.15	n = 85	5.01 $\pm$ 1.63	0.46
Skin temperature (°C)	n = 97	35.1 $\pm$ 1.9	n = 76	32.7 $\pm$ 2.0	<0.00001
Esophageal temperature (°C)	n = 98	36.6 $\pm$ 1.0	n = 67	33.9 $\pm$ 1.2	<0.00001
Blanket temperature (°C)	n = 92	8.0 $\pm$ 5.9	n = 63	19.3 $\pm$ 9.0	<0.00001

Results are median (inter-quartile range) for Apgar scores; percent infants for out-born infants and level of encephalopathy; mean $\pm$ SD for all other variables.

^ap-Value is derived from non-parametric median test.

TABLE 2. INDUCTION OF HYPOTHERMIA

	B2	B3	B3: Baseline $T < 35^{\circ}\text{C}$	B3: Baseline $T \geq 35^{\circ}\text{C}$	B3: Missing Baseline T
<i>n</i>	100	90	55	12	23
Time to initially surpass T_{es} of 33.5°C (hours)	0.93 ± 0.54	0.96 ± 2.16	0.39 ± 0.53	1.04 ± 0.56	2.27 ± 3.92
Max deviation of $T_{\text{es}} < 33.5^{\circ}\text{C}$ (minimum esophageal temp, $^{\circ}\text{C}$)	32.1 ± 0.59	32.7 ± 0.96	32.7 ± 0.67	32.6 ± 1.33	32.8 ± 1.32
Time to max deviation $< 33.5^{\circ}\text{C}$ (hours)	1.39 ± 1.27	1.11 ± 2.13	0.57 ± 0.53	1.17 ± 0.55	2.37 ± 3.89
Time to equilibration (return of T_{es} within 0.1°C of 33.5°C) after overshoot (hours)	1.83 ± 3.62	0.62 ± 0.60	0.64 ± 0.43	0.58 ± 0.49	0.60 ± 0.95
Time to equilibration (return of T_{es} within 0.1°C of 33.5°C) from baseline (hours)	3.18 ± 4.20	1.76 ± 2.44	1.24 ± 0.64	1.71 ± 0.58	3.03 ± 4.53
Number of infants with $T_{\text{es}} < 33^{\circ}\text{C}$	92 (93%)	45 (50%)	32 (58%)	5 (42%)	8 (35%)
Number of infants with $T_{\text{es}} < 32^{\circ}\text{C}$	35 (35%)	9 (10%)	7 (13%)	1 (8%)	1 (4%)
Number of recorded T_{es} /infant ($\bar{x} \pm \text{SD}$, range)	10.4 ± 4.6	5.6 ± 3.1	5.4 ± 1.8	7.3 ± 2.6	5.3 ± 5.1

Data are presented as mean $\pm$ SD or as number (%).
 T_{es} , esophageal temperature.

B3 infants excluding the three outliers was 1.36 ± 0.74 hours from baseline T_{es} .

Table 3 and Figure 1 provides data during maintenance of hypothermia. Due to the differences in induction of hypothermia, the maintenance phase of cooling, defined as achievement of equilibration to initiation of rewarming at end of 72 hours of cooling, occurred earlier in B3 compared with B2 infants. Mean T_{es} and skin temperature were statistically different between cohorts. Blanket temperatures did not differ between cohorts during maintenance reflecting the small differences of skin and T_{es} between groups. Longitudinal modeling of the temperature gradient between T_{es} and the blanket water indicated a small difference between T_{es} and blanket temperature ($\approx 1.2^{\circ}\text{C}$, $p=0.003$), not dependent on the device ($p=0.87$), which tended to increase over time ($\approx 1.7^{\circ}\text{C}$, $p=0.11$ for time).

The percent of time that T_{es} remained between 33°C and 34°C was similar between cohorts whether expressed as a mean, 95% confidence interval of the mean, or median and interquartile range. The number of infants with $T_{\text{es}} < 33^{\circ}\text{C}$ was greater for B2 compared with B3 but the number of infants with a $T_{\text{es}} < 32^{\circ}\text{C}$ did not differ. The number of infants with $T_{\text{es}} > 34^{\circ}\text{C}$ was greater for B3 compared with B2 but there was no difference in the number of infants with a $T_{\text{es}} > 34.5^{\circ}\text{C}$. Rewarming was not compared between cohorts due to the similarity of the temperatures (Fig. 1).

Discussion

With progressive dissemination of therapeutic hypothermia for neonatal hypoxia-ischemia there are an increasing

FIG. 1. Mean and standard deviation of esophageal temperatures are plotted for infants undergoing hypothermia using either the Blanketrol II (B2 group) or the Blanketrol III (B3 group). The results are plotted from the time of placement of the infant on the cooling blanket through the initial portion of rewarming.

TABLE 3. MAINTENANCE OF HYPOTHERMIA

	B2	B3	p-Value
<i>n</i>	100	90	N/A
Postnatal age (hours) at start of maintenance	8.18 ± 4.51	6.83 ± 2.99 (N=85)	0.0004
Skin temperature, °C (±SD) ^a	31.8 ± 1.03	32.3 ± 1.13	<0.0001 ^b
Esophageal temperature, °C (±SD) ^a	33.4 ± 0.31	33.5 ± 0.39	<0.0001 ^b
Blanket, °C (±SD) ^a	31.8 ± 6.69	32.1 ± 6.18	0.69 ^b
Cooling mode (% automatic/gradient 10C/gradient variable) ^c	100%/0%/0%	0%/98.4%/1.6%	N/A
Percentage of time (maintenance) spent between 33°C and 34°C			
Mean (SD) per infant	94.8% (0.10)	95.8% (0.09)	0.24
95% CI for mean	92.8%–96.8%	93.8%–97.7%	
Median (Q1, Q3)	99.6% (93.5%, 100%)	100% (94.4%, 100%)	
Range	43.6%–100%	39.1%–100%	
Number of infants with Tes <33°C	48 (48%)	24 (27%)	0.003
Number of infants with Tes <32°C	9 (9%)	5 (6%)	0.41
Number of infants with Tes >34°C	15 (15%)	35 (39%)	0.0003
Number of infants with Tes >34.5°C	9 (9%)	13 (14%)	0.27
Number of recorded Tes/infant (x ± SD [range])	28.4 ± 7.0 [1–36]	30.2 ± 6.9 [6–39]	0.008

^aAverage among all temperatures during maintenance (equilibration to 72 hours).

^bp-Values from longitudinal/repeated measures regression model.

^cFor cooling mode, percentages are among all time points during maintenance.

number of devices used to achieve the desired temperature control. There is a relative paucity of data regarding the extent of temperature control for the “newer” devices that were not used in randomized clinical trials. The precision of temperature control may have an important influence on the extent of neuroprotection and systems that produce as little variation in target temperature are desirable. The CSZ Blanketrol II was used in the NICHD whole body cooling trial and many centers that have adopted the NICHD protocol use a CSZ device. The Blanketrol III has new temperature modes designed to limit the extent of overshoot during induction of hypothermia, achieve less fluctuation in temperature during maintenance of hypothermia, and avoid the need to circulate water through a second blanket. There are no published data comparing temperature control for the two Blanketrol devices.

The results from this report indicate that the ability to maintain Tes within the target range of 33°C–34°C was similar for the Blanketrol II and III. The average Tes value was equal to the target temperature (B3) or within 0.1°C of the target (B2). The small but statistically different skin temperature and Tes between the B2 and B3 cohorts are not likely to be clinically meaningful. The number of infants with Tes below 33°C was greater with the Blanketrol II while the number of infants with Tes above 34°C was greater with the Blanketrol III. Although it is desirable to have all Tes within the target range, the average percent time outside of the target range was only 5% for B2 and 4% for B3 cohorts. Whether this extent of time outside of the target Tes range affects the extent of neuroprotection is not known. For Tes values out of range it is unclear whether it is more advantageous to have Tes values lower than 33°C (more frequent with B2) or Tes values above 34°C (more frequent with B3). The extent of temperature overshoot and time to equilibration at the target temperature from baseline was less among the B3 cohort. However, the results from this study cannot determine whether differences in the temperature profile during induction of hypothermia reflect the newer temperature control modes of the Blanketrol III or cooling on transport in the B3 cohort. It

remains unclear whether the extent of temperature overshoot during induction of hypothermia with the Blanketrol II is deleterious or potentially advantageous. Of note there were no additional adverse events among infants in the NICHD whole body cooling trial who had Tes values <32°C (Shankaran *et al.*, 2012).

There has been growing concern that subcutaneous fat necrosis may be exacerbated by hypothermia therapy (Zifman *et al.*, 2010; Fumagalli *et al.*, 2011; Strohm *et al.*, 2011). Perinatal hypoxia–ischemia is a known risk factor for subcutaneous fat necrosis, presumably reflecting the important contribution from systemic ischemia (Chen *et al.*, 1981; Tran and Sheth, 2003). Cutaneous vasoconstriction secondary to hypothermia therapy may exacerbate systemic hemodynamic alterations or induce local skin changes even in the absence of cardiovascular instability (Wilson *et al.*, 2007; Ergenekon *et al.*, 2013). Local pressure from minimal handling of patients may also alter local perfusion and affect oxygenation of the skin. Local skin necrosis has been reported in infants undergoing therapeutic hypothermia in the absence of subcutaneous fat necrosis (Demirel *et al.*, 2013). In a small retrospective study it was reported that subcutaneous fat necrosis was observed in 2 of 11 infants undergoing cooling with the Blanketrol III in the Automatic Control mode. Following a change to using the Gradient Variable Mode and Smart function, there were no cases of subcutaneous fat necrosis in the next 28 infants undergoing hypothermia therapy (Filippi *et al.*, 2012). In conjunction with the change in cooling mode, a nursing protocol was instituted to alternate prone and supine positions every 3 hours during cooling to avoid prolonged contact of a specific skin area with the cooling blanket. In the NICHD trial using the Blanketrol II, one infant (of the 100 cooled) had subcutaneous fat necrosis (Shankaran *et al.*, 2005).

In the above study comparing two modes of the Blanketrol III, the authors noted similar rectal temperatures with the Automatic and Gradient Variable modes of cooling, but as expected larger fluctuations of blanket temperature with the Automatic Control mode. A detailed analysis of the

temperatures was not provided. There are other evaluations of the precision of temperature control during therapeutic hypothermia using systems other than CSZ products (Hoque *et al.*, 2010; Strohm *et al.*, 2010). These reports conclude that both manual and servo control systems maintain core temperature close to target temperatures but servo-controlled systems provide less variability in measured temperature.

There are important limitations to this report. The data collected for the B2 cohort were from a clinical trial while data collected for the B3 cohort were during routine clinical care and over different time periods. The B3 cohort reflects application of therapeutic hypothermia 3–5 years following publication of the clinical trial. Application of interventions from randomized trials to clinical practice may yield different effects when compared to study conditions as they may differ in populations and the intervention implemented. Temperature control may be influenced by variable center practices (e.g., use of anticonvulsants, pressor agents, and sedative-hypnotic agents) (Thoresen *et al.*, 2000; Sant'Anna *et al.*, 2012); however, these effects are difficult to identify among multiple centers even within the context of a multi-center clinical trial. We did not attempt to identify these practices given the retrospective design of this study. We excluded 14 infants from the original B3 cohort to insure that all infants had moderate or severe encephalopathy. Of the analyzed infants in the B3 cohort, there were limited available data from the medical record to insure comparability of the two cohorts (Table 1) and there were more missing data for the B3 cohort.

Therapeutic hypothermia is an intervention currently gaining widespread acceptance within the neonatal community for hypoxic-ischemic encephalopathy. It is important to understand the performance of devices that provide hypothermia since the efficacy of treatment may vary as a function of temperature control. The results of this study support similar ability to maintain *Tes* at a target temperature of 33.5°C without excessive variability of temperatures below 33°C or above 34°C for both the Automatic Control mode with water circulating through two blankets (capable with both the Blanketrol II and III devices) and the Gradient modes with water circulating through a single blanket (Blanketrol III device only). In two recent clinical trials of the NICHD NRN (NCT 01192776 and NCT 00614744), hypothermia was provided using the Automatic Control mode with two blankets using either the Blanketrol II or III.

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NRN Steering Committee Chair: Alan H. Jobe, MD, PhD, University of Cincinnati.

Alpert Medical School of Brown University and Women & Infants Hospital of Rhode Island (U10 HD27904): William Oh, MD; Angelita M. Hensman, RN, BSN.

Case Western Reserve University, Rainbow Babies & Children's Hospital (U10 HD21364, M01 RR80): Michele C. Walsh, MD, MS; Avroy A. Fanaroff, MD; Nancy S. Newman, RN; Bonnie S. Siner, RN.

Children's Mercy Hospital (U10 HD68284): William E. Truog, MD; Cheri Gauldin, RN, BSN, CCRC; Barbara Haney, MSN, RNC, CPNP.

Cincinnati Children's Hospital Medical Center, University of Cincinnati Hospital, and Good Samaritan Hospital (U10 HD27853, M01 RR8084): Edward F. Donovan, MD; Kurt Schibler, MD; Barbara Alexander, RN; Cathy Grisby, BSN, CCRC; Marcia Worley Mersmann, RN, CCRC; Holly L. Mincey, RN, BSN; Jody Hessling, RN.

Duke University School of Medicine, University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (U10 HD40492, M01 RR30): Ronald N. Goldberg, MD; C. Michael Cotten, MD, MHS; Kathy J. Auten, MSHS.

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Stanford University, Lucile Packard Children's Hospital (U10 HD27880, M01 RR70): David K. Stevenson, MD; M. Bethany Ball, BS, CCRC.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (U10 HD34216, M01 RR32): Waldemar A. Carlo, MD; Namasivayam Ambalavanan, MD;

Monica V. Collins, RN, BSN, MaEd; Shirley S. Cosby, RN, BSN.

University of California–San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461): Neil N. Finer, MD; Maynard R. Rasmussen, MD; David Kaegi, MD; Kathy Arnell, RNC; Clarence Demetrio, RN; Chris Henderson, RCP, CRTT; Wade Rich, BSHS, RRT.

University of Miami Holtz Children's Hospital (U10 HD21397, M01 RR16587): Shahnaz Duara, MD; Charles R. Bauer, MD; Ruth Everett-Thomas, RN MSN.

University of Rochester Golisano Children's Hospital (U10 HD40521, M01 RR44): Ronnie Guillet, MD, PhD; Dale L. Phelps, MD; Linda J. Reubens, RN, CCRP.

University of Texas Southwestern Medical Center at Dallas, Parkland Health & Hospital System and Children's Medical Center Dallas (U10 HD40689, M01 RR633): Pablo J. Sánchez, MD; Walid A. Salhab, MD; Susie Madison, RN; Gaynelle Hensley, RN; Nancy A. Miller, RN; Alicia Guzman.

University of Texas Health Science Center at Houston Medical School, Children's Memorial Hermann Hospital, and Lyndon Baines Johnson General Hospital/Harris County Hospital District (U10 HD21373, M01 RR2588): Kathleen A. Kennedy, MD, MPH; Jon E. Tyson, MD, MPH; Esther G. Akpa, RN, BSN; Patty A. Cluff, RN; Claudia Y. Franco, RN, BSN; Anna E. Lis, RN, BSN; Georgia E. McDavid, RN; Patti L. Tate, RCP.

Wayne State University, Hutzel Women's Hospital and Children's Hospital of Michigan (U10 HD21385): Rebecca Bara, RN, BSN; Geraldine Muran, RN, BSN.

Yale University, Yale-New Haven Children's Hospital (U10 HD27871, M01 RR6022): Richard A. Ehrenkranz, MD; Monica Konstantino, RN, BSN; Patricia Gettner, RN; JoAnn Poul.

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Address correspondence to:

Abbot R. Laptook, MD

Department of Pediatrics

Women & Infants Hospital of Rhode Island

Alpert Medical School of Brown University

101 Dudley Street

Providence, RI 02905

E-mail: alaptook@wihri.org