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Later cooling within 6 hours and temperatures outside 33–34°C are not associated with dysfunctional autoregulation during hypothermia for neonatal encephalopathy

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Abstract

Background: Cooling delays, temperature outside 33–34°C, and blood pressure below the mean arterial blood pressure with optimal cerebral autoregulation (MAP_{OPT}) might diminish neuroprotection from therapeutic hypothermia in neonates with hypoxic-ischemic encephalopathy (HIE). We hypothesized that longer time to reach temperature <34°C and having temperature outside 33–34°C would be associated with worse autoregulation and greater brain injury.

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Methods: Neonates with HIE had rectal temperature and near-infrared spectroscopy autoregulation monitoring during hypothermia (n=63) and rewarming (n=58). All underwent brain MRI, and a subset received diffusion tensor imaging MRI before day 10 (n=41).

Results: Most neonates reached <34°C at 3–6 h of life. MAP_{OPT} was identified in 54/63 (86%) during hypothermia and in 53/58 (91%) during rewarming. Cooling time was not related to blood pressure deviation from MAP_{OPT}. Later cooling was associated with lower ADC scalar in unilateral posterior centrum semiovale but not in other regions. Temperatures above 34°C were associated with blood pressure above MAP_{OPT} but not with brain injury.

Conclusion: In neonates who were predominantly cooled after 3 h, cooling time was not associated with autoregulation or overall brain injury. Blood pressure deviation above MAP_{OPT} was associated with temperature above 34°C. Additional studies are needed in a more heterogeneous population.

INTRODUCTION

Neonatal encephalopathy causes major morbidity and mortality worldwide. Moderate to severe hypoxic-ischemic encephalopathy (HIE) is a major cause of neonatal encephalopathy and affects approximately 1.5–3 per 1,000 live term births in developed countries. (1) Initiating therapeutic hypothermia (TH) within 6 h of birth provides only partial neuroprotection, with 35–55% of survivors having persistent neurologic disabilities at age 6–7 years. (2–3) The risk of HIE and poor outcome is even higher in regions with limited access to early and rapid cooling. (4)

Brain injury from hypoxic-ischemia (HI) evolves from the primary injury to transient recovery and is followed by a latent phase over approximately 6 h. (5) TH to a core temperature of 33–34°C for 72 h should be initiated within 6 h of birth to reduce injury from subsequent secondary energy failure. (6) The time that passes before the goal temperature is reached and temperature deviations from 33–34°C may affect therapeutic efficacy. Though immediate TH after moderate HI is neuroprotective in rat pups, this protection declines linearly if cooling is delayed by 3–6 h. (7) Clinically, neonates who receive hypothermia within 1 h after birth have fewer seizures and shorter hospitalizations than do neonates cooled after the first hour of life. (8) Motor neurodevelopmental outcomes are also improved by initiating TH within 3 h of birth. (9) Thus, cooling delays, even within 6 h of birth, and failure to remain within 33–34°C might reduce neuroprotection.

Dysfunctional cerebrovascular autoregulation and vasoreactivity are also associated with greater brain injury and worse neurodevelopmental outcomes after HIE. (10–17) Autoregulation holds cerebral blood flow relatively constant across changes in perfusion pressure through changes in cerebrovascular resistance. The range of blood pressure with most robust vasoreactivity is the optimal mean arterial blood pressure (MAP_{OPT}), and greater blood pressure deviation from MAP_{OPT} indicates dysfunctional autoregulation. Several studies have shown that blood pressure deviation below MAP_{OPT} is associated with greater neurologic injury in neonates with HIE. (10–13,17)

In this pilot study, we examined whether time to achieve the target TH temperature (i.e. cooling time) and temperature deviation outside 33–34°C are associated with disturbed autoregulation and early brain injury in neonates with HIE. Because perinatal insults affect neurologic injury, we used a perinatal insult score to grade the neonate's clinical condition. (11) We tested the primary hypothesis that longer cooling time to achieve <34°C is associated with greater blood pressure deviation from MAP_{OPT} and greater brain injury on MRI when controlling for perinatal insults. We secondarily tested whether temperature fluctuations outside 33–34°C are associated with worse autoregulation and brain injury.

METHODS

The Johns Hopkins Medicine Institutional Review Board (IRB) approved this prospective, observational study. Written informed consent was obtained through May 2013; thereafter the IRB granted a waiver of consent because near-infrared spectroscopy (NIRS) became standard clinical care during TH for neonates with HIE at Johns Hopkins Hospital (JHH).

Subjects

HIE was diagnosed according to criteria of the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network. (18) All neonates initially diagnosed with moderate to severe HIE were screened upon admission to the JHH neonatal intensive care unit (NICU) from September 2010 to July 2015. Eligible infants had gestational age ≥35 weeks, arterial blood pressure monitoring, TH, and additional eligibility criteria that we have detailed previously. (10,13) All neonates in the current study were also reported in our past autoregulation studies. (10–13,17,19–20)

Protocol and clinical care

Neonates were cooled to a goal core temperature of 33.5±0.5°C for 72 h and then rewarmed to a rectal temperature of 36.5°C at a rate of 0.5°C /h. (13) Neonates inborn at JHH were actively cooled upon NICU admission, whereas outborn neonates from regional hospitals were passively cooled during transport to JHH. The transport team recorded the time that a newborn's core temperature reached <34°C if it was achieved by passive cooling alone. No outborn neonate received active cooling during transport.

Cooling time (h) was calculated as the difference between the time of first rectal temperature <34°C and time of birth. Hourly rectal temperatures, medications, presence of seizures, and blood gas data were obtained from the electronic medical record. Using common clinical criteria (Table 1), we assigned a perinatal insult score to describe the neonates' clinical status soon after birth. (11) We developed this score previously to provide an assessment of insult severity and generate a clinical description variable for multivariate analysis.

Autoregulation monitoring

Arterial blood pressure and bilateral cerebral NIRS (neonatal probes; INVOS 5100; Medtronic, Minneapolis, MN) were monitored continuously in the neonates, enabling us to calculate the hemoglobin volume index (HVx) as a continuous measure of cerebral vasoreactivity according to our published methods. (13,21–22) Briefly, the NIRS relative

total tissue hemoglobin (rTHb) is a surrogate measure of cerebral blood volume. Autoregulatory vasoreactivity causes slow wave changes in cerebral blood volume that are detected by rTHb as the blood pressure fluctuates. (21–22) HVx is generated by correlating mean arterial pressure (MAP) and rTHb. When vasoreactivity is functional, HVx is negative and approaches −1 because MAP and rTHb negatively correlate. HVx becomes positive and approaches +1 when vasoreactivity is dysfunctional, with pressure-passive MAP and rTHb positively correlated. The 5-mmHg blood pressure range with the most negative HVx (nadir) is the MAP_{OPT} at which autoregulatory vasoreactivity is most robust. (13,17) Neonates without an apparent HVx nadir were coded as having an unidentifiable MAP_{OPT}.

We measured autoregulatory vasoreactivity during hypothermia and rewarming using (1) the percentage of the monitoring period spent with blood pressure below, within, or above MAP_{OPT}; (2) the maximal blood pressure deviation below or above MAP_{OPT}; and (3) the area under the curve (AUC; min*mmHg/h) of time (min) with blood pressure below MAP_{OPT} and blood pressure deviation (mmHg) below MAP_{OPT} normalized to the monitoring duration (h). (11)

Brain MRI

Neonates received T1, T2, and diffusion tensor imaging (DTI) MRIs between 4 and 16 days from birth on a 1.5T (Avanto) or 3T (Siemens) clinical scanner (Erlangen, Germany) during natural sleep without anesthesia. We previously reported our MRI methods. (10–11) Qualitative brain injury was scored as none, mild, moderate, or severe in six regions (paracentral gyri, global white matter, basal ganglia, thalamus, posterior limb of the internal capsule (PLIC), and brainstem) in all neonates. We previously published the qualitative injury data in this cohort. (11)

Apparent diffusion coefficient (ADC) scalars were measured as the median of 3 region-of-interest measurements in the anterior and posterior centrum semiovale, PLIC, basal ganglia, thalamus, pons, and cerebellar white matter. Right and left sides were analyzed separately in all areas except for the pons. We analyzed DTI data only in neonates who received their MRI before day 10 of life to account for pseudonormalization of the ADC.[21] We previously published the DTI data collected by the 1.5T scanner. (10,12)

Statistical analysis

Cooling time was analyzed in two ways. First, we analyzed the time to reach core temperature <34°C as a dichotomous variable (<3 h or ≥3 h after birth) based on evidence that motor neurodevelopmental outcomes are improved if cooling is initiated within 3 h of birth. (9) We also analyzed cooling time as a continuous measure.

After the neonate reached rectal temperature <34°C, the temperature AUC (degree*min per h) was calculated as any deviation above or separately below 33–34°C during 72 h of TH. For example, a neonate at 35°C for 1 h would have an AUC of 60 degree*min per h. Having a temperature of 34.5°C for 1 h gives an AUC of 30 degree*min per h.

For univariate analyses, logistic and linear regressions were used to estimate the associations between cooling time or temperature AUC and the outcomes for blood pressure relative to

MAP_{OPT} (percentage of the monitoring period with blood pressure below, within, or above MAP_{OPT}; maximal blood pressure deviation below or above MAP_{OPT}; and AUC of blood pressure below MAP_{OPT}) during hypothermia and separately during rewarming. We used ordered logistic regression (for categorical measurements), assuming proportional odds and linear regressions, to estimate the associations between cooling time, temperature AUC, and perinatal insult score with the outcomes for regional qualitative (categorical) brain injury in all neonates and DTI MRI in neonates who received scans before 10 days of age. MRI analyses were corrected for multiple comparisons.

In addition, we adjusted the analyses by the perinatal insult score and the partial pressure of carbon dioxide ($PaCO_2$) during hypothermia and rewarming. The degree of perinatal insult may independently affect autoregulation, blood pressure regulation around MAP_{OPT}, and brain injury. $PaCO_2 < 35$ mmHg is also an independent risk factor for brain injury during HIE, (23) and $PaCO_2$ influences autoregulation. (24) We placed each neonate's $PaCO_2$ during hypothermia and rewarming into one of four categories: (1) all $PaCO_2$ levels 35–45 mmHg; (2) all <45 mmHg and some <35 mmHg; (3) all >35 mmHg and some >45 mmHg; or (4) some <35 mmHg and some >45 mmHg. (11)

Differences in clinical characteristics between the entire cohort and neonates who received DTI MRI prior to the tenth day of life were analyzed by chi square test, Student's t-test, or Fisher's exact test as appropriate. Finally, the cooling time for inborn and outborn neonates was compared by Mann Whitney test. A $p < 0.05$ was considered statistically significant.

Sample size calculation

Limited information is available about the effects of delayed clinical cooling and temperature fluctuations on autoregulation of neonates during TH for HIE. Because we did not have *a priori* data about the potential associations between cooling time or temperature deviation from 33–34°C and autoregulatory vasoreactivity or region-specific brain injury on MRI, we did not conduct sample size or power estimates for this exploratory, pilot study.

RESULTS

Among 122 screened neonates with HIE, 75 had HVx monitoring (Figure 1). Sixty-four neonates with brain MRI data had HVx monitoring during hypothermia (mean monitoring duration 46.5 h [SD, 19.8]), and 59 were monitored during rewarming (mean duration 6.3 h [SD, 2.6]). One outborn neonate who experienced extreme delays in HIE diagnosis and transport to the JHH NICU was excluded because the goal temperature was not achieved until 10 h after birth. Thus, 63 neonates were included in the study. MAP_{OPT} was identified in 54 of 63 neonates (86%) during hypothermia and in 53 of 58 (91%) during rewarming. We analyzed all neonates' qualitative brain injury on MRI. ADC measures were analyzed in 41 neonates who received DTI MRI before 10 days of age. Due to limitations related to changes in the electronic medical record system twice at JHH, hourly rectal temperatures to calculate temperature AUC outside 33–34°C were available in only 51 of 63 neonates (81%) with qualitative brain injury measures on MRI and in 35 of 41 (85%) with DTI MRI.

Clinical description

The mean gestational age was 38 weeks and 5 days (SD 1.5; n=63) with 47 of 63 (75%) born by cesarean section, and 59% were males (Table 2). In addition, the majority were outborn, diagnosed with moderate HIE (Sarnat score 2), and reached a core temperature <34°C after 3 h from birth. Three newborns diagnosed with moderate HIE at an outside hospital were passively cooled before and during transport. Their Sarnat scores of 1 were determined during hypothermia after arrival to JHH. Because these newborns were initially diagnosed with moderate HIE and they met our institutional criteria for cooling, (13) the clinical team continued the TH protocol.

Outborn neonates transported to the JHH NICU had a mean cooling time of 4.4 h (SD: 1.3; n=53), whereas those inborn were cooled by 1.7 h (SD, 0.9; n=10; p<0.001; Figure 2). Temperature was rarely less than 33°C (Table 2) and the mean was 33.5°C (SD, 0.79) during 72 h of TH. The subset of neonates with DTI MRI had temperature outside 33–34°C more often than the entire cohort (p=0.015) with the majority of these temperatures exceeding the target (p=0.027). MAP ranged from 30 to 75 mmHg during hypothermia and rewarming. (11)

Qualitative brain injury measures on MRI showed that most neonates had no or mild injury in the paracentral gyri, white matter, basal ganglia, thalamus, PLIC, and brainstem (Supplemental Table S1). Moderate or severe injury was most common in the white matter (35%) and thalamus (30%), followed by brainstem (26%) and basal ganglia (25%).

Electroencephalographic seizures were identified in 24 of 63 neonates (38%) during hypothermia and rewarming, and all received phenobarbital. Nine (14%) additionally received leviteracetam, 2 (3%) received fosphenytoin, and 1 (1.5%) received topiramate. Forty-two (67%) were administered dopamine, 12 (19%) dobutamine, 5 (8%) epinephrine, and 6 (10%) milrinone. Hydrocortisone was administered for hypotension refractory to inotropes in 11 (18%). Sedation was provided with morphine (63; 100%) per the clinical TH protocol, plus fentanyl (6; 10%), hydromorphone (3; 5%), clonidine (9; 14%), or benzodiazepines (7; 11%) as needed clinically.

Perinatal insult score

Higher perinatal insult score was associated with greater qualitative MRI injury in the paracentral gyri in univariate analysis (β=1.77; 95% confidence interval [CI]: 1.15, 2.27; p=0.012; n=63) and after adjusting for $PaCO_2$ (β=1.83; 95% CI: 1.16, 2.87; p=0.012). Higher perinatal insult score was also associated with greater microstructural injury in the left posterior centrum semiovale by DTI MRI when controlling for $PaCO_2$ (β = −31.7; 95% CI: −61.2, −2.3; p=0.042; n=41).

Cooling time

Cooling time <3 h or ≥3 h or as a continuous measure was not associated with MAP_{OPT} or blood pressure relative to MAP_{OPT} during hypothermia or rewarming in univariate analyses nor after adjustment for the perinatal insult score and $PaCO_2$ (Supplemental Tables S2 and S3). Moreover, cooling time <3 h or ≥3 h or as a continuous measure was not related to

regional qualitative brain injury by MRI in univariate or multivariate analyses (n=63; Supplemental Tables S4 and S5).

Among the 41 neonates with DTI MRI, those cooled to <34°C at ≥3 h had lower ADC scalars in the right posterior centrum semiovale by univariate analysis (p=0.036) and after adjustment for the perinatal insult score and $PaCO_2$ (p=0.035) when compared to neonates cooled earlier (Table 3). No other regional ADC scalars were associated with cooling time in univariate or multivariate analyses.

Temperature deviation from 33–34°C

Greater temperature AUC above 34°C was associated with more blood pressure deviation above MAP_{OPT} during hypothermia after we adjusted for the perinatal insult score and $PaCO_2$ (p=0.041; Table 4). Similarly, during rewarming, greater temperature AUC above 34°C related to greater time with blood pressure above MAP_{OPT} (p=0.013) and less time with blood pressure below MAP_{OPT} (p=0.027) in adjusted comparisons. Neonates rarely had temperature below 33°C (Table 2). Temperature above 34°C was not associated with regional qualitative brain injury (n=51) or ADC scalar (n=35) in univariate or multivariate analyses (Supplemental Tables S6 and S7).

DISCUSSION

Rapid cooling of core temperature and maintenance at 33–34°C are keys to effective TH when treating neonates with HIE. However, achieving these metrics can be clinically challenging. We tested whether the time to reach temperature <34°C and deviation from 33–34°C were related to blood pressure relative to MAP_{OPT} or early MRI brain injury in a single-center pilot study. Higher MAP_{OPT} and blood pressure deviation from MAP_{OPT} indicate disturbed autoregulatory vasoreactivity. In our cohort, most neonates were outborn, cooled at 3–6 h of life, and had moderate HIE with relatively mild brain injury on MRI. We did not identify a relationship between cooling time, MAP_{OPT}, and blood pressure relative to MAP_{OPT}. Longer time to reach core temperature <34°C was associated with lower ADC in unilateral posterior centrum semiovale but not in other brain regions after we adjusted for the perinatal insult score and $PaCO_2$. Cooling time had no relationship to qualitative brain injury on MRI. Temperature fluctuation above 34°C was associated with blood pressure above MAP_{OPT} without an effect on brain injury. Neonates rarely had temperatures below 33–34°C. While our pilot data suggest that cooling time and deviation from 33–34°C minimally impact autoregulation and early brain injury, additional studies are needed in a larger and more heterogeneous population.

Immediate hypothermia reduces cytotoxic edema in patients with HIE. (25) Additionally, greater cytotoxic edema with lower MRI ADC scalars (26) is associated with higher MAP_{OPT} in neonates with HIE. (12) This relationship suggests that severe cytotoxic edema might limit cerebral vasodilatory capacity at low blood pressures, thereby shifting MAP_{OPT} to a higher pressure with a rightward shift in the autoregulation curve. Because blood pressure below MAP_{OPT} is associated with greater neurologic injury, (10–11,13,17) we theorized that faster cooling and strict adherence to 33–34°C might reduce cytotoxic edema

on DTI MRI, improve blood pressure regulation to be within or close to MAP_{OPT}, and decrease neurologic injury.

Overall, we did not identify an association between cooling time or temperature fluctuations from 33–34°C and brain injury. Certainly this lack of association does not negate the importance of early cooling with vigilant temperature control. Clinical and preclinical studies clearly show that cooling must begin early and within 6 h of birth. (7,9,25,27) All of our neonates were appropriately cooled within 6 h and had a sustained mean core temperature of 33.5°C (SD, 0.79) for 72 h of TH. Our findings may be related to our patient sample being small with limited variability in cooling time owing to the predominance of outborn neonates. However, our findings are in agreement with a recent study that also showed no relationship between early cooling and MRI brain injury. (28) Though lower ADC scalars in unilateral posterior centrum semiovale were associated with later cooling after we adjusted for the perinatal insult score and $PaCO_2$, we did not identify any other relationships between temperature and brain injury.

Numerous factors could delay hypothermia induction, including resuscitation, delays in diagnosing moderate or severe HIE, prolonged transport, agitation, or shivering. Some outborn neonates must be passively cooled at a slower rate as not all NICU transport teams may have active cooling devices. Accordingly, our predominantly outborn population reached <34°C after 3 h. We could not directly study the independent effects of inborn or outborn status because too few neonates were inborn.

Greater temperature deviation above 34°C during TH was associated with having blood pressure above MAP_{OPT} during both hypothermia and rewarming after adjustment for $PaCO_2$ and the perinatal insult score. Maximal MAP was 75 mmHg, as previously reported for this cohort. (11) Blood pressure above MAP_{OPT} is related to lesser paracentral gyri injury in neonates with HIE (11) and lower risk of intraventricular hemorrhage in prematurity. (29) Accordingly, temperature above 34°C with blood pressure above MAP_{OPT} showed no association with early MRI brain injury in the current study. Given the risk of hyperemia, we do not advocate intentionally raising the blood pressure above typical clinical goal ranges.

We created the perinatal insult score (11) to describe the severity of a neonate's clinical condition in a single metric for multivariate analysis. Higher perinatal insult score was associated with greater paracentral gyri and posterior centrum semiovale injury. Though we adjusted our analyses using this score, we still cannot distinguish whether dysfunctional autoregulation causes secondary neurologic injury or whether severe brain injury causes dysfunctional autoregulation with blood pressure deviation from MAP_{OPT}.

We analyzed different regions of interest rather than using a global MRI score because HIE vulnerability varies by brain region. (30–33) Higher MAP_{OPT} from rightward shifts in the autoregulation curve are associated with injury detected by regional DTI but not all global MRI scores, such as the NICHD Neonatal Research Network score. (12) It is also critical to examine how NIRS autoregulation monitoring in frontal cortex relates to potential injury in more distal regions.

Most of our neonates had moderate HIE with limited variation in brain injury severity. Three were initially diagnosed with moderate encephalopathy at an outside hospital where passive cooling was initiated. Their Sarnat scores were subsequently assessed to be 1 after admission to the JHH NICU for active cooling. Some neonatologists initiate TH for milder HIE given that encephalopathy can evolve rapidly. (34) Moreover, perinatal acidosis predicts persistent neurologic injury even if the newborn is classified as having mild encephalopathy. (35) At our institution, these three newborns met criteria for TH and were thus enrolled in the study. It is possible that cooling time and temperature deviation from 33–34°C could have stronger influence on autoregulation and brain injury in neonates with more severe HIE.

We adjusted the analyses for the perinatal insult score (11) and $PaCO_2$ because birth injury and $PaCO_2$ are known to affect subsequent brain injury (23) and autoregulation (24) and may confound time to cooling. Hypercarbia can shift the autoregulation curve, (24) and hypocarbia is independently associated with poor neurologic outcome in those with HIE. (36) With the exception of a single association between longer time to goal temperature and lower unilateral ADC in posterior centrum semiovale, we found no relationships between cooling time, autoregulation, and brain injury in univariate and multivariate analyses. Temperature deviation above 34°C was also not associated with brain injury. Therefore, we did not adjust for other factors in the statistical modeling, such as vasoactive medications, seizures, or sex.

Limitations

This study was conducted in a single, university-based NICU, thus findings may not be generalizable to other centers. Without *a priori* data about cooling time, temperature deviation from 33–34°C, and autoregulation, we could not conduct a sample size estimate. We designed this exploratory pilot study to generate potential hypotheses for future studies. However, the small sample size of neonates cooled before 3 h may have left us underpowered to detect true differences. Our neonates had predominantly moderate HIE and relatively mild brain injury on MRI. Additional studies in a larger and more heterogeneous population with more neonates cooled earlier and greater brain injury variability are needed. Larger studies will also enable analytic adjustments for potential confounders, such as inborn or outborn status. We did not study clinical care at the birth hospital and during transport, which may influence the risk of brain injury. Many neonates with HIE were excluded due to study ineligibility and other factors described in Figure 1. Selection bias cannot be ruled out. Finally, we analyzed hourly rectal temperature data because continuous temperature recordings were not available.

CONCLUSION

In a population of predominantly outborn neonates cooled to <34°C at 3–6 h of life for moderate HIE, cooling time did not affect autoregulation or overall early brain injury on MRI. Longer time to reach core temperature <34°C was associated with lower ADC in unilateral posterior centrum semiovale but not in other brain regions. Temperature deviation above 34°C was related to blood pressure exceeding MAP_{OPT} but did not affect brain injury.

These pilot study findings do not negate the importance of rapid cooling with vigilant temperature control. Additional studies are needed in a larger and more heterogeneous population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Consent:

Written informed consent was obtained through May 2013. Thereafter the Johns Hopkins Medicine IRB granted a waiver of consent, as near-infrared spectroscopy became standard clinical care during therapeutic hypothermia for neonates with neonatal encephalopathy at Johns Hopkins Hospital.

Impact

1. Cooling time to reach target hypothermia temperature within 6 h of birth did not affect cerebral autoregulation measured by NIRS in neonates with hypoxic-ischemic encephalopathy (HIE).
2. Temperature fluctuations above 33–34°C were associated with blood pressures that exceeded the range of optimal autoregulatory vasoreactivity.
3. Cooling time within 6 h of birth and temperatures exceeding 33–34°C were not associated with qualitative brain injury on MRI.
4. Regional apparent diffusion coefficient scalars on diffusion tensor imaging MRI were not appreciably affected by cooling time or temperature above 33–34°C.
5. Additional research in a larger and more heterogeneous population is needed to determine how delayed cooling and temperatures beyond the target hypothermia range affect autoregulation and brain injury.

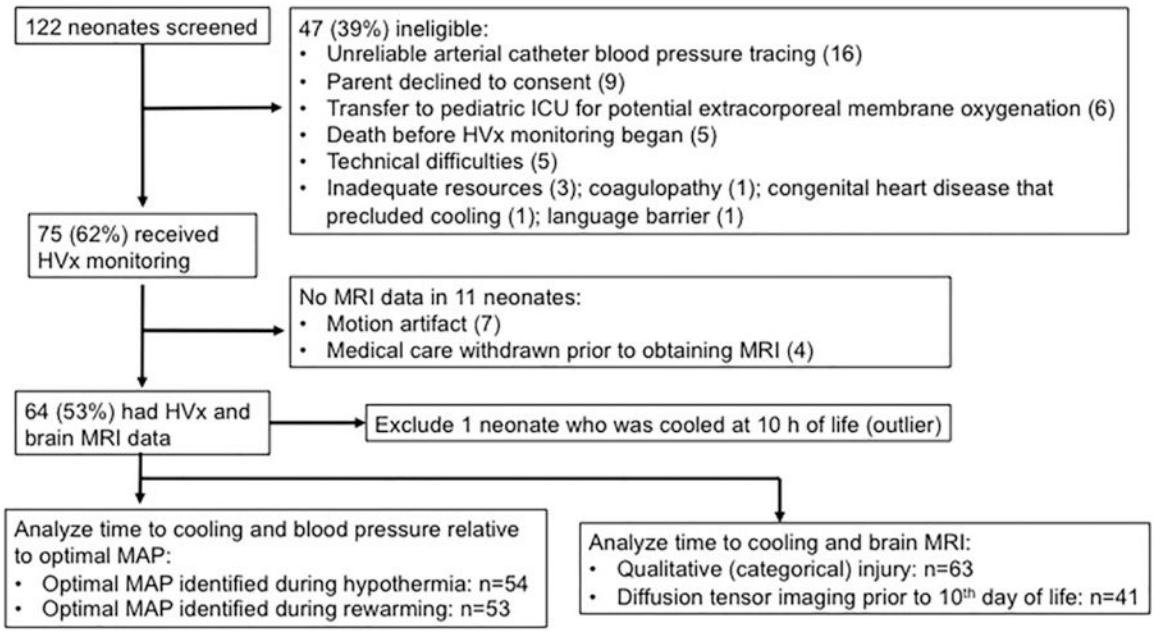

Figure 1.
Flow chart of study enrollment.

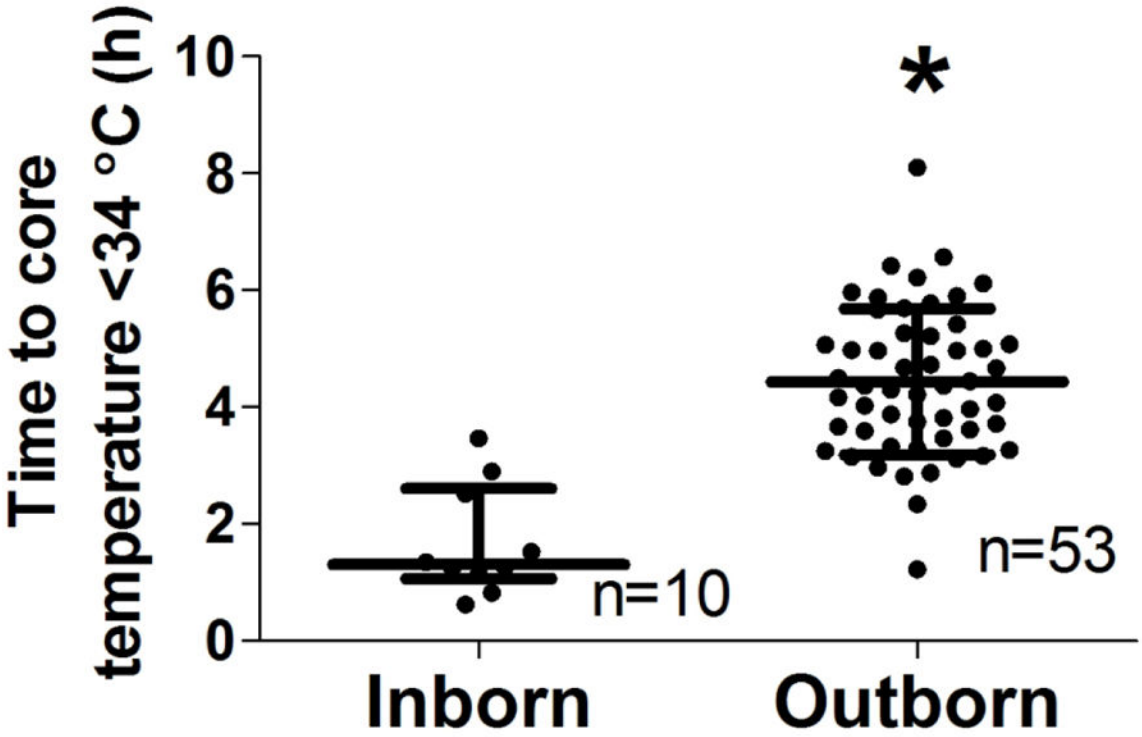

Figure 2.

Inborn neonates reached the goal core temperature faster than did outborn neonates (*p<0.001). Though cooling began within 6 h of birth for all neonates, outborn neonates were passively cooled during transport whereas inborn neonates received early active cooling. Medians with interquartile ranges are shown. Each circle represents one neonate.

Table 1.

Factors used in perinatal insult score calculation

Parameter	2 points	1 point	0 points
Emergency delivery[a]		Yes	No
Apgar score at 10 min[b]		≤ 5	>5
pH from the umbilical cord or arterial blood gas from 1st hour of life	≤7.00	7.01 to ≤7.15	>7.15
Base deficit from the umbilical cord or arterial blood gas from the 1st hour of life	≤ −16	−15 to ≤ −10	> −10
Sarnat stage	3	2	1
Mechanical ventilation		Yes	No

[a]Emergency delivery refers to unscheduled deliveries (e.g., delivery for fetal distress).

[b]If the Apgar score was not available, the baby received 1 point if mechanical ventilation was provided.

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Table 2.

Clinical characteristics of neonates included in the study

Parameter	All neonates n=63	Neonates with MRI prior to 10 days (subset for DTI MRI) n=41	*p* Value[a]
Gestational age, mean weeks.days [SD; range]	38.5 [1.5; 34.6 – 39.4]	38.5 [1.5; 34.6 – 39.4]	0.851
Delivery by Cesarean section, n (%)	47 (75)	30 (73)	1.000
Emergency birth, n (%)	44 (70)	28 (68)	0.780
Male, n (%)	37 (59)	26 (63)	0.446
Outborn, n (%)	53 (84)	34 (83)	1.000
Time to cooling, h, mean [SD]	4.0 [1.6]	3.9 [1.6]	0.321
Time to cooling <3 h, n (%)	14 (22)	11 (27)	0.377
Temperature AUC below 33ºC, degree*min per h, mean [SD]	1.0 [3.7][b]	0.8 [3.8][c]	0.594
Temperature AUC above 34ºC, degree*min per h, mean [SD]	30.4 [8.9][b]	32.1 [9.4][c]	0.027
Temperature AUC below or above 33–34ºC, degree*min per h, mean [SD][d]	31.4 [7.8][b]	32.9 [8.6][c]	0.015
Apgar 5 min, median [IQR] (n=61)	3 [2,6]	3 [2,5]	1.000
Apgar 10 min, median [IQR] (n=54)	5 [4,6]	5 [3,7]	0.913
Cord pH, mean [SD] (n=48)	7.0 [0.2]	6.9 [0.2]	0.553
Base deficit, cord gas, mean [SD]	−15.2 [6.9]	−16.2 [8.1]	0.213
First blood gas pH, mean [SD] (n=61)	7.1 [0.2]	7.1 [0.2]	0.563
Base deficit, 1st blood gas, mean [SD]	−16.8 [5.7]	−16.6 [5.6]	0.851
Sarnat encephalopathy score, n (%)			0.194
1	3 (5)	3 (7)	
2	51 (81)	34 (83)	
3	9 (14)	4 (10)	
Mechanical ventilation required, n (%)	46 (73)	27 (66)	0.147
Mechanical ventilation (days) among ventilated, mean [SD] (n=46, 27)	5.1 [4.2]	4.5 [3.6]	0.223
Perinatal insult score, n (%)[e]			0.164
3	2 (3)	2 (5)	
4	12 (19)	11 (27)	
5	7 (11)	3 (7)	
6	18 (29)	11 (27)	
7	19 (30)	12 (29)	
8	5 (8)	2 (5)	
$PaCO_2$ category, n (%)			0.257
All 35–45 mmHg	6 (10)	5 (12)	
Some < 35, all < 45 mmHg	11 (17)	9 (22)	
All > 35, some > 45 mmHg	28 (44)	18 (44)	
Some < 35, some > 45 mmHg	18 (29)	9 (22)	

AUC, area under the curve; DTI, diffusion tensor imaging; IQR, interquartile range; $PaCO_2$, partial pressure of arterial carbon dioxide; SD, standard deviation.

[a] Data were analyzed by chi square, Student's t-test, Fisher's exact text, or Mann-Whitney U test as appropriate.

[b] n=51 neonates with available hourly rectal temperature data.

[c] n=35 neonates with available hourly rectal temperature data.

[d] Used in the statistical analysis.

[e] Perinatal insult score: higher score indicates more severe birth asphyxia based on the clinical parameters in Table 1.

Table 3.

The association between the time to reach therapeutic hypothermia (≥3 h or <3 h after birth) and diffusion tensor imaging MRI (n=41).

Region	Unadjusted			Adjusted[a]		
	β	95% CI	*p*	β	95% CI	*p*
Anterior centrum semiovale, right	−79.6	−186.2, 27.1	0.152	−88.2	−195.8, 19.4	0.117
Anterior centrum semiovale, left	−90.7	−208.8, 27.4	0.140	−97	−216.0, 22.0	0.119
Posterior centrum semiovale, right	**−117.1***	**−222.6, −11.5**	**0.036**	**−118.1***	**−223.4, −12.8**	**0.035**
Posterior centrum semiovale, left	−70.2	−160.4, 20.0	0.135	−72.2	−161.5, 17.2	0.122
Basal ganglia, right	15.4	−63.1, 94.0	0.702	14.9	−67.9, 97.8	0.726
Basal ganglia, left	21.2	−61.1, 103.5	0.616	23.8	−62.5, 110.0	0.593
Thalamus, right	15.0	−50.0, 80.0	0.653	13.5	−55.2, 82.2	0.703
Thalamus, left	19.1	−49.5, 87.8	0.588	20.9	−51.7, 93.6	0.576
PLIC, right	3.0	−57.8, 63.8	0.925	0	−63.3, 63.3	1.000
PLIC, left	4.9	−53.0, 62.9	0.868	6.9	−53.9, 67.7	0.825
Pons	−15.3	−61.9, 31.2	0.522	−18.2	−65.9, 29.6	0.461
Cerebellar white matter, right	−19.0	−71.6, 33.6	0.483	−15.1	−68.0, 37.9	0.581
Cerebellar white matter, left	−17.1	−71.8, 37.5	0.543	−13.8	−70.1, 42.6	0.635

The β coefficient shows the change in apparent diffusion coefficient for ≥3 h versus <3 h of cooling. Bolding indicates statistical significance.

CI, confidence interval; PLIC, posterior limb of the internal capsule.

[a]Adjusted for perinatal insult score and $PaCO_2$.

*$p<0.05$.

Table 4.

The association between the area under the curve of temperature above 33–34°C and blood pressure relative to optimal mean arterial blood pressure

	Unadjusted			Adjusted[a]		
	β[b]	95% CI	*p*	β[b]	95% CI	*p*
Hypothermia (n=44)						
MAP_{OPT} (mmHg)	−0.2	−0.4, 0.0	0.087	−0.1	−0.3, 0.1	0.362
AUC (min*mmHg/h)	−3.7	−9.7, 2.3	0.238	−2.7	−8.8, 3.4	0.388
Time below MAP_{OPT} (%)	−0.7	−1.6, 0.3	0.174	−0.4	−1.4, 0.5	0.377
Time within MAP_{OPT} (%)	**−0.4***	**−0.7, −0.1**	**0.012**	−0.2	−0.5, 0.0	0.107
Time above MAP_{OPT} (%)	1.1	−0.0, 2.2	0.061	0.7	−0.4, 1.8	0.229
Maximal blood pressure below MAP_{OPT} (mmHg)	−0.2	−0.5, 0.1	0.260	−0.1	−0.5, 0.2	0.422
Maximal blood pressure above MAP_{OPT} (mmHg)	**0.5***	**0.1, 0.8**	**0.007**	**0.3***	**0.0, 0.7**	**0.041**
Rewarming (n=42)						
MAP_{OPT} (mmHg)	−0.2	−0.5, 0.0	0.062	−0.2	−0.5, 0.1	0.143
AUC (min*mmHg/h)	−9	−17.9, −0.0	0.056	−8.2	−17.6, 1.2	0.096
Time below MAP_{OPT} (%)	**−1.5***	**−2.6, −0.3**	**0.015**	**−1.4***	**−2.5, −0.2**	**0.027**
Time within MAP_{OPT} (%)	0	−0.5, 0.4	0.883	0	−0.5, 0.5	0.948
Time above MAP_{OPT} (%)	**1.5***	**0.5, 2.5**	**0.007**	**1.4***	**0.3, 2.4**	**0.013**
Maximal blood pressure below MAP_{OPT} (mmHg)	**−0.3***	**−0.5, −0.0**	**0.042**	−0.3	−0.5, 0.0	0.062
Maximal blood pressure above MAP_{OPT} (mmHg)	**0.4***	**0.1, 0.8**	**0.022**	0.3	−0.0, 0.7	0.060

Bold indicates statistical significance.

AUC, area under the curve; CI, confidence interval; MAP_{OPT}, optimal mean arterial blood pressure.

[a] Adjusted for perinatal insult score and $PaCO_2$.

[b] β represents a 1% change in time or 0.5 mmHg change in MAP per change in temperature AUC of 1 degree*min per hour. For example, β of 1.5 for time spent with blood pressure above MAP_{OPT} indicates that 1 additional degree*minute per hour of temperature outside the 33–34°C range is related to a 1.5% increase in time with blood pressure above MAP_{OPT}.

* $p<0.05$.