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ORIGINAL ARTICLE

Relationship between temperature variability and brain injury on magnetic resonance imaging in cooled newborn infants after perinatal asphyxia

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OBJECTIVE: The objective of the study was whether temperature management during therapeutic hypothermia correlates with the severity of brain injury assessed on magnetic resonance imaging in term infants with hypoxic-ischemic encephalopathy.
STUDY DESIGN: Prospectively collected register data from the National Asphyxia and Cooling Register of Switzerland were analyzed.
RESULT: Fifty-five newborn infants were cooled for 72 h with a target temperature range of 33 to 34 °C. Individual temperature variability (odds ratio (OR) 40.17 (95% confidence interval (CI) 1.37 to 1037.67)) and percentage of temperatures within the target range (OR 0.95 (95% CI 0.90 to 0.98)) were associated with the severity of brain injury seen on magnetic resonance imaging (MRI). Neither the percentage of measured temperatures above (OR 1.08 (95% CI 0.96 to 1.21)) nor below (OR 0.99 (95% CI 0.92 to 1.07) the target range was associated with the severity of brain injury seen on MRI.
CONCLUSION: In a national perinatal asphyxia cohort, temperature variability and percentage of temperatures within the target temperature range were associated with the severity of brain injury.

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INTRODUCTION

To date, the only evidence-based intervention for hypoxic-ischemic encephalopathy (HIE) in the term newborn infant is therapeutic hypothermia (TH).[1] TH has therefore become the standard of care in high-income countries, given the strong evidence that, for moderate-to-severe HIE, it reduces mortality and neurodevelopmental disability at 18 to 24 months of age.[1] This effect seems to persist into childhood.[2–4] Yet, despite these benefits, approximately half of cooled newborn infants still die or survive with significant neurological impairments, and the search continues for therapeutic strategies to refine or supplement hypothermic neuroprotection.

The optimal absolute temperature range and the duration of TH have not been established. It is not clear whether high temperature variability or over- or undercooling during TH influence brain injury as seen on MRI scans or in neurodevelopmental outcome.[5] A recent study by Shankaran *et al.*[6] investigated whether deeper and longer cooling leads to further reduction in death or later disability, by extending TH from 72 to 120 h and to a lower target temperature of 32.0 °C. The probability of detecting a statistically significant benefit for longer or deeper cooling for death in the neonatal intensive care unit was $< 2\%$; hence, this study was closed for emerging safety and futility issues.[6] In an editorial, Thoresen[7] discussed the optimal absolute temperature range of TH and suggested that a trial with milder hypothermia should be performed, because of the lack of treatment benefit with deeper temperatures[6] and results from cooling treatments in adults.[8] Nielsen *et al.*[8] showed that in adult patients with out-of-hospital cardiac arrest, hypothermia at a target temperature of 33 °C did not confer extra benefit over a target temperature of 36 °C. They concluded that the most important factor for favorable neurologic recovery is preventing fever.[8] This conclusion is further supported by the study of Zeiner *et al.*,[9] who showed that in adult patients with out-of-hospital cardiac arrest the risk of an unfavorable outcome increases for each degree Celsius higher than 37 °C. Similarly Laptook *et al.*[10,11] showed that elevated temperature after HIE is a risk factor for poor neurodevelopmental outcome in non-cooled term newborn infants.

The influence of temperature management, for example, temperature variability per newborn infant has not yet been fully investigated. Indeed, little is reported in the literature about temperature variability during TH and the potential influences of temperature variations on the severity of brain injury. In Switzerland, therapeutic cooling of term newborn infants with HIE started in 2005 and the majority of newborn infants with HIE have been passively cooled. Temperature variations are significantly higher and overcooling more frequent with passive than with active cooling.[12] We therefore investigated whether higher temperature variability within the target range or the length of time the core temperature is above, within or below the target range correlated with the severity of brain injury assessed on conventional magnetic resonance imaging[6] obtained in the first 1 to 2 weeks after birth.

METHODS

Register centers and data collection

Eight tertiary-level neonatal intensive care units and two pediatric intensive care units are part of the National Asphyxia and Cooling Register

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in Switzerland. Data from all cooled newborn infants with HIE were collected prospectively with an electronic case report form. Data collection and evaluation (including publication) for this study were approved by the institutional ethical review boards and by the Swiss Federal Commission for Privacy Protection in Medical Research.

Cooling

Newborn infants were cooled according to a cooling protocol, adapted from the TOBY trial register.[12] Whole-body cooling was performed for 72 h with a target temperature range of 33 to 34 °C, followed by a rewarming period (0.2 °C per h to 36.5 ± 0.5 °C). Both active and passive cooling methods were used in these infants.[12] The core temperature was continuously monitored by rectal probe and hourly temperature point measurements were recorded in the notes. Cooling was started at a median postnatal age of 3 h (range 0.5 to 8.5 h). For our analysis, we included only the temperature measurements obtained during the maintenance phase of TH and excluded the induction and rewarming phases. The median time to reach target temperature was 3 h (range 1 to 4), thus we defined the maintenance phase as the time between 6 and 72 h from the start of cooling. The temperature variability from hour to hour within the temperature target range for each newborn infant and the percentage of hourly temperature measurements above, within or below the target temperature range were calculated for each newborn infant during TH.

Neurological examination during hospitalization

All newborn infants had neurological examinations[13] performed by a senior neonatal consultant before the start of TH, and on days 1, 2, 3 and 4 after birth. Clinical seizures or seizure activity seen on amplitude integrated electroencephalogram during TH and the rewarming phase were noted.

Cranial MRI

Cranial MRI was performed at median postnatal day 6 (range 4 to 12 days). Conventional T1 and T2-weighted images were assessed according to a previously published injury score[14] by an experienced pediatric neuroradiologist (RG) blinded to all clinical parameters. The combined basal ganglia/watershed injury score (BG/W score) was used for further analysis because this score includes components of both patterns of injury, and the BG/W score has been shown to be able to discriminate accurately between patients with good and poor neuromotor and cognitive outcome at 3 and 12 months of age.[14] In addition to the above outcome categories, we defined a dichotomous outcome consisting of a 'favorable' outcome (MRI BG/W score = 0 to 2) and a 'poor' outcome that included all newborn infants with a moderately or severely abnormal MRI (MRI BG/W score 3 to 4). The presence or absence of a normal signal from myelin in the posterior limb of the internal capsule (PLIC) was also assessed on T1- and T2-weighted images.[15]

Statistics

Descriptive statistics were used, with counts (percentages) for categorical variables, mean (s.d.) for normally distributed continuous variables or median (range) for non-normally distributed continuous variables. The variability of rectal measured core temperature during TH was measured with s.d. for each newborn infant over time.

We performed the Fisher's exact test or the Kruskal–Wallis test (as appropriate) to analyze the association of clinical variables or temperature management details with the BG/W score. The Fisher's exact test or the Wilcoxon rank sum test (as appropriate) were used to evaluate the association of clinical variables or temperature management details with the presence or absence of a normal signal from myelin in the PLIC. A logistic regression analysis was performed to evaluate the correlation of the clinical variables and temperature variables with the presence or absence of a normal signal from myelin in the PLIC and for the dichotomous outcome categories (poor outcome MRI BG/W score 3 to 4, favorable outcome MRI BG/W score = 0 to 2). To adjust for potential confounds relating to the severity of HIE before cooling, we included the neurological examination from the Sarnat assessment to determine early clinical severity from before cooling in every analysis. To evaluate the degree of over- and undercooling during TH and the correlation between over and undercooling and the MRI findings, we divided the temperatures measured outside the target range into different categories. Temperatures below target range (< 33.0 °C) were defined as: category 1, 32 to 33 °C; category 2, 31 to < 32 °C; category 3, 30 to < 31 °C; and temperatures above target range (> 34 °C): category 1, > 34 to 35 °C; category 2, > 35 to 36 °C; category 3, > 36 to 37 °C. We created a scoring system by multiplying the number of the category above or below the temperature range with the number of measurements within that specific category and evaluated the score against MRI findings. The Wilcoxon test or the Kruskal–Wallis test was used to assess differences in score values and MRI outcome categories.

A *P*-value below 5% was considered statistically significant. Analyses were performed with SPSS for windows version 20.0 (IBM, Armonk, New York, USA) and R for windows version 3.2.2 (IBM, Armonk, New York, USA).

RESULTS

Patients and TH

Of 89 registered newborn infants treated with TH, 55 (62%) had a MRI performed during the neonatal period. Baseline characteristics of these 55 newborn infants are shown in Table 1.

Figure 1 shows the boxplots of the median and interquartile ranges of all temperature measurements over time. Ten percent (95% CI 6 to 15) of the measured temperatures of all newborn infants were above target temperature range during TH, 80% (95% CI 75 to 85) were within the target temperature range and 10% (95% CI 7 to 13, 34.1 to 37.2 °C) were below the target temperature range. In only three newborn infants 5.5% was all measured temperatures within the target range at all time points, whereas 13 (23.5%) newborn infants had some measured temperatures below, 12 (22%) newborn infants had some measured temperatures above and 27 (49%) newborn infants had some measured temperatures both above and below target range.

Neurological examinations during admission

Median (range) age of the neurological examination[13] before cooling was 3 (0 to 9) h. The second examination was performed at a median age of 39 (24 to 48) h, the third at a median age of 60 (48 to 72) h and the fourth at a median age of 84 (72 to 96) h. All newborn infants ($n = 55$) had a neurological examination performed before cooling was started. The majority of these newborn infants were classified as Sarnat stage 2 ($n = 33$, 60%) (Table 1). After cooling on day 4, of the 30 infants most were classified to be in Sarnat stage 1 ($n = 17$, 56.7%), 7 in stage 2 (23.3%) and 6 in stage 3 (20%) (Table 1). Clinical or electrographic seizures were noted in 26 (47%) newborn infants during the first 4 days (before cooling, during TH, during the rewarming phase). All newborn infants received some analgesic medication/sedative (midazolam, morphine or fentanyl) during TH.

Correlation between neurological findings and temperature management

There was a statistically significant correlation of Sarnat Score before cooling and the percentage of measured temperatures below target range ($P = 0.01$) depicted in Figure 2a. Additionally, in newborn infants with mild encephalopathy before cooling, more temperatures were measured above target range during TH, although this did not reach statistical significance (Figure 2b).

Cranial MRI findings and correlation to clinical variables

A BG/W score ranging from 0 to 4 was obtained for all scans. Twenty newborn infants (36%) demonstrated scans with a score of 0, 9 (16%) had a score of 1, one (2%) had a score of 2, 18 (33%) a score of 3 and the remaining 7 (13%) a score of 4. In 35 newborn infants the PLIC was either abnormal ($n = 30$) or equivocal ($n = 5$). BG/W score and the abnormal PLIC correlated significantly ($P = 0.002$).

Table 1. Baseline characteristics of study population

	N = *55 (100%)*
Gestational age, weeks median (range)	40 (35–41)
Birth weight, grams mean (s.d.)	3366 (595)
Outborn *n* (%)	43 (78)
Resuscitation required >10 min *n* (%)	39 (72)
Apgar at 10 min of age median (range)	5 (0–10)
Umbilical artery pH mean (s.d.)	6.9 (1.8)
Lowest pH within 60 min after birth mean (s.d.)	6.9 (0.17)
Lowest base excess (mmol l^{-1}) within 60 min after birth mean (s.d.)	19.7 (6.2)
Highest lactate (mmol l^{-1}) within 60 min after birth mean (s.d.)	13.8 (4.7)
Highest CO_2 (kPa) within 60 min after birth mean (s.d.)	9.3 (3.7)
Hypoglycemia, *n*	0
Sarnat Score before cooling, n (%)	
Stage 1	8 (14)
Stage 2	33 (60)
Stage 3	14 (26)
Not recorded in the notes	0
Sarnat Score on day 1, n (%)	
Stage 1	11(20)
Stage 2	23 42)
Stage 3	7 (13)
Not recorded in the notes	14 (25)
Sarnat Score on day 2, n (%)	
Stage 1	14 (26)
Stage 2	21 (38)
Stage 3	5 (9)
Not recorded in the notes	15 (27)
Sarnat Score on day 3, n (%)	
Stage 1	16 (29)
Stage 2	15 (27)
Stage 3	7 (13)
Not recorded in the notes	17 (31)
Sarnat Score on day 4 (after cooling), n (%)	
Stage 1	17 (31)
Stage 2	7 (13)
Stage 3	6 (11)
Not recorded in the notes	25 (45)
Maintenance phase of therapeutic hypothermia (all patients)	
Hours above target range, median (range)	4.0 (0.5–6.0)
Hours within target range, median (range)	42 (33–53)
Hours below target range, median (range)	4.0 (0.0–8.5)

Continuous variables are presented as mean (s.d.) for normally distributed and median (range) for non-normally distributed. Categorical variables are presented as number and (percentage).

There was no statistically significant correlation between the MRI BG/W score or the absence of a normal signal from myelin in the PLIC and any of the investigated clinical variables (resuscitation >10 min after birth, Apgar score at 10 min, umbilical artery pH, lowest pH and lactate within 60 min of birth).

Correlation between cranial MRI findings and neurological variables

Sarnat staging on days 1, 3 and 4 correlated significantly with BG/W score ($P = 0.047$, $P = 0.021$, $P = 0.032$). The absence of a normal signal from myelin in the PLIC did not correlate with Sarnat stage at any time point. Clinical seizures or seizure activity as shown on amplitude integrated electroencephalogram correlated with the BG/W score ($P = 0.028$), but not with an abnormal PLIC.

After defining a dichotomous outcome consisting of a 'favorable' MRI (MRI BG/W = 0 to 2, no-to-mild injury) and a 'poor' MRI (MRI BG/W score 3 to 4, moderate-to-severe injury), a logistic regression analysis (Table 2) revealed that the Sarnat stages on day 1 ($P = 0.028$), day 3 ($P = 0.016$) and day 4 ($P = 0.038$) was statistically significantly associated with moderate-to-severe abnormal MRI findings, hence poor outcome.

Cranial MRI findings and correlation to temperature management

The analysis revealed no significant correlation between the MRI BG/W score with age at start of cooling or percentage of temperature measurements outside (above or below) the target temperature range after adjustment for Sarnat stage during admission. The degree of over- and undercooling was also not associated with the MRI BG/W score. There was no statistically significant difference between the average (median) temperature per newborn infant according to the severity of brain injury on MRI (Figure 3).

However the temperature variability per newborn infant and percentage of time the temperature was within the temperature target range was statistically associated with poor MR outcome (Table 3), even after adjustment for Sarnat stage during admission. Logistic regression analysis of the dichotomous imaging outcome categories (BGT/WS score 0 to 2, favorable; BGT/WS score 3 to 4, poor) against temperature management during TH is shown in Table 3. Figure 4 shows that there is a correlation between higher temperature variability per newborn infant and more severe MRI outcome categories.

The absence of normal signal from myelin in the PLIC did not correlate with temperature management details during TH (age at start of cooling (OR 1.1 (95% CI 0.77 to 1.57)), temperature variability per newborn infant (OR 1.27 (95% CI 0.08 to 18.5)), hours above (OR 0.97 (95% CI 0.85 to 1.09)), within (OR 0.9 (95% CI 0.95 to 1.03)) or below (OR 0.97 (95% CI 0.85 to 1.09)) target temperature range) and the degree of over- and undercooling.

DISCUSSION

There are many unanswered questions regarding temperature management during TH, but emerging evidence suggests that the temperature should not be <32 °C and that elevated temperatures after hypoxic-ischemic injury represent a risk factor for poor neurodevelopmental outcome.[6–8,11]

In animal models of HIE, even small increases in brain temperature are associated with increased severity of brain injury.[16] Indeed, several clinical studies concluded that the most important factor for favorable neurological outcome is preventing fever during the first days after the ischemic insult, therefore high core temperature should be lowered by medication and physical methods.[8–10]

In our small cohort of cooled infants with HIE, we did not find any correlation between high temperature during the first 4 days after birth and the severity of brain injury as seen on MRI. However, we found a correlation between the severity of encephalopathy and the proportion of measured temperatures outside the target temperature range during TH: infants with mild encephalopathy had more temperature measurements above the target range than infants with moderate-to-severe encephalopathy. This may be explained by the fact that newborn infants with mild encephalopathy are more active and less frequently ventilated and sedated than newborn infants with severe encephalopathy and hence, maintaining target temperature in newborn infants with mild encephalopathy may be more difficult. In contrast, we found that infants with severe encephalopathy had more temperatures below the temperature target range, perhaps because they are inactive and are more easily cooled. However,

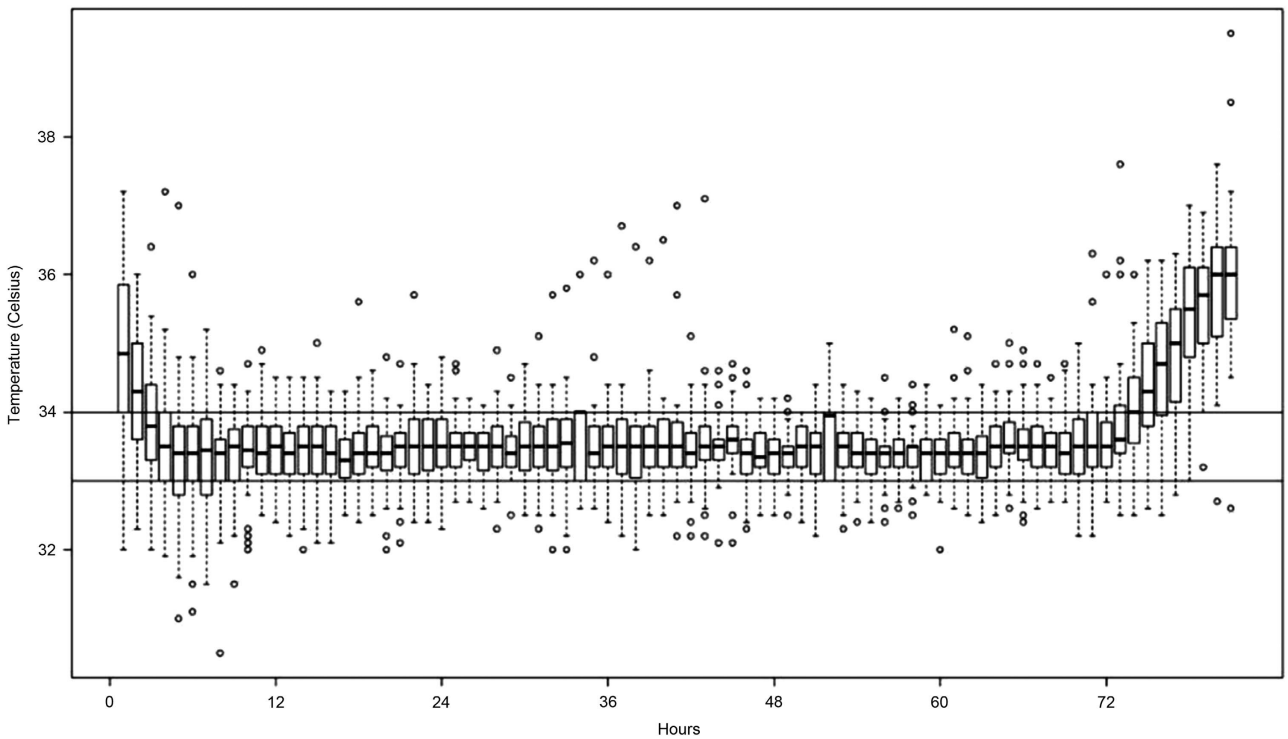

Figure 1. Temperature measurements during therapeutic hypothermia. Boxplots of median and interquartile range of temperature measurements over time for all included newborn infants ($n = 55$).

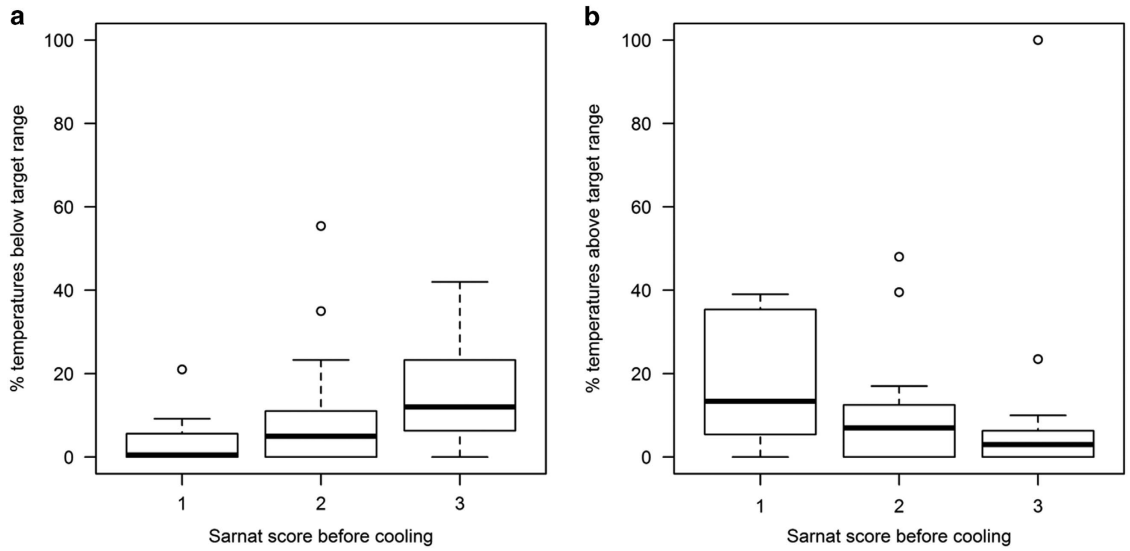

Figure 2. Influence of the severity of encephalopathy on overcooling (**a**) and overheating (**b**) during therapeutic hypothermia. Boxplots of median and interquartile range of percentage of measured temperatures below target temperature range (**a**) and above target temperature range (**b**) in relation to the Sarnat stage before cooling.

overcooling in our cohort was not associated with the severity of brain injury. One reason for the lack of an observed link between overcooling and poor outcome may be related to the relatively short time spent at < 33 °C and the low degree of overcooling. However, our findings are in agreement with the study of Shankaran *et al*.,[5] in which the temperature profile and outcome were analyzed in cooled newborn infants and no association was observed between the number of hours spent at a temperature < 32 °C and their primary outcome, which was death or moderate/severe disability at 18 months of age. This observation is also in agreement with the experimental findings of Wood *et al.*[17] They recently showed in a rat model of moderate hypoxic-ischemic injury that there is a distinct temperature-dependent neuroprotective effect of hypothermia for moderate hypoxic-ischemic injury, whereas with severe hypoxic-ischemic injury, hypothermia did not provide neuroprotection, regardless of treatment temperature. They describe a U-shaped curve of hypothermic neuroprotection after moderate hypoxia-ischemia, with overcooling resulting in a loss of benefit below 30 °C.[17] In our study no newborn infant had temperatures below 30 °C, which

may explain the lack of an observed association between overcooling and poor outcome.

On the basis of their findings, Wood *et al.* suggest a further trial of hypothermia looking at milder hypothermia, or maintenance of normothermia and prevention of hyperthermia. This is in agreement with studies in human beings.[6–8,11] Most RCTs of TH in term infants reduced temperature to 33.5 °C (range 33.0 to 34.0 °C) for whole-body cooling or to 34.5 °C for selective head cooling.[1] Some studies suggest less severe MRI findings in newborn infants who had whole-body cooling compared to selective head cooling, however other studies suggest equal benefit from both cooling methods[18,19] However, none of these clinical studies examined the variability of the temperature within the temperature range during TH or the correlation of temperature variability to outcome. In our cohort of cooled infants with HIE, individual temperature variability and the percentage of measured temperatures within the target temperature range were associated with the severity of brain injury seen on conventional MRI, even after adjustment for the degree of encephalopathy. Hence, infants who showed a higher variability of temperature measurement and spent less time within the target range during TH had more severe brain injury on MRI. This implies that not only is it important to maintain temperature within the target range but also that temperature variability within the target range should be avoided in infants during TH, independent of the severity of encephalopathy. This reduction in temperature variability (and maintenance of target temperature) is better achieved with active cooling methods than with passive cooling, as we have shown previously.[12]

Our study is limited by the small sample size, and the fact that we performed our analysis only during the maintenance phase of

Table 2. Logistic regression analysis of clinical variables for dichotomous MRI BG/W outcome

Variables	*OR*	*95% CI*	P-value
Resuscitation required >10 min	2.1	0.6–7.3	0.24
Apgar score at 10 min	0.84	0.64–1.08	0.28
Umbilical artery pH	0.34	0.01–9.18	0.53
Lowest pH within 60 min of birth	1.12	0.5–2.4	0.77
Highest lactate (mmol l^{-1}) within 60 min of birth	1.03	0.88–1.19	0.52
Sarnat stage day 1	3.46	1.13–10.61	0.028
Sarnat stage day 2	2.02	0.73–5.5	0.17
Sarnat stage day 3	3.51	1.26–9.80	0.016
Sarnat stage day 4	3.02	1.06–8.53	0.038
Seizures (clinical and/or electrical)	3.04	1.01–9.1	0.048

Abbreviations: BG/W, basal ganglia/watershed; CI, confidence interval; MRI, magnetic resonance imaging; OR, odds ratio. MRI BG/W outcome: Favorable outcome: MRI BG/W score 0 to 2, poor outcome: MRI BG/W score 3 to 4. Outcome parameters: 0 = favorable, 1 = poor outcome.

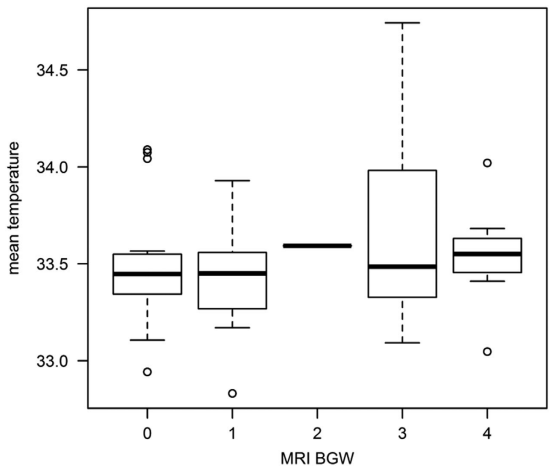

Figure 3. The average temperature per newborn infant during hypothermia therapy according to the severity of brain injury on magnetic resonance imaging (MRI). Boxplots of median of measured temperatures per newborn infant during hypothermia therapy according to the different MRI basal ganglia/watershed (BG/W) score categories. About 36% of the newborn infants had a normal MRI scan (score = 0), 16% had a score of 1, 2% a score of 2, 33% a score of 3 and 13% a score of 4.

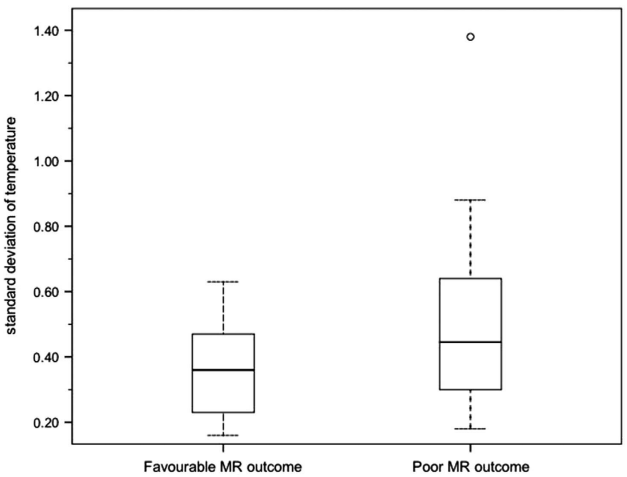

Figure 4. Temperature variability per newborn infant during hypothermia therapy in association with the severity of brain injury on magnetic resonance imaging (MRI). Boxplots of temperature variability per newborn infant in association with the different MRI basal ganglia/watershed (BG/W) outcome score categories.

Table 3. Multiple logistic regression analysis of temperature variables for MRI BG/W score

Variables[a]	*OR*	*95% CI*	P-value
Temperature measurements above TT	1.23	0.96–1.21	0.17
Temperature measurements within TT	0.95	0.90–0.98	0.014
Temperature measurements below TT	0.78	0.92–1.07	0.78
Temperature variability (s.d.)	40.17	1.37–1037.67	0.03
Age when cooling was started	0.97	0.70–1.34	0.88

Abbreviations: BG/W score, basal ganglia/watershed injury score; CI, confidence interval; MRI, magnetic resonance imaging; OR odds ratio; TT, target temperature range. Favorable outcome: MRI BG/W score 1 to 2, poor outcome: MRI BG/W score 3 to 4. [a]Adjusted for Sarnat Score before cooling.

TH. Thus, we did not assess any possible influence on severity of brain injury of over- and undercooling during the induction and rewarming phases, however rewarming is performed slowly with a temperature increase of 0.2 °C per h and we did not find any measured temperature above 37.5 °C. Additionally, the temperature measurements were only recorded on an hourly basis, so we do not know if there are temperatures above or below target range in between those measured and documented in the patient notes.

CONCLUSION

In our national cohort of cooled infants with HIE, temperature variability within the target temperature range and the amount of time spent within the target temperature range are associated with the severity of brain injury as assessed on MRI, even after adjustment for the degree of encephalopathy. Over- and undercooling to a minimal extent did not influence the severity of brain injury. Therefore, clinicians should pay attention not only to achieving the target temperature but also to avoiding variability of temperature during TH. The putative link between temperature variability and neurodevelopmental outcome in term infants with HIE in infancy and later childhood should be investigated in future studies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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