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Oldenmark, B.O. van; Steenis, A. van; Vries, L.S. de; Groenendaal, F.; Steggerda, S.J.

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Fifteen Years of Neonatal Therapeutic Hypothermia: Clinical Trends Show Unchanged Post-Rewarming Outcomes despite Reduction in Hypoxic-Ischemic Encephalopathy Severity

Bregje O. van Oldenmark[a] Andrea van Steenis[a] Linda S. de Vries[a]
Floris Groenendaal[b] Sylke J. Steggerda[a]

[a]Division of Neonatology, Department of Pediatrics, Willem-Alexander Children's Hospital, Leiden University Medical Center, Leiden, The Netherlands; [b]Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht and Utrecht University, Utrecht, The Netherlands

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Keywords
Therapeutic hypothermia · Hypoxic-ischemic encephalopathy · Perinatal asphyxia

Abstract

Introduction: Hypoxic-ischemic encephalopathy (HIE) affects 1–2 per 1,000 births and is associated with mortality and long-term neurodevelopmental challenges. At present, therapeutic hypothermia (TH) is the only neuroprotective intervention for these infants. This study examines whether HIE severity, clinical management during TH, and post-rewarming outcomes have changed since its introduction 15 years ago. ***Methods:*** Neonatal characteristics, HIE severity, management during TH, and post-rewarming MRI of all infants with HIE undergoing TH between 2008 and 2023 were compared across three five-year epochs. Linear regression was used to estimate annual changes over time. ***Results:*** In total, 252 infants underwent TH. Median gestational age (39.5 weeks), birth weight (3,376 g), and time to start TH (4.25 h) remained stable over time. Apgar score at 5 min ($p = 0.031$) and lowest pH <1 h postpartum ($p = 0.020$) increased over time. Thompson score at 1–3 h decreased across epochs ($p = 0.046$). There was an increase in percentage with normal-mild aEEG background patterns on admission ($p = 0.041$) and a decrease in aEEG-confirmed seizures ($p < 0.001$) and antiseizure medication ($p < 0.001$). Inotropic support decreased ($p = 0.007$), and use of invasive mechanical ventilation decreased over the last 5 years. Mortality (28.6%) and post-rewarming composite adverse outcome (i.e., neonatal mortality and/or adverse MRI score) (37.9%) remained unchanged. Number of infants seen at 2-year follow-up increased ($p < 0.001$). ***Conclusion:*** Over the last 15 years, we treated more infants with milder HIE, as indicated by lower Thompson and milder aEEG scores, and the need for invasive cardiorespiratory support declined. However, there were no improvements in composite adverse outcome (mortality and/or adverse MRI score).

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Introduction

Perinatal asphyxia followed by hypoxic-ischemic encephalopathy (HIE) is a severe neurological condition affecting 1–2 per 1,000 (near)term births in high-income countries [1]. It accounts for approximately 23% of the 4 million neonatal deaths worldwide [2] and is associated with acute symptoms as well as lifelong impairments such as cerebral palsy, epilepsy, intellectual disability, and

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Correspondence to:
Sylke J. Steggerda, s.j.steggerda@lumc.nl

behavioral disorders [2, 3]. HIE involves a "therapeutic window" between initial and delayed cell death, allowing interventions like therapeutic hypothermia (TH) to reduce further neurological damage [4].

Following publications in 2005, TH has significantly improved care of infants with HIE by offering neuroprotection and potentially improving long-term outcomes [5–7]. In our unit, TH is now standard of care for all infants meeting the criteria for HIE [8–10]. For 15 years, we have followed a national protocol for selection, monitoring and support during TH and follow-up (FUP). In 2021, minor protocol changes were implemented, reducing gestational age (GA) from >35.0 to ≥35.0 weeks and Thompson score from >7 to ≥7 [11]. Others have shown that growing bedside experience and insights from literature have led to the selection of milder HIE cases and infants with lower GA, a reduced use of invasive cardiorespiratory support, and a more comfort-oriented approach during TH [4, 12]. Subsequently, these potential changes may contribute to a change in outcomes.

Therefore, the aim of this single-center study was to examine whether experience and evolving knowledge impacted care practices and outcomes of neonates receiving TH over the past 15 years. Our primary objective was to investigate changes in clinical parameters before and support during TH. Secondary aim was to examine trends in neonatal mortality and post-rewarming MRI findings.

Patients and Methods

Participants and Treatment of Data

For this single-center retrospective study, all neonates, admitted to the neonatal intensive care unit of the Leiden University Medical Center (LUMC) between August 2008 and December 2023, undergoing TH for HIE were enrolled. Throughout the entire study period a standardized national protocol was used to assess eligibility for TH (see Supplement 1 at https://doi.org/10.1159/000541472). Neonates with birth weight <1,800 g or major congenital abnormalities did not qualify for TH and were excluded. According to the national guidelines, GA <36 weeks (from 2021 onwards <35 weeks) was an exclusion criterion for TH, but as we expected some shift in GA over time, this was not considered an exclusion criterion for the study. As only retrospective and pseudonymized data were used, written informed consent was waived (reference number LUMC G23-3101).

Inclusion Characteristics prior to TH

To examine whether selection of infants for TH changed over the past 15 years, baseline perinatal characteristics were collected (Table 1) including sex, GA and birth weight, presence of a sentinel event, inborn status, Apgar scores (AS), pH and base excess (BE) of either cord blood or blood gas <1 h postpartum, highest lactate <6 h, highest Thompson score 1–3 h postnatally, and the predominant amplitude-integrated EEG (aEEG) background pattern on admission. Thompson score was categorized as "mild" (<7), "moderate" (7–11), or "severe" (>11) [13]. For aEEG background patterns, "continuous normal voltage" (CNV) and "discontinuous normal voltage" (DNV) were considered "normal/mild," whereas "burst suppression" (BS), "continuous low voltage" (CLV), and "flat trace" (FT) were considered "moderate/severe." A sentinel event was defined as a clearly identifiable acute cause of perinatal asphyxia (i.e., umbilical cord prolapse, uterine rupture, placental abruption, shoulder dystocia, major maternal hemorrhage, trauma, or cardiorespiratory arrest).

We assessed time between birth and start of active cooling, as the time recorded in the electronic patient file when cooling was initiated in hours and minutes. If the medical record indicated that the target core temperature of 33.5°C had already been reached before, this specific time point was used.

Supportive Care during TH

Data on care during TH included need for ventilation (noninvasive or invasive), duration of mechanical ventilation, need for inotropic support, inhaled nitric oxide (iNO) for persistent pulmonary hypertension, arterial and central venous lines, and use and highest maintenance dosage of morphine for analgesia and midazolam for sedation during TH. Information on the infant's clinical status during TH included seizures ([a]EEG-confirmed), antiseizure medication, documented hypocapnia (temperature-corrected $PaCO_2$ <4 kPa between birth and first 24 h of TH), and sepsis during hospitalization (positive blood culture).

Outcomes

Post-rewarming data included the use of neonatal MRI and MRI brain abnormality score. Since 2006, all MRI scans were performed on a 3T scanner with similar protocol. Brain abnormalities were scored according to the Rutherford classification with the addition of diffusion weighted imaging. Deep gray matter (DGM), cortical gray matter (CGM), and white

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Table 1. Characteristics prior to TH over three 5-year epochs

Inclusion criteria	Epoch 1 2008–2013 (n = 75)	Epoch 2 2014–2018 (n = 75)	Epoch 3 2019–2023 (n = 98)	p value
Male	39/75 (53.0)	44/75 (58.7)	52/98 (53.1)	0.672
Gestational age – weeks/days	39.5 (38.1–41.0)	39.5 (38.0–40.6)	39.5 (38.0–40.6)	0.202
Infants with GA <36 weeks	2/75 (2.7)	4/75 (5.3)	11/98 (11.2)	0.072
Birth weight, g	3,362 (618)	3,349 (633)	3,408 (676)	0.683
Inborn	10/75 (13.3)	9/75 (12.0)	19/98 (19.4)	0.347
Sentinel intrapartum event	30/75 (40.0)	32/75 (42.7)	57/98 (58.2)	**0.033**
Apgar score at 5 min	2 (1–4)[1]	3 (1–4)[2]	3 (1–4)	**0.031**
Apgar score at 10 min	4 (2–6)[3]	4 (3–6)[4]	5 (4–6)	0.137
Lowest pH, cord or blood <1 h, mmol/L	6.85 (0.30)	6.86 (0.18)	6.90 (0.19)	**0.020**
Lowest BE, cord or blood <1 h, mmol/L	−19. 1 (7.4)[5]	−18.6 (5.7)[6]	−17.9 (6.5)[7]	0.512
Highest lactate <6 h, mmol/L	12.7 (6.5)[8]	13.7 (4.8)[9]	13.3 (4.8)[10]	0.213
Time to cooling, hours: minutes	4:09 (2:59–5:50)[11]	4:39 (3:41–5:43)	4:21 (3:31–5:26)	0.475
Infants admitted after 6 h	10/73 (13.7)	9/75 (12.0)	10/88 (11.4)	0.780
Highest Thompson score 1–3 h	10 (8–14)[12]	10 (8–12)[13]	10 (8–13)[14]	**0.046**
Severity Thompson score				0.555
Mild: <7	4/55 (7.3)	7/69 (10.2)	12/93 (12.9)	
Moderate: 7–11	28/55 (50.9)	43/69 (62.3)	54/93 (58.1)	
Severe: >11	23/55 (41.8)	19/69 (27.5)	27/93 (29.0)	
aEEG BGP at admission				0.041[15]
CNV	8/70 (11.4)	15/75 (20.0)	25/96 (26.1)	
DNV	28/70 (40.0)	32/75 (42.7)	38/96 (39.6)	
BS	21/70 (30.0)	19/75 (25.3)	15/96 (15.6)	
CLV	6/70 (8.6)	7/75 (9.3)	8/96 (8.3)	
FT	7/70 (10.0)	2/75 (2.7)	10/96 (10.4)	

Outcomes are presented as mean (standard deviation [SD]), median (interquartile range [IQR]) or n/N (%). aEEG BGP, amplitude electroencephalogram background pattern; CNV, continuous normal voltage; DNV, discontinuous normal voltage; BS, burst suppression; CLV, continuous low voltage; FT, flat trace. [1]Data available in 74 cases. [2]Data available in 73 cases. [3]Data available in 73 cases. [4]Data available in 72 cases. [5]Data available in 74 cases. [6]Data available in 71 cases. [7]Data available in 88 cases. [8]Data available in 69 cases. [9]Data available in 71 cases. [10]Data available in 92 cases. [11]Data available in 73 cases. [12]Data available in 56 cases. [13]Data available in 69 cases. [14]Data available in 93 cases. [15]"CNV/DNV" versus "BS/CLV/FT" χ^2 test.

matter (WM) involvement were scored separately as normal, mild, moderate, or severe [14]. An adverse MRI score was defined as moderate-severe DGM/CGM and/or severe WM involvement. Brain injury patterns were further classified as "predominantly WM," "predominantly DGM," or "near total" (severe DGM and WM). Early neonatal mortality and composite adverse outcome (defined as mortality and/or adverse MRI outcome) were assessed. FUP rate at 2 years was determined.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 29.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 8.0.3 (GraphPad Software, San Diego, CA, USA). Baseline characteristics, clinical management, and outcomes were compared across three nonoverlapping epochs (2008–2013, 2014–2018, 2019–2023). One-way ANOVA was used for normally distributed continuous variables, while Kruskal-Wallis tests were used for non-normally distributed continuous variables. Categorical variables were analyzed

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Table 2. Characteristics prior to TH – univariable regression analysis over 15 years

Variable	Coefficient linear regression	95% CI	*p* value
Twin pregnancy – *n/N* (%)	−0.677	(−1.537 to 0.183)	0.120
Sentinel event – *n/N* (%)	1.416	(−0.040 to 2.871)	0.056
Apgar score at 5 min	0.051	0.012–0.090	**0.010**
Lowest pH, cord or blood <1 h	0.005	0.002–0.009	**0.004**
Highest Thompson score 1–3 h	−0.137	−0.233 to −0.040	**0.016**
aEEG BGP at admission – *n/N* (%)			
CNV	0.483	−0.814 to 1.780	**0.033**
DNV	0.300	−0.917 to 1.571	0.877
BS	−1.381	−2.741 to −0.021	**0.047**
CLV	−0.121	−1.121 to 0.879	0.859
FT	−0.424	−1.431 to 0.582	0.958

using χ^2-tests. To compare the proportion of infants with mild HIE across the periods, appropriate dichotomization of scores was performed followed by χ^2 tests. This included aEEG BGP (dichotomized into "CNV/DNV" vs. "BS/CLV/FT") and Thompson severity (dichotomized into "mild" vs. "moderate/severe"). Rutherford scores for DGM, WM, and CGM on MRI were dichotomized into "normal/mild" versus "moderate/severe" and compared using χ^2 tests. A sample size of over 75 patients per epoch provided sufficient power (0.80) to detect a one-point increase in the Thompson score with an alpha of 0.05. When differences between the three epochs were significant, linear regression analysis was conducted to assess trends over the entire study period, using patient's year of birth as independent variable.

Results

From September 2008 till December 2023, 252 infants underwent TH. Four infants received TH but were excluded (congenital anomaly). Tables 1–6 illustrate differences between the three 5-year epochs. Tables 1 and 2 compare baseline characteristics and variables reflecting HIE severity prior to TH. Tables 3 and 4 detail management and complications during TH and Tables 5 and 6 detail post-rewarming outcomes.

Variables before and during TH

Baseline Characteristics

Male sex (54.4%), mean birth weight (3,376 g), and median GA (39.5 weeks) remained stable over time. The percentage of infants born <36 weeks shifted from 2.7% in epoch 1 to 11.2% in epoch 3 (not significant) (Table 1; Fig. 1a). The presence of sentinel events differed significantly between the three epochs, although not significant using linear regression (Fig. 1b).

HIE Severity

Apgar score at 5 min ($p = 0.031$) and lowest pH ($p = 0.020$) significantly increased across the three epochs (Table 1), both confirmed by linear regression (Table 2). Median Thompson score 1–3 h postpartum decreased ($p = 0.046$) (Table 1) from 11 in 2008 to 9 in 2023 ($\beta_1 = -0.137$; 95% CI: −0.233 to −0.040) (Table 2). Figure 1b shows the distribution of aEEG background patterns per period. Across the three epochs, the percentage with CNV/DNV increased ($p = 0.041$). The percentage of FT scores increased from 2.7% in epoch 2 to 10.4% in epoch 3 (Table 1), but without a statistically significant annual increase (Table 2).

Time between Birth and Start of TH

The median time between birth and initiation of TH (4.25 h) did not change significantly between the three epochs.

Complications and Management during TH

The proportion of infants with invasive ventilation decreased from 84.0% in epoch 1 to 71.4% in epoch 3 (not significant) (Fig. 2a). The number of infants with documented hypocapnia did not change (Table 3). There was a decrease in the use of inotropic support ($p = 0.007$), particularly evident after 2014 (Fig. 2b). The incidence of aEEG-confirmed seizures and use of antiseizure medication decreased over time (both $p < 0.001$) (Fig. 2c, d). Conversely, the highest maintenance dosage of morphine for analgesia increased ($p < 0.001$), while the use of midazolam for sedation decreased ($p < 0.001$) (Fig. 2c, d).

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Table 3. Care during TH over three 5-year epochs

Variable	Epoch 1 2008–2013 (n = 75)	Epoch 2 2014–2018 (n = 75)	Epoch 3 2019–2023 (n = 98)	p value
Inotropic support	61/75 (81.3)	56/75 (74.7)	58/98 (59.1)	**0.007**
Ventilation				0.236[1]
None	1/75 (1.3)	1/75 (1.3)	1/98 (1.0)	
Noninvasive	11/75 (14.7)	12/75 (16.0)	27/98 (27.6)	
Invasive	63/75 (84.0)	62/75 (82.7)	70/98 (71.4)	
Hypocapnia				0.964[2]
None	23/73 (31.5)	25/75 (33.3)	31/98 (31.6)	
<3 h	23/73 (31.5)	26/75 (34.7)	47/98 (48.0)	
≥3 h	27/73 (37.0)	24/75 (32.0)	20/98 (20.4)	
Sepsis	4/75 (5.4)	7/78 (9.3)	1/100 (1.0)	0.125
aEEG-confirmed seizures				<**0.001**[3]
No seizure	24/71 (33.8)	37/75 (49.3)	72/97 (74.2)	
Single	8/71 (11.3)	14/75 (18.7)	5/97 (5.2)	
Repetitive	26/71 (36.6)	13/75 (17.3)	17/97 (17.5)	
Status epilepticus	13/71 (18.3)	11/75 (14.7)	3/97 (3.1)	
Antiseizure medication	50/71 (70.4)	41/75 (54.7)	34/97 (35.1)	<**0.001**[4]
0	21/71 (29.6)	34/75 (45.3)	63/97 (64.9)	
1	18/71 (25.3)	22/75 (29.3)	24/97 (24.7)	
2	17/71 (23.9)	9/75 (12.0)	6/97 (6.2)	
3 or more	15/71 (21.1)	10/75 (13.3)	4/97 (4.1)	
iNO treatment	15/75 (20.0)	19/75 (25.3)	27.6 (27.6)	0.171
Sedation				0.567[5]
None	0/75 (0.0)	1/75 (1.3)	1/98 (1.0)	
Midazolam	58/75 (77.3)	60/75 (80.0)	80/98 (81.6)	
Morphine	72/75 (96.0)	74/75 (98.7)	95/98 (96.9)	
Midazolam, mg/kg/h	0.17 (0.12)[6]	0.11 (0.08)[7]	0.10 (0.09)[8]	**0.001**
Morphine, µg/kg/h	11.5 (4.79)[9]	13.2 (4.69)[10]	13.6 (5.96)[11]	**0.008**
Arterial-venous lines	75/75 (100.0)	72/75 (96.0)	98/98 (100.0)	0.339

Outcomes are presented as mean (standard deviation [SD]), median (interquartile range [IQR]) or n/N (%). aEEG, amplitude electroencephalogram; iNO, inhaled nitric oxide. [1]"None" versus "noninvasive/invasive ventilation" χ^2 test. [2]"None" versus "<3 h/≥3 h" χ^2 test. [3]"Seizure" versus "no seizure" χ^2 test. [4]"ASM" versus "no ASM" χ^2 test. [5]"None" versus "midazolam/morphine" χ^2 test. [6]Data available in 58 cases. [7]Data available in 59 cases. [8]Data available in 70 cases. [9]Data available in 71 cases. [10]Data available in 73 cases. [11]Data available in 97 cases.

Short-Term Outcomes

Mortality

Regarding mortality rate (28.2%), no significant changes were observed across epochs (Table 5).

Use of MRI and Patterns of Brain Injury

The use of MRI increased across epochs (p = 0.049), and scans were performed earlier from median day 7 in 2008 to day 5 in 2023 (p < 0.001) (Table 5). Almost all infants without MRI in the first epoch were too unstable and died before undergoing an MRI. In three infants, either the parents did not give consent for MRI or the ultrasound showed no abnormalities and it was decided not to perform MRI. There were no changes in MRI severity scores for DGM, WM and CGM. Similarly, no changes were observed in predominant MRI patterns. The proportion of infants with an adverse MRI outcome decreased from 36.2% to 30.8% between epoch 2 and 3, and the proportion with a composite adverse outcome declined from 44.4% in epoch 1 to 34.7% in epoch 3 (Table 5). However, both reductions were not statistically significant.

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Table 4. Care during TH – univariable regression analysis over 15 years

Variable	Coefficient linear regression	95% CI	*p* value
Inotropic support – *n/N* (%)	−1.417	−2.820 to −0.014	<**0.001**
Seizures – *n/N* (%)			
Single	−0.442	(−1.540 to 0.656)	0.422
Repetitive	−1.515	(−2.852 to 0.178)	**0.027**
Status epilepticus	−1.752	−2.802 to −0.702	**0.002**
No seizure	3.059	1.658–4.460	<**0.001**
Antiseizure medication – *n/N* (%)			
0	3.055	1.687–4.424	<**0.001**
1	−0.648	−2.075 to 0.779	0.336
2	−1.650	−2.767 to −0.532	**0.005**
3 or more	−1.531	−2.682 to −0.379	**0.010**
Midazolam – *n/N* (%)	−0.006	−0.008 to −0.003	<**0.001**
Morphine – *n/N* (%)	0.168	0.074–0.263	<**0.001**

Table 5. Post-rewarming diagnostics over three 5-year epochs

Variable	Epoch 1 2008–2013 (*n* = 75)	Epoch 2 2014–2018 (*n* = 75)	Epoch 3 2019–2023 (*n* = 98)	*p* value
Infants receiving MRI	61/75 (81.3)	69/75 (92.0)	91/98 (92.9)	**0.049**
Postnatal day of MRI	6 (6–7)[1]	6 (5–7)[2]	5 (4–6)[3]	<**0.001**
DGM score				0.205[4]
Normal	35/61 (57.4)	38/69 (55.1)	57/91 (62.6)	
Mild	11/61 (18.0)	13/69 (18.8)	9/91 (9.9)	
Moderate	7/61 (11.5)	5/69 (7.2)	10/91 (11.0)	
Severe	8/61 (13.1)	13/69 (18.8)	15/91 (16.5)	
WM score				0.127[4]
Normal	1/61 (1.6)	4/69 (5.8)	6/91 (6.6)	
Mild	30/61 (49.1)	35/69 (50.7)	42/91 (46.2)	
Moderate	22/61 (36.0)	19/69 (27.5)	26/91 (28.6)	
Severe	8/61 (13.1)	11/69 (15.9)	17/91 (18.7)	
CGM score				0.137[4]
Normal	28/61 (45.9)	27/69 (39.1)	44/91 (48.4)	
Mild	19/61 (31.1)	24/69 (34.8)	26/91 (28.6)	
Moderate	8/61 (13.2)	5/69 (7.2)	7/91 (7.7)	
Severe	6/61 (9.8)	13/69 (18.8)	14/91 (15.3)	
Predominant pattern				0.902
Normal	28/61 (45.9)	36/69 (52.2)	44/91 (48.4)	
Predominantly WM	19/61 (31.1)	15/69 (21.7)	23/91 (25.3)	
Predominantly DGM	10/61 (16.4)	10/69 (14.5)	11/91 (12.1)	
Near total	4/61 (6.6)	8/69 (11.6)	13/91 (14.3)	
Adverse MRI outcome, *n/N* (%)	21/61 (34.4)	25/69 (36.2)	28/91 (30.8)	0.823
Neonatal mortality	23/75 (30.7)	20/75 (26.7)	27/98 (27.5)	0.426
Composite adverse outcome	32/75 (44.4)	27/75 (36.0)	34/98 (34.7)	0.609
Surviving infants at 2-year FUP[5]	44/52 (84.6)	46/55 (83.6)	34/36 (94.4)	<**0.001**

Outcomes are presented as mean (standard deviation [SD]), median (interquartile range [IQR]) or *n/N* (%). MRI, magnetic resonance imaging; DGM, deep gray matter; WM, white matter; CGM, cortical gray matter. [1]Data available in 71 cases. [2]Data available in 71 cases. [3]Data available in 91 cases. [4]"Normal/mild" versus "moderate/severe" χ^2 test. [5]No data available after October 2021.

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Table 6. Post-rewarming diagnostics – univariable regression analysis over 15 years

Variable	Coefficient linear regression	95% CI	*p* value
Infants receiving MRI – *n/N* (%)	1.141	(0.075–2.208)	**0.029**
Postnatal day of MRI – *n/N* (%)	−0.112	(−0.140 to −0.083)	<**0.001**
Surviving infants at 2-year FUP – *n/N* (%)	2.175	(0.745–3.524)	<**0.001**

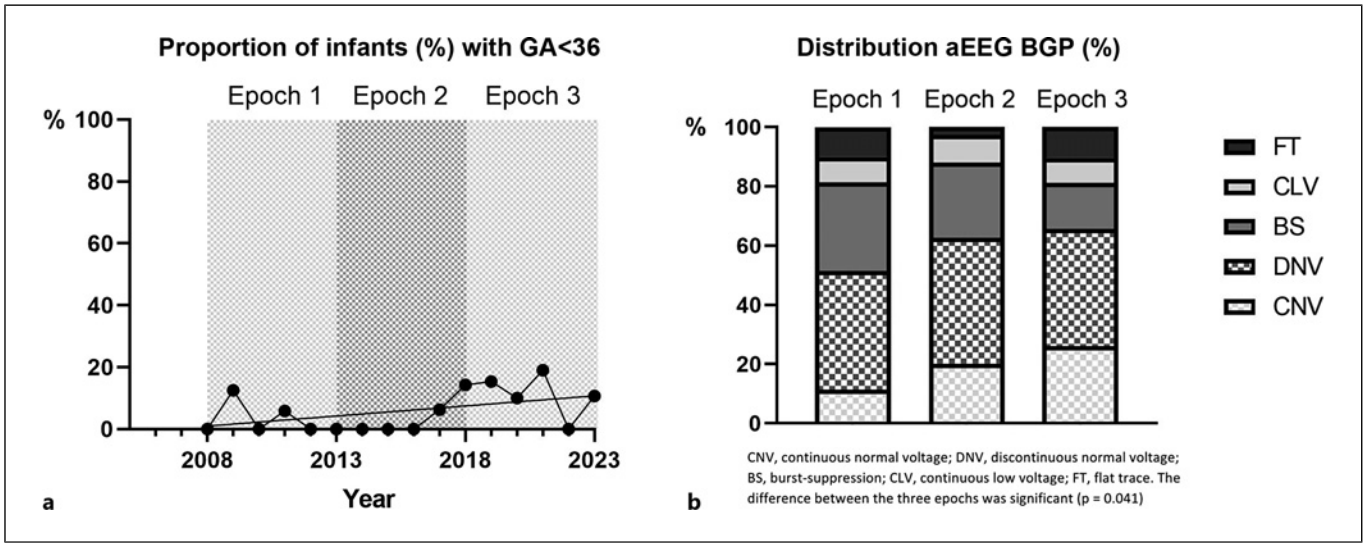

Fig. 1. Characteristics prior to initiation therapeutic hypothermia. **a** Proportion of infants (%) wth GA36. **b** Distribution of aEEG BGP scores (%).

Follow-Up Rate at 2 Years

The number of surviving infants seen at 2-year FUP increased from 84.6% in epoch 1 to 94.4% in epoch 3 ($p < 0.001$).

Discussion

In this retrospective observational study, we examined changes in bedside practice over a 15-year period following the introduction of TH. This study shows that over time more infants with milder encephalopathy were considered eligible for TH, as evidenced by increasing Apgar scores and pH, decreasing Thompson scores, a less severe background pattern on the admission aEEG, and decrease in neonatal seizures. We also noticed a significant reduction in the use of inotropic support and a nonsignificant reduction in proportion of infants on invasive mechanical ventilation. Nearly all infants received analgesia or sedation, with an increase in morphine and a decrease in midazolam dosage over time.

Despite our increasing clinical experience, the time to initiate TH remained relatively constant. With most cases (84.7%) being outborn, this is probably difficult to change, with logistic challenges for timely transportation to a tertiary center. Another possible explanation is the increasing proportion of infants with mild HIE over the years. In these milder cases, there may be delay in decision-making and transfer to a tertiary center. Still, the median time to cooling was comparable to the 3–4 h window observed in NICHD, NRN, and TOBY trials for initiating TH [15, 16].

The increasing number of infants with a GA below 36 weeks, mostly observed after 2017, is likely due to more units changing the threshold for eligibility to 35.0 weeks. Our national guideline was subsequently revised in 2021 recommending including these infants with a lower GA [11].

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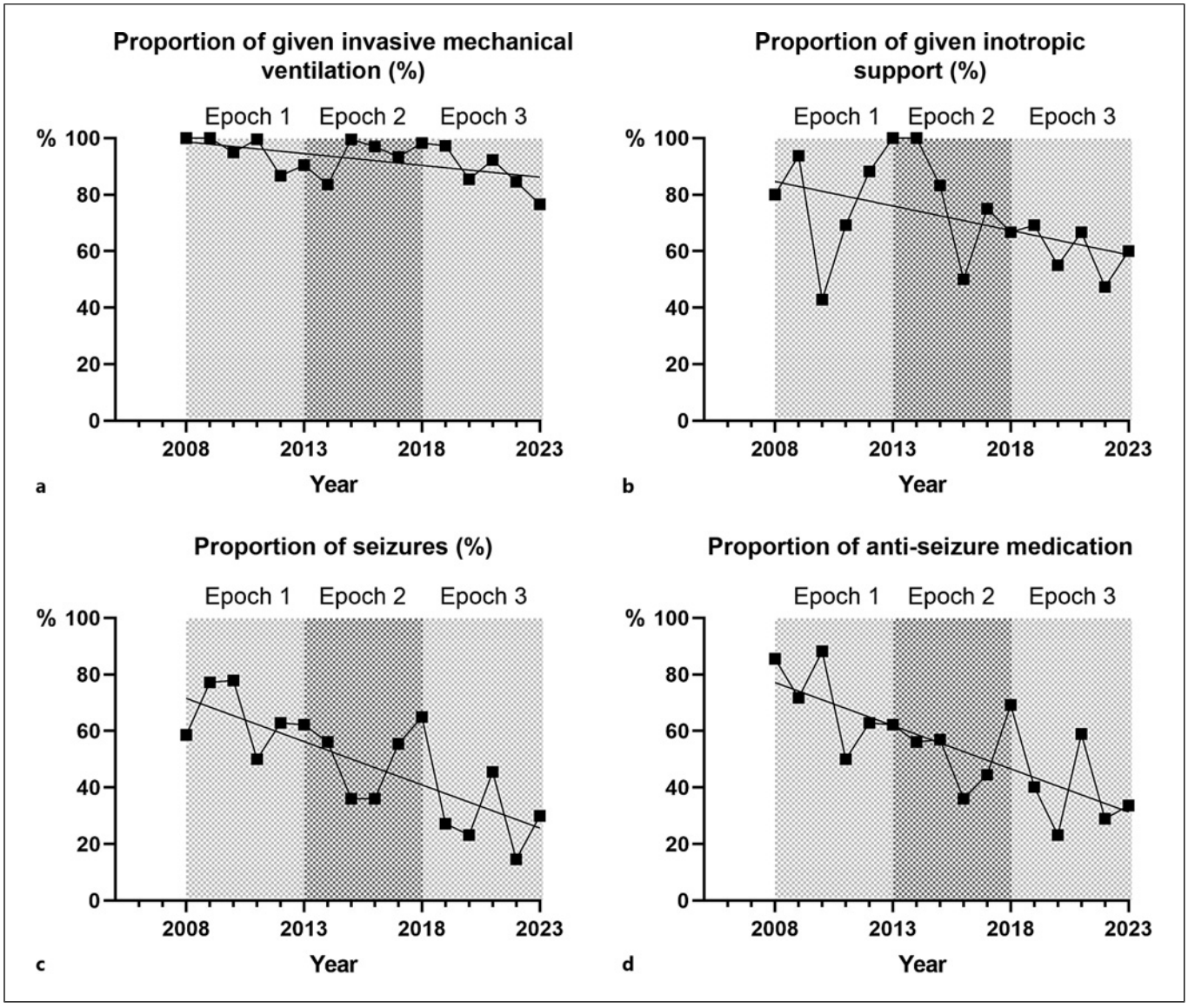

Fig. 2. Complications and management during therapeutic hypothermia. **a** Proportion of given invasive mechanical ventilation (%). **b** Proportion of given inotropic support (%). **c** Proportion of seizures (%). **d** Proportion of anti-seizure medication (%).

It is of interest that despite changes in TH selection and management over time, we did not observe a decrease in overall short-term outcomes. Mortality rates and MRI severity scores did not change. This contradicts our expectation of improved outcome as milder cases were cooled. A possible explanation for the stable mortality rate is that, in addition to including more cases with milder HIE, our growing experience may have also led to inclusion of some very severe cases. The number of FT background patterns increased from 2.7% in epoch 2 to 10.4% in epoch 3, suggesting that some infants considered as being too severe to be cooled in previous epochs, were now cooled.

Two-year FUP rates increased over time, reflecting our hospital's logistic improvements of 2-year FUP visits with doctor and psychologist for all infants. Whether the neurodevelopmental outcomes have changed needs to be addressed in future studies.

Our increased use of TH for mild HIE is supported by several studies. A significant increase was reported from

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38% to 55% between 2010 and 2012 [17]. Notably, 75% of UK centers offered TH for mild HIE [11]. A meta-analysis of 13 observational studies reported that 22% of cooled infants had mild HIE [4]. Despite this trend, the effectiveness of TH for mild HIE still needs further investigation. In a recent trial, it was found that TH did not improve cerebral MR biomarkers after mild HIE [18]. Therefore, the ongoing COOL PRIME study (NCT04621279), examining practice variation across 15 participating sites to compare the effectiveness of TH versus normothermia for mild HIE on neuro-developmental outcomes at 2 years of age, is aimed at answering this uncertainty.

Our study indicates a significant decrease in Thompson scores and an increase in number of infants with a normal or mildly subnormal aEEG background pattern. Parmentier et al. [18] (2020) suggested a growing role of aEEG in the initiation of TH, as evidenced by higher percentages of infants cooled based on aEEG patterns despite Thompson scores ≤7. In the present protocol in the Netherlands either an abnormal Thompson score or an abnormal aEEG is sufficient to initiate TH.

Regarding the observed decrease in inotropic support, this may be attributed to two factors: inclusion of milder cases and a shift toward a less strict blood pressure management over time. Additionally, the decline in midazolam dosage, associated with accumulation and hypotension, might be another factor [19, 20]. This decrease in midazolam might be further explained by the observed reduction in aEEG-confirmed seizures. Additionally, our data align with the NEOPAIN study, suggesting a growing emphasis on minimizing neonatal discomfort during TH. This is reflected in the increased use of morphine, a medication with a strong safety profile [21, 22].

Limitations

The retrospective and single-center design affected our findings. Missing data, particularly Thompson scores in initial years, did not allow to draw clear conclusions over 15 years. Furthermore, focusing solely on TH-admitted patients introduced selection bias by excluding potentially eligible but untreated infants. However, the most important limitation of our study is the small sample size, making it difficult to have sufficient power to detect differences in several outcomes. With the present sample size, the decrease in composite adverse outcome from 44.4% to 34.7% was not significant.

Finally, our study did not consider other potential contributing factors like pre-TH hyperthermia, dysglycaemia, and an abnormal hepatic and/or renal function, which could indicate multi-organ failure. Moreover, some variables have shown to be good markers for adverse outcome, for example LDH [23] and lactate [24], but these were not performed in a standardized way in our hospital. In contrast, a recent study in the Netherlands shows the opposite, suggesting that early multi-organ failure may not be a strong predictor of long-term adverse outcomes [25]. This study examined $PaCO_2$ levels from birth until the first 24 h of TH, with low $PaCO_2$ levels previously associated in literature to poor outcomes at 18–22 months of age [26]. However, it did not show significant changes across the three five-year epochs.

Conclusions

Our study identified several trends: a shift toward milder HIE cases selected for TH, reduced use of inotropes, fewer seizures and antiseizure medication, increased dosage of morphine and reduced midazolam, and a significant increase in 2-year FUP rate. Despite these trends, post-rewarming MRI findings remained unchanged. The trend in a decrease of the adverse short-term outcome warrants further investigation in a multicenter study. The impact on neurodevelopmental outcome awaits further analysis.

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Statement of Ethics

This study protocol was reviewed and approved by the Non-WMO Committee of the Leiden University Medical Center with Approval No. G23-3101. As only retrospective and pseudonymized data were used, the need for written informed consent was waived by the Non-WMO Committee of the Leiden University Medical Center.

Conflict of Interest Statement

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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Author Contributions

Bregje O. van Oldenmark conceptualized and designed the study, collected data, drafted the initial manuscript, and critically reviewed and revised the manuscript. Drs. Andrea van Steenis contributed data and critically reviewed and revised the manuscript. Dr. Floris Groenendaal assisted with statistical analysis and critically reviewed and revised the manuscript. Dr. Linda S. de Vries and Dr. Sylke J. Steggerda conceptualized and designed the study, collected data, and critically reviewed and revised the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary materials. For further inquiries, please contact the corresponding author.

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