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ORIGINAL ARTICLE

Persistent pulmonary hypertension in neonates with perinatal asphyxia and therapeutic hypothermia: a frequent and perilous combination

Vijverberg Joanna R. G.[a], Enrico Lopriore[a], Arjan B. te Pas[a], Monique Rijken[a], Erik W. van Zwet[b], Francisca T. de Bruine[c] and Sylke J. Steggerda[a]

[a]Department of Neonatology, Leiden University Medical Center, Leiden, The Netherlands; [b]Department of Medical Statistics, Leiden University Medical Center, Leiden, The Netherlands; [c]Department of Neuroradiology, Leiden University Medical Center, Leiden, The Netherlands

ABSTRACT

Therapeutic hypothermia in neonates with perinatal asphyxia may increase the risk of PPHN. This potentially affects outcome.

Objectives: (1) To investigate whether neonates with perinatal asphyxia and therapeutic hypothermia more often developed PPHN compared to a control group with perinatal asphyxia not treated with hypothermia; (2) To identify risk factors for severe PPHN during hypothermia and evaluate short-term outcome.
Methods: This single-center retrospective cohort study included (near-)term neonates with perinatal asphyxia admitted between 2004 and 2016. Neonates with perinatal asphyxia and hypothermia were compared to a historical control group without hypothermia. Primary outcome was PPHN, defined as severe hypoxemia requiring mechanical ventilation and inhaled nitric oxide, confirmed by echocardiography. Short-term adverse outcome was defined as mortality within one month and/or severe brain injury on MRI.
Results: Incidence of PPHN was 23% (26/114) in the hypothermia group and 11% (8/70) in controls. In multivariate analysis, PPHN was 2.5 times more common among neonates with hypothermia. Neonates developing PPHN during hypothermia often had higher fraction of inspired oxygen at baseline. PPHN was not associated with a higher risk of severe brain injury. However, early mortality was higher and three infants died due to severe refractory PPHN during hypothermia.
Conclusions: In this study PPHN occurred more often since the introduction of therapeutic hypothermia. This was usually reversible and did not lead to overall increased adverse outcome. However, in individual cases with PPHN deterioration occurred rapidly. In such cases the benefits of hypothermia should be weighed against the risk of a complicated, fatal course.

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Introduction

Neonates with perinatal asphyxia and moderate-to-severe hypoxic-ischemic encephalopathy (HIE) are currently treated with therapeutic hypothermia (TH) [1].

Perinatal asphyxia is a risk factor for the development of persistent pulmonary hypertension of the newborn (PPHN) [2,3]. In these neonates, TH may have an additional effect on the development of PPHN. In animal studies hypothermia was associated with an increase in pulmonary vascular resistance [4]. In neonates with perinatal asphyxia it was suggested that increasing oxygen requirement during TH is probably attributable to PPHN and may have serious clinical consequences [5]. The findings of a multicentre, randomized, controlled pilot trial also indicated a possible causal relation between TH and PPHN [6]. In contrast, several other randomized, controlled trails did not show a difference in PPHN between neonates with HIE treated with or without TH [7–9]. However, the definition and incidence of PPHN in these trials varied.

Since the introduction of TH as standard of care treatment for HIE only two recent studies reported on

CONTACT Sylke J. Steggerda S.J.Steggerda@lumc.nl Department of Neonatology, Leiden University Medical Center, Albinusdreef 2, Leiden, 2333 ZA, The Netherlands

the incidence, risk factors and short-term outcome of PPHN during hypothermia [10,11]. The first study analyzed infants who were enrolled in two randomized trials of TH and concluded that PPHN is common in neonates with moderate-to-severe HIE (22%) but the prevalence was not different between neonates receiving hypothermia and those with normothermia. However, length of hospital stay and mortality were higher in the PPHN group [10]. Because PPHN by itself may be a risk factor for adverse outcome, another study analyzed the short-term hospital outcomes of neonates with HIE accompanied by PPHN [11]. In this study length of hospital stay was longer in neonates with PPHN but EEG and MRI findings were similar to those without PPHN.

With the current knowledge, TH is not considered as contraindicated in neonates with PPHN. Nevertheless, the co-occurrence of PPHN and HIE may be of importance [12,13].

Primary aim of the present study was to investigate whether neonates with perinatal asphyxia and treated with hypothermia more often developed PPHN as compared to a control group of neonates with perinatal asphyxia not treated with hypothermia. Secondary aims were to identify risk factors for developing PPHN in the group with TH and to investigate short-term outcome of neonates with perinatal asphyxia and TH.

Methods

All consecutive (near-)term neonates with perinatal asphyxia admitted to our neonatal intensive care unit between January 2004 and December 2016 were included in this retrospective cohort study. The Leiden University Medical Center (LUMC) is one of the nine tertiary neonatal intensive care units in The Netherlands. Inclusion criteria are listed below. We excluded patients with birth weight $<$1800 grams or severe congenital anomalies.

The study was approved by the institutional review board. As this retrospective study did not fall under the Medical Research Involving Human Subjects Act and clinically obtained anonymized data were used, the need for informed consent was waived.

Hypothermia group

Hypothermia for perinatal asphyxia was introduced at our center in September 2008. All neonates with perinatal asphyxia admitted between September 2008-December 2016 and treated with TH were included in the hypothermia group. The Dutch national treatment protocol for TH is adapted from the TOBY trial [14]. Neonates had to meet up with all four of the following criteria: (1) Gestational age (GA) at birth $\geq$36 weeks: (2) Perinatal asphyxia (defined as one of the following: (a) Apgar score at 5 min $\leq$5; (b) Respiratory failure requiring resuscitation during at least 10 min postpartum; (c) Arterial pH $<$7,0 and base excess ≤ -16 mmol/L d. Lactate $>$10 mmol/L (both in either arterial umbilical cord or blood gas sample within one hour after birth)); (3) Encephalopathy (defined as one of the following: (a) Thompson score $>$7 between 1 and 3 h after birth; (b) Abnormal aEEG background pattern); (4) Start of hypothermia within 6 h after birth.

Neonates were cooled by whole body hypothermia with a core temperature of 33.5 °C for 72 h (Criticool, The Surgical Company, Amersfoort, The Netherlands). After 72 h they were rewarmed in intervals of 0.4 °C per hour till a body temperature of 36.5 °C was reached.

Control group

For the control group we selected neonates with perinatal asphyxia and a GA $\geq$36 weeks, admitted between January 2004 and August 2008. This was before TH was available.

Perinatal asphyxia was defined as the presence of 3 or more of the following:

- (a) Apgar score at 5 minutes $\leq$5; (b) Respiratory failure requiring resuscitation during at least 10 minutes postpartum; (c) Arterial pH $<$7.0 and base excess $\leq$-16 mmol/L (in either arterial umbilical cord or blood gas sample within one hour after birth); (d) Fetal distress defined as late decelerations on fetal monitoring or meconium staining; (e). Multi-organ failure or seizures

These selection criteria were adapted from Cowan et al. [15]. Encephalopathy was not used as inclusion criterion because information on the Thompson score and aEEG background pattern was not available before August 2008.

Variables

We reviewed medical records and collected maternal, perinatal and postnatal data. Maternal and perinatal data included selective serotonin reuptake inhibitor use during pregnancy, preeclampsia, gestational age

at birth, birth weight, gender, mode of delivery, Apgar score, perinatal sepsis (defined as positive blood culture) and meconium aspiration syndrome (MAS; defined as meconium stained amniotic fluid, need of oxygen, and lung x-ray showing signs of MAS). Base excess, pH and lactate were collected from the umbilical cord or blood gas within one hour postpartum. The diagnosis of PPHN was based on clinical signs (severe hypoxemia requiring mechanical ventilation and inhaled nitric oxide (iNO) treatment, with a starting dose of 20 parts per million) and echocardiographic evidence of PPHN. We registered the number of days with iNO treatment, number of days on mechanical ventilation, presence of hypotension (defined as need for inotropic support, number of inotropes used, and number of days), treatment with hydrocortisone and surfactant. Neurological data included neonatal seizures and treatment. Mortality was categorized as early (<72 h) or late (>72 h) postnatal and the cause of mortality was registered.

To identify additional risk factors for developing PPHN in the group with TH we obtained the following data in the hypothermia group only: highest Thompson score (1–3 h postnatal), highest mean fraction of inspired oxygen (FiO2), and need for inotropic support at baseline, before start of hypothermia.

To assess neurologic morbidity, we defined the severity of cerebral injury on MRI. MRI scans were conducted between day 4–7 after birth, using a 3.0 Tesla MR system (Achieva, Philips Medical Systems, Best, The Netherlands) with a neonatal head coil. Images were obtained using a standardized protocol, including 3-D T1-, T2- and diffusion-weighted sequences. Scans were scored by a neuroradiologist and neonatologist specialized in neonatal neurology (SS, FTdB), blinded to the patients' names and clinical history. Severe cerebral injury was classified as one or more of the following: moderate-severe lesions in the basal ganglia and thalamus, loss of the posterior limb of the internal capsule, and/or severe cortical or white matter involvement [16].

Statistical analysis

Categorical variables were described in percentages and compared using the chi-square test (or Fisher's exact). Continuous variables were described in means with standard deviation (SD) and compared using an independent-sample t-test. In case of a skewed distribution we used medians. To examine the effect of TH on PPHN, we used a logistic regression model. We conducted univariate regression analysis on the perinatal and postnatal data. Variables with a p value less than 0.10 were put into the multivariate model. A two-tailed p value less than 0.05 was considered statistically significant. We used SPSS Statistics software (version 25.0, SPSS Inc, Chicago, IL, USA) for data analyses.

Results

Participants

A total of 184 neonates with a GA ≥36 weeks were admitted for perinatal asphyxia between January 2004 and December 2016. In 114, hypothermia was given in the period September 2008–December 2016; 70 neonates admitted before September 2008, did not receive TH.

In 9/114 neonates the full 72 h of hypothermia treatment were not completed. In four neonates hypothermia was discontinued because of severe, refractory PPHN. Three of these infants died. Four other infants died because of severe brain injury and an end-of-life decision during hypothermia treatment. One neonate died because of pulmonary hemorrhage.

Neonates with and without hypothermia treatment

Perinatal and postnatal characteristics of neonates with and without TH are shown in Table 1. The hypothermia group had a lower median Apgar score at 5 min (3 (IQR 1–4) vs. 5 (IQR 3–6)) and higher lactate level (12.4 (SD 6.0) vs. 9.8 (SD 6.3), p=0.006). The other perinatal characteristics were not different between the two groups.

In the hypothermia group 26/114 neonates (23%) developed PPHN, as compared to 8/70 neonates (11%) in the control group (p = 0.054). In the hypothermia group treatment with inotropic support for hypotension occurred more often (80 vs. 33%, p < 0.0001) (Table 1). In a multivariate analysis adjusting for variables that may increase the risk for PPHN, TH was an independent risk factor for the development of severe PPHN (Odds ratio of 2.53 (95% Confidence Interval of [1.014–6.327])) (Table 2).

Risk factors for the development of PPHN in neonates with hypothermia

Within the hypothermia group there were no differences in maternal and perinatal variables between neonates with and without severe PPHN. Neonates with TH and PPHN did have higher FiO2 at baseline, before

Table 1. Perinatal, postnatal and outcome data in neonates with and without hypothermia.

	Hypothermia group $N = 114$	Control group $N = 70$	p-Value
Male gender (%)	58 (51)	28 (40)	0.15
Gestational age (weeks)†	39.2 (1.7)	39.6 (1.8)	0.14
Birth weight (grams)†	3411 (607)	3350 (637)	0.52
Caesarean delivery (%)	65 (57)	43 (61)	0.56
Apgar score at 5 min○	3 (25^{th} 1–75^{th} 4)	5 (25^{th} 3–75^{th} 6)	
pH†	6.9 (0.2)	6.9 (0.2)	0.50
BE in mmol/L†	−16.7 (7.7)	−16.8 (7.2)	0.94
Lactate in mmol/L†	12.4 (6.0)	9.8 (6.3)	0.006
Sepsis (%)	6 (5)	3 (4)	1.00
MAS (%)	10 (9)	5 (7)	0.70
Inotropes needed (%)	91 (80)	23 (33)	<0.0001
Seizures (%)	82 (72)	48 (69)	0.63
PPHN (%)	26 (23)	8 (11)	0.054
Mortality within one month (%)	36 (32)	17 (24)	0.29

†Mean (standard deviation); ^Median (Interquartile range). BE: base excess, MAS: meconium aspiration syndrome. pH, BE and lactate were collected from the umbilical cord or blood gas within one hour postpartum.

Table 2. Multivariate regression analysis with odds ratios(OR) on developing PPHN in neonates with and without hypothermia.

	Univariate regression analysis		Multivariate regression analysis	
	OR (CI)	p-Value	OR (CI)	p-Value
Therapeutic hypothermia	2.290 (0.972–5.392)	0.058	2.534 (1.014–6.327)	0.047
Female gender	2.091 (0.952–4.591)	0.066	2.671 (1.104–6.464)	0.029
Gestational age	0.964 (0.780–1.192)	0.736		
Birth weight	1.001 (1.000–1.001)	0.041	1.001 (1.000–1.002)	0.015
Caesarean delivery	1.170 (0.545–2.511)	0.687		
Apgar score at 5 min	0.956 (0.789–1.159)	0.647		
pH	6.345 (0.813–49.518)	0.078	4.324 (0.489–38.220)	0.188
BE	1.034 (0.982–1.088)	0.204		
Lactate	1.045 (0.985–1.110)	0.145		
Sepsis	2.323 (0.551–9.795)	0.251		
MAS	4.602 (1.540–13.751)	0.006	3.502 (1.103–11.117)	0.033

CI: confidence interval; BE: base excess; MAS: meconium aspiration syndrome. pH, BE, and lactate were collected from the umbilical cord or blood gas within one hour postpartum.

hypothermia treatment. There was no difference in the need for inotropic support before treatment (Table 3).

Short-term outcome in neonates with hypothermia

Neonates with PPHN had a more complicated respiratory and circulatory course with a higher mean FiO2 during hypothermia. They more often required high-frequency oscillation ventilation, surfactant, inotropic support, and hydrocortisone. However, there was no difference in total duration of mechanical ventilation between both groups. There were no differences in treatment for seizures. Overall mortality was similar between infants with or without PPHN.

In infants with TH early mortality (<72 h postnatal) was higher in the PPHN group, with three infants dying due to severe refractory PPHN. Infants with PPHN did not have more severe brain injury on MRI. Combined adverse outcome (mortality and/or severe brain injury) was comparable between the two groups (Table 3).

Discussion

This single center retrospective cohort study, comparing neonates with TH with a historical control group, showed a higher incidence of PPHN during TH. In a multivariate analysis the incidence of PPHN was 2.5 times higher in neonates treated with hypothermia. Although the confidence interval was fairly wide, the difference was statistically significant. This is in agreement with a randomized, controlled trial investigating the safety outcomes of TH [6], but in contrast to other studies that did not show an effect of hypothermia on PPHN [7–10]. One explanation may be that both the definition and incidence of PPHN in these trials were variable. In our study population, we only included patients with severe PPHN, requiring iNO treatment. These neonates needed high FiO2 during hypothermia, often received a rescue strategy of

Table 3. Risk factors for PPHN in neonates with therapeutic hypothermia and short-term outcomes.

Hypothermia ($n = 114$)	PPHN ($n = 26$)	No PPHN ($n = 88$)	p-Value
Maternal factors			
• SSRI use (%)	0 (0)	1 (1)	1.00
• Preeclampsia (%)	1 (4)	2 (2)	0.55
Perinatal factors			
• 5 min Apgar score○	2 (25^{th} 1 – 75^{th} 4)	3 (25^{th} 1 – 75^{th} 4)	
• pH†	6.9 (0.2)	6.9 (0.2)	0.31
• BE in mmol/L†	−15.0 (5.0)	−17.3 (8.3)	0.11
• Lactate in mmol/L†	13.6 (6.3)	12.1 (6.0)	0.26
• Sepsis (%)	2 (8)	4 (5)	0.62
• MAS (%)	4 (15)	6 (7)	0.23
Respiratory variables			
• FiO2 before T*H* > 30% (%)	21 (81)	16 (20)	<0.001
• Highest FiO2 before TH†	76.0 (33.0)	27.3 (15.1)	<0.001
• Highest FiO2 during TH†	84.4 (26.3)	29.7 (12.8)	<0.001
• Days mechanical ventilation†	5.5 (2.3)	4.5 (2.9)	0.11
• HFOV (%)	17 (65)	1 (1)	<0.001
• Surfactant (%)	16 (62)	7 (8)	<0.001
Circulatory variables			
• Inotropes before TH (%)	8 (31)	18 (21)	0.28
• Inotropes needed (%)	25 (96)	66 (75)	0.018
• If needed days†	4.2 (2.2)	2.6 (2.2)	<0.01
• If needed number†	2.5 (1.1)	1.1 (0.8)	<0.001
• Hydrocortisone (%)	18 (70)	12 (14)	<0.001
Neurological variables			
• Thompson score○	11 (25^{th} 8–75^{th} 13)	10 (25^{th} 8–75^{th} 13)	
• Seizures (%)	15 (58)	67 (76)	0.066
• >2 Types of AED (%)	7 (27)	31 (35)	0.43
Outcome			
• Mortality < 28 d (%)	7 (27)	29 (33)	0.56
• Early mortality (<72 h)			
PPHN	3	–	
Pulmonary hemorrhage	1	–	
Severe brain injury	1	3	
• Late mortality (>72 h)			
Severe brain injury	2	26	
• Mortality < 28 d and/or severe brain injury on MRI (%)	10 (40)	33 (39)	0.92

†Mean (SD); ○Median. SSRI: selective serotonin reuptake inhibitor; MAS: meconium aspiration syndrome; BE: base excess; FiO2: fraction of inspired oxygen; HFOV: high-frequency oscillation ventilation; AED: anti-epileptic drugs; SD: standard deviation.
pH, BE, and lactate were collected from the umbilical cord or blood gas within one hour postpartum.

high-frequency ventilation and nearly all needed inotropic support.

Despite intensive respiratory and circulatory support, four neonates with PPHN had ongoing deterioration of their clinical condition and required discontinuation of TH. Three of these neonates died because of a combination of refractory PPHN and circulatory failure. In the group without TH, none of the neonates died due to PPNN. So, PPHN during TH in neonates with HIE is a perilous complication requiring prompt interventions.

We investigated additional risk factors for the development of PPHN in neonates with TH and short-term outcome. Neonates with PPHN during TH had a higher mean FiO2 at baseline, before the start of hypothermia. So, the need for high FiO2 on admission or early during hypothermia should alert the clinician on the development of PPHN. This can be an indication for echocardiographic evaluation, iNO treatment and to aim at higher blood pressure levels to minimize right-left shunting. In neonates with PPHN in whom hypothermia treatment was completed, PPHN was reversible and the duration of mechanical ventilation and mortality did not differ from neonates without PPHN.

An additional concern is that PPHN in neonates with hypoxic-ischemic encephalopathy may contribute to the severity of brain injury. A recently published case series stated that PPHN may be an additional risk factor for brain injury in neonates with asphyxia and if not well controlled may lead to impaired brain oxygenation [12]. Our study did not show a difference in the severity of brain injury on MRI or in the composite short-term outcome (mortality and/or severe brain injury) in neonates with PPHN. This is in line with a recent study not showing a difference in brain MRI findings between neonates with and without PPHN during hypothermia [11]. In contrast, another study did report higher mortality rates in patients with PPHN [10]. This was mainly explained by PPHN and/or MAS and not by brain injury. However, it was not reported whether fatal deterioration of PPHN also occurred early and more often in neonates who received TH.

The findings of our study support current literature stating that in an intensive care setting with respiratory and circulatory support and iNO available, PPHN during hypothermia is often reversible and does not lead to an overall increase in adverse outcome [5,9]. It is therefore not a contraindication for TH. However, in individual cases with severe PPHN, deterioration can occur rapidly and may result in a very complicated, fatal course.

This study has several limitations. First, we compared the hypothermia group with a historic control group and had to use slightly different inclusion criteria because in the control group no detailed information on Thompson score or aEEG background pattern was available. Therefore, there may be a difference in the severity of perinatal asphyxia between both groups. The hypothermia group had a lower Apgar score at 5 min and a higher lactate level; in further analysis these variables did not increase the risk of PPHN. Secondly, we defined PPHN as severe hypoxemia requiring mechanical ventilation and iNO treatment with echocardiographic confirmation. Due to the retrospective nature of our study and the long period of inclusions we were not able to assess the echocardiographic features of PPHN in more detail. Concerns for PPHN during hypothermia may have changed treatment policy during the past years leading to an increase in echocardiographic evaluation and use of iNO. Therefore, ideally this should have been investigated with structured echocardiographic reports describing features such as rectification of the septum, tricuspid regurgitation, and mean pulmonary arterial pressure in both the group with hypothermia and the control group. Finally, we only analyzed short-term outcomes and not long-term neurodevelopmental outcome.

In conclusion, in our population of neonates with perinatal asphyxia, the incidence of PPHN and use of iNO have increased since the introduction of TH. Although neonates with PPHN required more intensive respiratory and circulatory support, the majority stabilized during treatment. PPHN did not lead to prolonged mechanical ventilation, more severe brain injury or higher overall mortality. However, three infants died early because of severe refractory PPHN during TH. For the clinician, this means that there is no contraindication for TH in infants with perinatal asphyxia and PPHN as long as they show good response to treatment. However, in individual cases with severe and rapid deterioration the benefits of hypothermia should be weighed against the risk of a very complicated, fatal course. We recommend to stay alert on signs of PPHN in infants with HIE and hypothermia, such as a high FiO2, in order to start proper treatment early.

Future studies on the incidence of PPHN in larger cohorts of cooled infants could provide more information on the incidence, severity and outcome of PPHN in neonates with TH. The optimal treatment strategy for PPHN during hypothermia also deserves further attention.

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No potential conflict of interest was reported by the author(s).

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