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Multiorgan Dysfunction in Infants of 33-35 Weeks Gestation with Severe Hypoxic-Ischemic Encephalopathy Treated with Hypothermia

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Abstract

Background: The benefits of hypothermia on neurodevelopment of newborns ≥ 36 weeks gestation with hypoxic-ischemic encephalopathy have been shown in large clinical trials. The security of hypothermia in premature infants ≤ 36 weeks has not been rigorously evaluated, although its feasibility has been suggested in recent studies. The present study aims: 1) To describe extraneural involvement in infants 33-35 weeks gestation with severe hypoxic-ischemic encephalopathy treated with hypothermia 2) To compare organ dysfunction with infants ≥ 36 weeks gestation.

Methods: Retrospective observational study of prospective data collected. Consecutive newborns of 33-35 weeks gestation, ≥ 1800g birth weight and severe hypoxic-ischemic encephalopathy were included. Data were compared with a cohort of newborn infants ≥ 36 weeks with severe encephalopathy. Twenty clinical and laboratory variables of 6 organ-systems (cardiovascular, respiratory, renal, haematological, hepatic and pH and electrolytic imbalance) were studied and a multiorgan dysfunction scale was applied daily during the first 3 days of life.

Results: Eight preterm newbors with severe HIE were compared with 31 term neonates with severe HIE. All infants presented with moderate-to-severe organ injury. There were no differences in most of organ variables, the number of affected organ-systems or the scores in the Multiorgan dysfunction Scale between both gestational age groups in the first 3 days of life (p>0.05).

Conclusion: Organ injury in infants of 33-35 weeks gestation with severe HIE evaluated for hypothermia is not more severe regarding newborns ≥ 36 weeks gestation. Therapeutic hypothermia appears feasible in this gestational age group although clinical trials are needed to answer this question.

Keywords: Hypothermia; Hypoxic-ischemic encephalopathy; Multiorgan dysfunction; Organ-system; Preterm

Abbreviations: HIE: Hypoxic-ischemic Encephalopathy; NEC: Necrotizing Enterocolitis; VON: Vermont Oxford Network; IQR: Interquartile Range; NICU: Neonatal Intensive Care Unit; Eol: End-of Life

Background

The beneficial effect of moderate hypothermia on neurodevelopment of term and near term infants with hypoxic-ischemic encephalopathy (HIE) has been rigorously demonstrated [1-5]. Although this therapy has been shown to be safe, severe pulmonary hypertension or refractory bleeding contraindicate the initiation of hypothermia, modulate cooling or even are an indication for early rewarming [6].

Hypothermia has become standard practice in the last decade based on large clinical trials including infants ≥ 36 weeks gestational age [1-3]. Some clinical trials have included newborn infants ≥ 35 weeks [4,5]. The neuroprotective effect of hypothermia in preterm infants has been suggested by several studies, based on short case reports [7-9]. Recently, data on 31 preterm infants from 34 to 35 weeks gestation who underwent hypothermia have been reported; this study showed a higher incidence of hyperglycaemia and an increased risk of overcooling in this group, without impact on mortality [10]. On the other hand, the use of hypothermia has also been evaluated in 15 preterm infants with a median gestational age at birth of 27 weeks (IQR 26-30) to modulate reperfusion in necrotizing enterocolitis (NEC) without major adverse effects [11].

The security and benefits of hypothermia for infants ≤ 36 weeks gestational age have not been clearly defined, due to the lack of clinical trials. However, the consistent evidence on the reduction of death and neurological disability at 18 months of age in newborn infants ≥ 36 weeks gestation, has raised the interest for the use of this therapy to treat preterm infants with extreme caution. In fact, an ongoing trial on hypothermia is recruiting preterm neonates 33-35 weeks gestational age (ClinicalTrials.gov: NCT01793129) [12], and results from the Vermont Oxford Network (VON) encephalopathy registry show that 2.4% of infants undergoing moderate hypothermia therapy are <36 weeks of gestational age [13].

The present study aims to provide a new inside onto this issue. The objectives were 1) To describe the profile of extraneural involvement in the preterm infants from 33 to 35 weeks gestation with severe HIE, evaluated for therapeutic hypothermia during the first 3 days of life and, 2) To evaluate the differences between these patients and infants born ≥ 36 weeks gestation with severe HIE.

Methods

Patients

Consecutive newborn infants born at 33 to 35 weeks of gestation and birth weigh ≥ 1800 g admitted to the NICU between April 2010 and December 2012 were studied. Patients were admitted if presented with diagnosis of severe HIE in the first 6 hours of life, defined by: 1) severe neonatal encephalopathy: neurological dysfunction manifested as severe altered level of consciousness with or without seizures and, 2) at least one of the following surrogates of hypoxic-ischemic insult: altered fetal heart rate patterns, sentinel event, Apgar at 5 minutes ≤ 5, or acidosis at birth (umbilical arterial pH ≤ 7.0). Newborns were excluded if presented a) severe congenital anomalies or b) other identifiable causes of neurological dysfunction, or c) if parents refused to sign informed consent. Data on infants ≥ 36 weeks gestation have been previously reported [14].

Severity of HIE

The severity of HIE was classified according to our previously reported Scale [15], supervised by an expert neonatal neurologist (AGA). Infants with severe HIE underwent hypothermia as compassionate treatment. All patients were evaluated and treated according to a strict clinical protocol for the management of HIE. Contraindications of hypothermia or indications for early rewarming included a moribund state, severe refractory pulmonary hypertension, severe coagulopathy, or any degree of intraventricular bleeding. The Research Committee of Hospital Sant Joan de Déu approved the study.

Multiorgan dysfunction

Twenty clinical and laboratory variables of 6 organ-systems involvement were studied. Blood tests were performed at admission, 12, 24, 48 and 72 hours of life, subjected to the criteria of the clinician in charge. Data were recorded daily for the first 3 days of life. The most altered value of each variable within every day was recorded. To determine the severity of every organ dysfunction, our previous reported multiorgan dysfunction scale for term infants was used [14].

Statistical analysis

Quantitative variables are described as centralization and dispersion measures: mean and standard deviation or median and interquartile range (Q1-Q3). Qualitative variables are described by absolute (N) and relative (%) frequencies. The distribution of the quantitative variables was compared by the nonparametric test U of Mann Witney for the small sample size. To study the differences of the qualitative variables, the Chi-square test or Fisher's exact test was applied. Hypothesis contrasts were in all cases bilateral and with a significance level of 0.05. Statistical analyses were performed using SPSS version 20 (SPSS, Inc., Chicago, IL, USA).

Results

Eight patients were included. Perinatal data, compared with 31 infants ≥ 36 weeks gestation with severe HIE, are shown in Table 1. No significant differences were found except for birth weight and Apgar score at the first minute of life, that were lower in the group 33-35 weeks gestation. All infants, except one patient with coagulopathy, underwent therapeutic hypothermia following standard practice for patients ≥ 36 weeks of gestation.

Mortality

Six of the 8 patients 33-35 weeks gestation with severe HIE died. One of them died on the first day, 1 on the second day, 2 on the third day and 2 beyond 72 hours. All of them died after life support withdrawal, preceded by end-of life (EoL) decisions. Twenty-one of the 37 patients (68%) died in the group of ≥ 36 weeks gestation with severe HIE. One patient died of refractory shock and another died of severe coagulopathy, while the rest of patients died after life support withdrawal. There were no significant differences in mortality between the two groups (Table 1).

Organ variables

The 24 variables of organ damage during the first 3 days of life are reflected in Table 2. Significant differences between gestational age groups were found only in Glutamic Pyruvic Transaminase (GPT) levels on the first and second day of life, which were less altered in the 33-35 weeks gestation group, whereas this group had lower levels of sodium on the first day of life. None of the patients in the preterm group required inhaled nitric oxide for treatment of pulmonary hypertension.

Severity of multiorgan damage

All patients presented extraneural involvement in the first day of life. There were no differences in the MOD Scale scores between both gestational age groups in the 3 days evaluated (Figure 1). The 33-35 weeks gestation group had a median of 5.5 (4.2-6) affected organ-systems and, 2.5 (1-4.75) moderate or severely affected organ-systems. While the 36 weeks group had a median of 6 (5-6) affected organ-systems and 3 (1-4.75) moderate or severely affected organ-systems. There were no differences between both gestational age groups (p=0.29 and p=0.76, respectively).

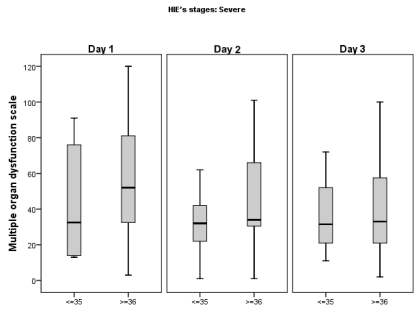

Figure 1: Multiple organ dysfunction scale scores according to gestational age.

	≤ 35 weeks N=8	**≥ 36 weeks** N=31	**P value**
Gestational age, mean (SD), weeks	34.1 (0.8)	38.9 (1.9)	<0.001
Birth weight, mean (SD), grams	2290 (207)	3175 (600)	<0.001
Male, No (%)	3 (38)	22 (71)	0.11
Outborn birth, No (%)	6 (75)	26 (84)	0.62
Age at admission, mean (SD), hours	3.9 (2.7)	5.3 (3.6)	0.53
Growth restriction, No (%)	0 (0)	3 (10)	NS
Sentinel event, No (%)	4 (50)	8 (26)	0.22
Labor dystocia, No (%)	8 (100)	31 (100)	NS
Emergency cesarean section, No (%)	8 (100)	27 (87)	0.56
Meconium-stained liquor, No (%)	2 (25)	16 (52)	0.25
Altered fetal heart rate pattern (%)	6 (75)	27 (87)	0.58
Apgar 1 min, median (IQR)	0 (0-1.5)	2 (0-4)	0.026
Apgar 5 min, median (IQR)	2 (0.3-3.8)	4 (1.8-5.3)	0.13
Apgar 10 min, median (IQR)	5 (2-7)	6 (4-7)	0.55
Artery pH at birth, mean (SD)	6.8 (0.12)	6.93 (0.20)	0.21
Advanced resuscitationa, No (%)	8 (100)	25 (81)	0.31
Whole-body hypothermia, No (%)	7 (88)	28 (90)	NS
Hospitalization, mean (SD), days	9.1 (13.6)	11,1 (13.8)	0.35
Neonatal death, No (%)	6 (75)	21 (68)	NS
a) Included intubation for ventilation, or chest compressions, or use of medications (epinephrine, sodium bicarbonate, and volume expansion)			

Table 1: Perinatal data.

Organ-systems	**Variables**	**Day of life**		**≤ 35weeks**	**≥ 36weeks**	**P value**
		Day 1		N=8	N=31	
		Day 2		N=7	N=27	
		Day 3		N=4	N=23	
Cardiovascular	Troponin T, µg/mL, mean (SD)	Day 1		1.07 (2.14)	1.08 (1.63)	0.98
		Day 2		1.05 (0.04)	1.11 (1.85)	0.78
		Day 3		0.46 (0.46)	0.49 (0.71)	0.68
	Need for vasoactive drugs[a], N(%)	Day 1	None	1 (13)	5 (16)	0.31
			1	5 (62)	10 (32)	
			2	2 (25)	16 (52)	
		Day 2	None	1 (14)	3 (11)	0.90
			1	4 (57)	13 (48)	
			2	2 (29)	11 (41)	

		Day 3	None	1 (25)	4 (17)	0.64
			1	1 (25)	11 (48)	
			2	2 (50)	8 (35)	
Renal	Plasma creatinine, mg/dl, mean (SD)	Day 1		1 (0.28)	1.16 (0.38)	0.29
		Day 2		1.03 (0.57)	1.25 (0.57)	0.48
		Day 3		0.68 (0.44)	1.13 (0.73)	0.20
	Diuresis, mean (SD), ml/kg/h	Day 1		1.2 (0.9)	1.3 (1.6)	0.64
		Day 2		2.5 (0.5)	2 (1.7)	0.25
		Day 3		2.4 (1)	2.4 (1.7)	0.87
	Need for renal replacement therapy, N(%)	Day 1		0 (0)	0 (0)	NS
		Day 2		1 (14)	2 (7)	0.51
		Day 3		1 (25)	2 (9)	0.40
Respiratory	Mechanical ventilation due to other causes than central apnea[b] N(%)	Day 1		7 (88)	26 (84)	NS
		Day 2		6 (86)	23 (85)	NS
		Day 3		3 (75)	19 (83)	NS
	FIO_2 ≥ 0,4 and ≥ 24h, N(%)	Day 1		2 (25)	9 (29)	NS
		Day 2		3 (43)	9 (33)	0.68
		Day 3		1 (25)	5 (22)	NS
	Nitric oxide, N(%)	Day 1		0 (0)	3 (10)	NS
		Day 2		0 (0)	4 (15)	0.56
		Day 3		0 (0)	2 (9)	NS
	HFV[b], N(%)	Day 1		1 (13)	7 (23)	NS
		Day 2		0 (0)	8 (30)	0.16
		Day3		0 (0)	6 (26)	0.55
Hematologic	Leukocytes <4,5 (mm^3), N(%)	Day 1		0 (0)	1 (3)	NS
		Day 2		0 (0)	1 (4)	NS
		Day3		1 (25)	1 (5)	0.31
	Leukocytes >30 (mm^3), N(%)	Day 1		2 (25)	7 (23)	NS
		Day 2		0 (0)	0 (0)	NS
		Day 3		0 (0)	0 (0)	NS
	Platelet count (mm^3), mean (SD),	Day 1		181 (107)	140 (73)	0.41
		Day 2		183 (57)	131 (69)	0.24
		Day 3		148 (20)	110 (71)	0.58
	Platelet or fresh frozen Plasma concentrate (units), median (IQR)	Day 1		0.5 (0-1.8)	1 (0-3)	0.23
		Day 2		0 (0 - 0.4)	0 (0-2)	0.15
		Day 3		0 (0 - 3)	0 (0-1)	NS

	TTPA >45, sec, N(%)	Day 1		6 (75)	18 (62)	0.69
		Day 2		2 (33)	8 (35)	NS
		Day 3		1 (25)	4 (29)	0.33
Hepatic	GOT, (UI/l), mean (SD)	Day 1		433 (531)	784 (934)	0.223
		Day 2		218 (52)	809 (1087)	0.12
		Day 3		96 (43)	455 (677)	0.32
	GPT, (UI/l), mean (SD)	Day 1		94 (105)	285 (303)	0.035
		Day 2		66 (6)	347 (424)	0.015
		Day 3		47 (13)	202 (207)	0.1
	Prothrombin activity, mean (SD), %	Day 1		33 (15)	24 (20)	0.53
		Day 2		51 (21)	44 (24)	0.45
		Day 3		70 (70)	52 (27)	0.8
pH and electrolytic imbalance[c]	pH, lower limit, mean (SD),	Day 1 ≥ 12 hours of life.		7.17 (0.16)	7.13 (0.13)	0.23
		Day 2		7.26 (0.12)	7.2 (0.14)	0.32
		Day 3		7.23 (0.16)	7.23 (0.16)	0.66
	Na^+ lower limit, mmol/L, mean (SD)	Day 1		130 (3)	135 (5)	0.005
		Day 2		131 (9)	133 (6)	0.55
		Day 3		131 (5)	135 (6)	0.15
	Ca^+ lower limit, mmol/L, mean (SD)	Day 1		1.0 (0.1)	1.0 (0.2)	0.38
		Day 2		1.0 (0.2)	1.0 (0.2)	0.63
		Day 3		1.0 (0.2)	1.0 (0.2)	0.94

NS: Non Significative; MV: Mechanical Ventilation; FiO_2: Fraction of Inspired Oxygen; HFOV: High Frequency Oscillatory Ventilation; GOT: Glutamic Oxaloacetic Transaminase; GPT: Glutamic Pyruvic Transaminase; APTT: Activated Partial Thromboplastin Time

a) Use of inotropic agents in our unit is aimed at maintaining a mean blood pressure above 40 mmHg. Dobutamine and dopamine are drugs of first choice and rescue epinephrine and hydrocortisone are used.

b) According to the protocol in force in the unit, the ventilation mode of onset is conventional pressure ventilation, whereas high frequency ventilation would be the rescue mode.

c) Values of pH were temperature corrected. According to the current protocol initial intake volume is between 40 and 50 ml/kg/day for the first 24 hours, with routine administration of 10% calcium gluconate at 2 mEq/kg/day. Sodium and potassium are introduced in the subsequent days, depending on urine output and serum electrolyte values.

Table 2: Multiorgan dysfunction profile during the first 3 days of life.

Discussion

This is the first reported cohort of preterm infants from 33 to 35 weeks gestational age with HIE evaluated for therapeutic hypothermia. The strength of this study relies in the description of organ involvement profile during the first 3 days of life.

The consistent benefits of hypothermia on neurodevelopment in newborns ≥ 36 weeks of gestational age [1-5], has prompted the use, with extreme caution, of hypothermia in preterm newborns with HIE [7,8,10], and other clinical settings such as NEC [11], as the Vermont Oxford Network registry data has shown [13]. Although the safety profile of hypothermia cannot be determined without clinical trials, the comparison of the dysfunction organ profile with patients of ≥ 36 weeks of gestational age may give some insight on this issue.

In this study hypothermia has been used as compassionate treatment for a group of patients at high risk of poor outcome and birth weight ≥ 1800g which reduces the risk of adverse effects such overcooling and glycaemia disorders. Our results depict that multiorgan dysfunction is universal in the group of 33-35 weeks gestation with severe HIE evaluated for hypothermia, as described in term newborn infants [14,16,17]. However, these patients do not seem to present greater organ dysfunction in the first 72 hours of life compared to infants ≥ 36 weeks, which is observed in the number of affected organ-systems, MOD scale scores and every of the organ

variables assessed in this study. Therefore, this study supports the security of this therapy for this group of patients. Although Rao et al. reported 3 patients (10%) with intraventricular or parenchymal haemorrhage, no patient from 33 to 35 weeks gestation in our study presented with intracranial bleeding in agreement with other reported cases [9].

All the patients in this study had severe HIE, and therefore the mortality was high (75%). The mortality rate described in the Cochrane review, based on five trials [1,5,18-20], was of 60% (171 of 285 infants with severe encephalopathy died). Support life withdrawal precede most deaths in HIE [5,18,21]. All deads in our study were preceded by withdrawal from cardiorespiratory support within the first 120 hours of life, considered in patients who had clinical findings consistent with persistent severe encephalopathy (coma) in combination with severe altered aEEG, and severe neuroimaging findings (brain ultrasound scans and/or MRI). In our NICU this prudential decision is performed after having the most accurate prognosis, with the entire team involved (physicians, nurses, and other therapists), and involving excellent communication with parents, so that their decisions are taken with the full support of the medical team. On the other hand, it should be noted that there was no difference in the mortality rate compared to the group of ≥ 36 weeks (68%).

This study has several limitations. Results may be affected by the small cohort size; nevertheless it is of interest to note that most variables were similar in both gestational age groups, and tended to be less involved in the 33-35 weeks group. It should be noted that in this study the burden of hypoglycaemia or hyperglycaemia was not recorded, this is a relevant factor within the adverse effects of both perinatal asphyxia and hypothermia.

Conclusion

This is the first reported cohort of preterm infants between 33-35 weeks of gestation evaluated for therapeutic hypothermia. In agreement with the previous studies or short reports, these patients did not present greater organic dysfunction compared with newborns ≥ 36 weeks of gestation, which reinforces the urgent need of clinical trials that endorse the extension of the benefits of hypothermia to this group of patients.

Declarations

Ethics approval and consent to participate

The Research Committee of Hospital Sant Joan de Déu approved the study. Written parent consent was required for all infants 33-35 weeks gestation.

Consent for Publication

Not applicable

Availability of Data and Material

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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Authors' Contributions

Miguel Alsina Casanova, Ana Martin-Ancel, and Alfredo García-Alix, wrote the first draft of the manuscript. Marisol Leon and Gemma Arca-Diez made significant contributions to the design, execution analysis and reviewed the drafts of the manuscript. Elia Pérez was the statistician who conducted the statistical analysis.

Competing Interests

The authors declare no Competing interests.

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