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Original Article

Population-Based Study of the National Implementation of Therapeutic Hypothermia in Infants with Hypoxic-Ischemic Encephalopathy

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Data on the incidence of hypoxic-ischemic encephalopathy (HIE) in the first 6 hours of life together with the implementation of therapeutic hypothermia (TH) are relevant to delineate actions to achieve the lowest rates of neonatal mortality, morbidity, and long-term impact on health associated with HIE. This is population-based national survey study, including newborns ≥ 35 weeks of gestation with moderate-to-severe HIE from all level III neonatal care units, to provide the incidence of HIE for the period 2012–2013, and the implementation of TH up to June 2015 in Spain. Incidence rate was 0.77 per 1000 live births (95% confidence interval 0.72–0.83). By June 2015, 63% (57/90) of the units had implemented TH; 95% of them performed servo-controlled whole-body TH. For the 2-year period, 86% of the newborns diagnosed with moderate-to-severe HIE received TH. Active TH increased in use from 78% in 2012 to 85% in 2013 ($p = 0.01$). The main reasons for not cooling were a delay in the diagnosis (31/682) and the fact that the treatment was not offered (20/682). Interhospital patient transfer was performed using passive hypothermia, by appropriately trained personnel in 61% of centers. Eighteen percent of newborns with moderate or severe HIE died, without significant differences between the 2 years. Up-to-date knowledge of the national coverage of neonatal care of infants with HIE in developed countries is a prerequisite to reducing the load of HIE in this area and to facilitating coordinated, eliminate investigation.

Keywords: hypoxia-ischemia, encephalopathy, hypothermia, incidence, neuroprotection

Introduction

Neonatal encephalopathy after birth asphyxia is a major cause of death and disability worldwide. The global burden of hypoxic-ischemic encephalopathy (HIE) is high even in developed countries, with high estimates of disability-adjusted life years, years of life lost, and years lived with disability, as well as a great financial cost to families and society (Blencowe *et al.*, 2013; Eunson, 2015). The reported incidence of HIE is imprecise even in developed countries, which hinders accurate understanding of the burden of HIE, with estimates ranging from 1 to 8 per 1000 live births (Kurinczuk *et al.*, 2010; Lee *et al.*, 2013).

The introduction of therapeutic hypothermia (TH) as the standard of treatment for moderate or severe HIE has narrowed the time frame for establishing the diagnosis and severity of HIE to around 6 hours of life (Olsen *et al.*, 2013). However, nationwide population-based studies on the incidence of moderate and severe HIE diagnosed in the first hours of life before TH is initiated have not yet been reported. National incidences of HIE are important, particularly if linked to programmatic solutions and therapeutic actions such as the implementation of TH.

Data on national coverage of neonatal care to infants with HIE and on the implementation of TH are scarce even in high-income countries (Chevallier *et al.*, 2013; Kracer *et al.*, 2014; Brotschi *et al.*, 2015; Battin *et al.*, 2016). These data are increasingly relevant not only for individuals and families but also for the purpose of guiding future policy in each country or region to achieve the lowest rates of neonatal

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mortality and morbidity, and to reduce the long-term impact on health associated with HIE.

We performed a cross-sectional national survey involving all level III neonatal units in Spain to obtain a comprehensive picture of neonatal care of the infant with HIE. We report (1) the incidence of moderate-to-severe HIE diagnosed in the first 6 hours of life in newborns ≥ 35 weeks gestational age (GA) for the period January 2012 to December 2013, (2) the neonatal mortality associated with HIE, and (3) the implementation of TH up to June 2015.

Methods

We conducted a cross-sectional national study on moderate-to-severe HIE in newborns ≥ 35 weeks GA. A questionnaire was designed to obtain a comprehensive picture of the care of the infant with HIE. The questionnaire was designed by two of the authors (J.A. and A.G.A.) and approved by the rest of the investigators. All public and private level III neonatal and pediatric-neonatal units in Spain were contacted, and the clinical head in the neurological area in each of the units was personally contacted by one of the authors. Each coordinator was given access to the questionnaire online with detailed instructions for answering. Missing data or inconsistencies in the answers were followed up and contact was made with the centers whenever necessary to review and guarantee the veracity of the data.

The collected data included (1) number of live births ≥ 35 weeks GA per year (2012 and 2013); (2) number of diagnosed infants of moderate-to-severe HIE (2012 and 2013), origin of the infants (inpatient or transferred patient), number of deaths, number of infants who received TH treatment, and causes for not providing it; (3) implementation of TH and cooling during transport up to June 2015 in each unit (year TH was initiated, number of cooling devices, and amplitude-integrated electroencephalography [aEEG] monitoring systems available).

Definitions

Infants were considered to have moderate or severe HIE if they met the following criteria: (1) Apgar score ≤ 5 at 10 minutes; need for resuscitation in the delivery room, including endotracheal intubation or mask ventilation for >10 minutes after birth; or acidosis (pH ≤ 7.0 and/or base deficit ≥ 16 mmol/L in umbilical cord blood or arterial, venous, or capillary blood within 60 minutes from birth) and (2) a syndrome of neurological dysfunction manifested by an abnormal level of consciousness with or without seizures within 6 hours of birth. Different staging scales, such as Sarnat's (Sarnat and Sarnat, 1976), Garcia-Alix's (Garcia-Alix *et al.*, 1994), or Thompson's (Thompson *et al.*, 1997), were used to classify the severity of HIE.

Incidence of moderate-to-severe HIE was expressed as cases of infants ≥ 35 weeks GA that met the inclusion criteria (criteria 1 and 2) per live births of all gestations. An estimate of the HIE incidence rate for newborns ≥ 35 weeks GA data was derived from hospitals that provided the number of inborn infants diagnosed with moderate-to-severe HIE per live births ≥ 35 weeks GA.

TH: cooling at temperature of 33–34°C for 72 hours. When the target temperature was reached using manual or servo-controlled devices, TH was considered active, whereas the use of gel packs and/or turning off radiant warmers was considered passive TH.

Neonatal mortality referred to the death of a born baby within the first 28 days. Moribund infants were included in this definition to refer to a severely ill newborn whose vital constants could not be stabilized within the first hours after birth, and who subsequently died.

Statistical analysis

Numbers (with percentages) are presented for binary and categorical variables. Formal statistical comparisons of proportions between the 2 years were carried out using chi-squared or Fisher test. A p-value <0.05 was considered statistically significant. Statistical analysis was made with Epidat 3.1.

Results

HIE data

Data from all 90 hospitals with neonatal or pediatric/neonatal level III units were collected. A total of 682 (353 in 2012; 329 in 2013) newborns ≥ 35 weeks GA out of 880,363 (454,648 in 2012 and 425,715 in 2013) live births were diagnosed with moderate-to-severe HIE during the study period, which represents an incidence of 0.77 per 1000 live births (95% confidence interval [CI] 0.72–0.83). There were no differences in the 2 years: 0.78 [95% CI 0.69–0.86] versus 0.77 [95% CI 0.69–0.86] per 1000 live births. Forty-three percent (290/682) of the infants were born at units that already provided TH, with an increase from 36% (126/353) to 50% (164/329) during the study period ($p = 0.002$).

Regarding the 75 hospitals out of 90 that provided the number of live births of GA ≥ 35 weeks, a total of 406 (203 in 2012; 202 in 2013) inborn newborns ≥ 35 weeks GA out of 372,894 (190,220 in 2012 and 182,674 in 2013) ≥ 35 weeks GA live births were diagnosed with moderate-to-severe HIE during the study period. This represents a global incidence of 1.09 per 1000 live births ≥ 35 weeks GA (95% CI 0.98–1.20), without differences between the 2 years (1.07 [95% CI 0.92–1.22] and 1.11 [95% CI 0.95–1.26] in 2012 and 2013, respectively).

Fifty-five of the 90 centers (61%) reported that inter-hospital patient transfer was performed by appropriately trained personnel, and that passive hypothermia was always used to maintain targeted temperature.

Mortality data

Of the total of 682 newborns, 126 (18%) with moderate or severe HIE died during the neonatal period: 72 out of 353 (20%) in 2012 and 54 out of 329 (16%) in 2013 (differences not significant). The death rate attributable to HIE during the 2-year period was 0.14 per 1000 live births [95% CI 0.12–0.17].

Implementation of TH

During the study period, 86% (588/682) of the newborns diagnosed with moderate-to-severe HIE received TH. There were no differences between the 2 years (Table 1). However, the number of newborns that received active TH significantly increased during the study period from 78% (274/353) in

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Table 1. Data on Newborns Diagnosed with Hypoxic-Ischemic Encephalopathy and the Implementation of Therapeutic Hypothermia

	Total	*Year 2012*	*Year 2013*	p
Newborns diagnosed with moderate-to-severe HIE	682	353	329	0.950
Born at hospitals with TH	290 (43)	126 (36)	164 (50)	0.002
Death before discharge	126 (18)	72 (20)	54 (16)	0.181
Newborns who received TH for 72 hours	588 (86)	297 (84)	291 (88)	0.102
Active TH	553 (81)	274 (78)	279 (85)	0.016
Passive TH	35 (5)	23 (7)	12 (4)	0.089
Elective passive TH	22 (3)	15 (4)	7 (2)	0.087
Passive TH because of instability for patient transfer	13 (2)	8 (2)	5 (2)	0.334
Newborns who did not receive TH	94 (14)	56 (16)	38 (12)	0.102
Moribund	18	9	9	0.357
Contraindicated because of severe pulmonary hypertension or coagulopathy	3	2	1	0.643
Cardiovascular or respiratory instability impeding patient transfer to a TH referral center.	6	4	2	0.535
Delay in the diagnosis of moderate-to-severe HIE	31	14	17	0.458
Arrival at the TH referral center after the sixth hour of life	7	3	4	0.292
Patient not accepted by the TH referral center[a]	4	2	2	0.534
TH was not offered	20	19	1	0.001
Unknown	5	3	2	0.676

Data are shown on *n* and (%).
[a]Cooling device unavailable/neonatal unit full.
HIE, hypoxic-ischemic encephalopathy; TH, therapeutic hypothermia.

2012 to 85% (279/329) in 2013 ($p = 0.01$). In 21 newborns (3%), TH was considered contraindicated because of a moribund state, severe pulmonary hypertension, or uncontrollable bleeding. After excluding these newborns, 89% (588/661) of all eligible infants were cooled during the study period.

The main reasons for not cooling the remaining 73 eligible infants during the 2-year period were a delay in the diagnosis (HIE was diagnosed after 6 hours) in 31 out of 73 infants, and the fact that the treatment was not offered for 20 out of 73 infants. The latter improved in 2013 when only one infant was not offered TH despite being eligible for the treatment ($p = 0.001$). Other reported reasons for not providing TH are given in Table 1.

By June 2015, 57 of 90 centers (63%) had implemented TH: in 2008 (2 centers), 2009 (10 centers), 2010 (9 centers), 2011 (10 centers), 2012 (9 centers), 2013 (7 centers), 2014 (8 centers), and 2015 (2 centers). Most of them, 95% (54/57), performed active TH and all of them had servo-controlled whole-body devices (only one center performed selective-head cooling—Coolcap® system). Most of the hospitals had Tecotherm® (70%) and Criticool® (21%) systems, and 14/54 (26%) had more than one device. By June 2015, only three neonatal units cooled their infants passively. Fifty-one of the 57 centers (89%) had at least one aEEG monitoring system: 39 out of 51 (76%) had one device, and 12 out of 51 (24%) had two or more devices available. aEEG monitoring during the whole period of hypothermia was the rule in these centers.

Discussion

The updated HIE incidence rates and data on the nationwide implementation of active TH are needed to delineate areas for improvement and guide the national or regional policy to achieve the lowest rates of neonatal mortality and morbidity, and reduce the long-term impact on health associated with HIE. However, the data are scarce worldwide (Kurinczuk *et al.*, 2010), probably because of the difficulty either in getting information from every hospital where HIE infants are born or in obtaining reliable case ascertainment because of a lack of uniform definition of HIE in the centers. We believe this is a strength of our study, as we succeeded in gathering information from all units where these infants are admitted using a uniform definition of HIE.

Previous studies have reported a trend toward decreasing incidence of HIE in high-income countries, with incidence rates around 1–2 per 1000 live births (Smith *et al.*, 2000; Becher *et al.*, 2007; Garcia-Alix *et al.*, 2009). The two most recent national studies on the incidence of HIE, from Japan (Hayakawa *et al.*, 2014) and New Zealand (Battin *et al.*, 2016), reported an incidence of moderate or severe HIE of 0.37 and 1.3 per 1000 term births, respectively. The diagnosis of HIE in these series was made within the first 3 days in the Japanese study (Hayakawa *et al.*, 2014) and the first 7 days in the study from New Zealand (Battin *et al.*, 2016).

However, since TH should be indicated within 6 hours of life, it is necessary to grade HIE before TH is started and to report incidence rates of moderate or severe HIE at that age. We did not find any other population-based study regarding infants with moderate or severe HIE diagnosed within the first 6 hours of life. This is particularly important in that HIE has programmatic therapeutic actions indicated within the first 6 hours of age. We want to emphasize that our analysis included newborns ≥ 35 weeks GA and not only term newborns, because it is standard practice in our country to perform TH in these patients (Eicher *et al.*, 2005; Jacobs *et al.*, 2011).

The implementation of TH in Spain started in 2008 and has been extended to 57 units (63% out of all tertiary centers) by June 2015. TH in our country is only provided at tertiary hospitals and its implementation is not performed according to any national health plans, but rather is provided at each

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center's discretion. In accordance with what other countries have reported, the implementation of this therapy has increased after the publication of national healthcare guidelines, as occurred in Spain in 2011 (Blanco *et al.*, 2011). All our centers used whole-body hypothermia, and only one center reported additionally using selective brain cooling. By June 2015, all cooling units except for three, provided active TH using servo-controlled devices, which has advantages when it comes to reducing temperature oscillations and nursing interventions (Brotschi *et al.*, 2015).

According to our data, 89% of the HIE cases eligible for TH were cooled, which is higher than what some national studies have reported, although some of these studies failed to include most of the centers where TH is performed (Chevallier *et al*., 2013) and others used different time criteria to grade the severity of HIE (Kracer *et al.*, 2014; Battin *et al.*, 2016). Unfortunately, most published studies regarding TH did not collect data on patients with HIE who were not cooled (Azzopardi *et al.*, 2012; Groenendaal *et al.*, 2013; Gardiner *et al.*, 2014), which has limitations in shedding light on the effectiveness of implementation of hypothermia protocols in each region, and in assessing the long-term impact of this treatment (Chevallier *et al.*, 2013; Brotschi *et al.*, 2015; Battin *et al.*, 2016).

Most of the newborns cooled in our series received active TH; in our setting, some studies reported a similar use of active TH (Azzopardi *et al.*, 2012; Chevallier *et al.*, 2013), whereas others cooled mainly passively (Brotschi *et al.*, 2015; Gerstl *et al.*, 2015). Our data of an increase in the number of infants cooled with active TH as well as a decrease in the rates of newborns who did not receive TH might be related to a growing number of neonatal units offering active TH, and an evolution toward a better diffusion and a deeper knowledge of TH in our country.

The overall death rate of 18% is lower than that observed in clinical trials ($\approx$25%) but is similar to what was seen in other series (Azzopardi *et al.*, 2012; Chevallier *et al.*, 2013), although some authors have reported lower rates (13–14%) probably because of a greater representation of mild HIE cases in their cohorts (Gardiner *et al.*, 2014; Kracer *et al.*, 2014). Since neonatal outcomes are highly dependent on the quality of care received and medical attitudes (Garcia-Alix *et al.*, 2013), the decrease in the death rate from 20% in 2012 to 16% in 2013 might be related to an evolution in practice toward a more active role for neonatologists in the management of HIE, in accordance with other reports (Azzopardi *et al*., 2012; Brotschi *et al.*, 2015). In contrast, since the breakdown of encephalopathy by moderate or severe grades was not provided, the lower mortality could reflect the inclusion of mild cooled encephalopathic infants or more of those who had moderate HIE as compared with severe HIE.

More than half (57%) of the newborns diagnosed with moderate-to-severe HIE in the period 2012–2013 were born in facilities where TH was not available, necessitating urgent transfer to TH reference centers. In Spain, interhospital patient transfer is performed with passive TH, even though servo-controlled systems would be more effective in preventing the risk of unintended overcooling during patient transfer (Chaudhary *et al.*, 2013). Regardless of the type of cooling system available, it is relevant to our national health service to point out that only 61% of the centers reported that appropriately trained pediatric teams performed these urgent interhospital transfers. Establishing a coordinated system with both regional referral cooling centers and a pediatric transport team (Neonatal Emergency Medical System) for asphyxiated infants is a challenge for the coming years in many parts of our country.

Although we have succeeded in gathering information from all the level III neonatal care facilities in Spain, there are some limitations inherent in the analysis of data obtained from surveys, such as reporting bias and incomplete or erroneous data. Nevertheless, we made a special effort to avoid these pitfalls.

In conclusion, the incidence rate of around 1 per 1000 live births with a high rate of implementation of TH in a country in southern Europe is encouraging and reflects the generalization of this therapeutic intervention. Nevertheless, the existence of about 14% of noncooled children, the deficiencies in the transport system, and a mortality rate of 18% highlight the need to implement strategies and policies at the regional and national levels that will allow for improvement in the overall approach to HIE. Up-to-date knowledge of the national coverage of neonatal care of infants with HIE in developed countries is a prerequisite to reducing the load of HIE in this area and to facilitating coordinated investigation.

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No competing financial interests exist.

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Appendix

SPAIN-HIE Group: J. Diez-Delgado (Torrecárdenas, Almería), I. Tofé (Reina Sofía, Córdoba), A.E. Jerez (S. Cecilio, Granada), J.A. Hurtado (Virgen de las Nieves, Granada), J.M. Ceballos (JR. Jiménez, Huelva), M.L. Millán (C. Hospitalario, Jaén), M.D. Esquivel (Materno-Infantil, Jerez), C. Ruiz (Costa del Sol, Marbella), M. Baca (Quirón, Málaga), E. Tapia (G. Universitario, Málaga), M. Losada (Quirón S. Corazón, Sevilla), E. Torres (Valme, Sevilla), A. Pavón (Virgen del Rocío, Sevilla), P.J. Jiménez (Virgen Macarena, Sevilla), F. Jiménez (S. Ángela de la Cruz, Sevilla), M.P. Ventura (Lozano Blesa, Zaragoza), S. Rite (Miguel Servet, Zaragoza), T. González (Cabueñes, Gijón), R.P. Arias (Central Asturias, Oviedo), P.R. Balliu (Son Espases, Mallorca), J.M. Lloreda-García (S. Lucía, Cartagena), J.L. Alcaráz (Virgen de la Arrixaca, Murcia), C. Tapia (General, Alicante), A. de la Morena (S. Juan, Alicante), I. Centelles (General, Castellón), I. Güemes (Casa de Salud, Valencia), J. Estañ (Clinico, Valencia), A. Alberola (La Fé, Valencia), S. Aparici (Quirón, Valencia), R. López (Nisa_9 de Octubre, Valencia), J. Beceiro (Príncipe de Asturias, Alcalá de Henares), B. García (General, Fuenlabrada), L. Martínez (General, Getafe), E. González (Severo Ochoa, Leganés), L. Arruza (Clínico S. Carlos, Madrid), M.D. Blanco (Gregorio Marañón, Madrid), B. Arias (La Zarzuela, Madrid), F. Mar (Ruber I., Madrid), J. Jiménez (Sanitas_La Moraleja, Madrid), G. Romera (Montepríncipe, Madrid), A. Cuñarro (Alcorcón), C. Muñóz (Puerta de Hierro_Majadahonda, Madrid), F. Cabañas (H.U. Quirón Madrid), R. Montero (Nisa_Pardo de Aravaca, Madrid), J.C. Tejedor (General, Móstoles), C. Santana (Materno Insular, Las Palmas), B. Reyes (Universitario de Canarias, Tenerife), S. Romero (N.S. de Candelaria, Tenerife), A. Orizaola (Marqués de Valdecilla, Santander), M. Baquero (General, Albacete), D. Hernández (General, Ciudad Real), A. Pantoja (Virgen de la Salud, Toledo), C. Vega (HUBU, Burgos), L. Castañón (CAULE, León), E.P. Gutiérrez (Universitario, Salamanca), M. Benito (Clínico, Valladolid), M.J. García (S. Creu i S. Pau, Barcelona), M.A. López-Vílchez (H. del Mar, Barcelona), L. Castells (General de Catalunya, Barcelona), M. Domingo (Parc Taulí, Sabadell), W. Coroleu (Germans Trias i Pujol, Badalona), H. Boix (Vall d'Hebrón, Barcelona), R. Porta (I. Dexeus_Quirón, Barcelona), S. Martínez-Nadal (SCIAS, Barcelona), E. Jiménez (Dr. J. Trueta, Girona), E. Sole (Arnau de Vilanova, Lleida), M. Albújar (Joan XXIII, Tarragona), E.M. Fernández (Infanta Cristina, Badajoz), A.R. Barrio (S. Pedro de Alcántara, Cáceres), E. Piñán (Mérida), A. Avila-Alvarez (CHU A Coruña), M.E. Vázquez (Lucus Augusti, Lugo), N. Balado (CHU, Orense), P.A. Crespo (CHU, Pontevedra), M.L. Couce (Clínico, Santiago de Compostela), A. Concheiro-Guisán (Xeral, Vigo), I. Esteban (S. Pedro, Logroño), A. Lavilla (CH, Navarra), V. Alzina (C. Universidad de Navarra), A. Aguirre (Basurto, Bilbao), B. Loureiro (Cruces, Bilbao), I. Echániz (Quirón, Bilbao), M.D. Elorza (HU. Donostia, San Sebastián), A. Euba (HUA Txagorritxu, Vitoria).

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