

Hypoxic Ischemic Encephalopathy in Units Reporting to the Ibero-American Society of Neonatology Network: Prevalence and Mortality

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ABSTRACT

INTRODUCTION Hypoxic ischemic encephalopathy is a neurological condition occurring immediately after birth following a perinatal asphyctic episode. Therapeutic hypothermia is a safe and effective intervention to reduce mortality and major disability in survivors. In Latin America, perinatal asphyxia is a major problem, but no data are available characterizing its current situation in the region or the impact of hypoxic ischemic encephalopathy on its management.

OBJECTIVE Understand the prevalence, mortality and use of therapeutic hypothermia in newborns at ≥ 36 weeks gestational age with hypoxic ischemic encephalopathy admitted to neonatal units reporting to the Ibero-American Society of Neonatology Network.

METHODS The Ibero-American Society of Neonatology Network groups various neonatology centers in Latin America that share information and collaborate on research and medical care. We evaluated data on newborns with ≥ 36 weeks gestational age reported during 2019. Each unit received a guide with definitions and questions based on the Society's 7th Clinical Consensus. Evaluated were encephalopathy frequency and severity, Apgar score, need for resuscitation

at birth, use of therapeutic hypothermia and clinical evolution at discharge. Our analysis includes descriptive statistics and comparisons made using the chi-square test.

RESULTS We examined reports of 2876 newborns from 33 units and 6 countries. In 2849 newborns with available data, hypoxic encephalopathy prevalence was 5.1% (146 newborns): 27 (19%) mild, 36 (25%) moderate, 43 (29%) severe, and 40 (27%) of unknown intensity. In those with moderate and severe encephalopathy, frequencies of Apgar scores ≤ 3 at the first minute ($p = 0.001$), Apgar scores ≤ 3 at the fifth minute ($p < 0.001$) and advanced resuscitation ($p = 0.007$) were higher. Therapeutic hypothermia was performed in only 13% of newborns (19). Neonatal mortality from encephalopathy was 42% (61).

CONCLUSION Hypoxic ischemic encephalopathy is a neonatal condition that results in high mortality and severe neurological sequelae. In this study, the overall prevalence was 5.1% with a mortality rate of 42%. Although encephalopathy was moderate or severe in 54% of reported cases, treatment with hypothermia was not performed in 87% of newborns. These data reflect a regional situation that requires urgent action.

KEYWORDS Hypoxia ischemia, brain; encephalopathy, neonatal; mortality; hypothermia, induced; neonatology; Latin America

INTRODUCTION

Hypoxic ischemic encephalopathy (HIE) is a neurological syndrome that presents immediately after birth after a perinatal asphyctic episode. It is characterized by alterations in alertness, with decreased ability to awaken and maintain muscle tone, decreased motor responses and reactivity. It occurs as a consequence of oxygen deprivation in the brain, from arterial hypoxemia or cerebral ischemia, or both.[1,2]

Therapeutic hypothermia (TH) is the reduction of body temperature by 3–4 °C in the first 6 hours of life, maintained for 72 hours. It is a safe and effective intervention for reducing mortality and major disability in survivors.[3–5] It is currently the only standard therapy specific to HIE.[1,6–10] The Ibero-American Society of Neonatology (SIBEN) published a guide establishing standards and recommendations for HIE management in Latin America aimed at promoting a comprehensive therapeutic approach, including recommendation of TH.[1]

IMPORTANCE

This study, the first of its kind, provides data from health-care institutions in Latin America related to hypoxic ischemic encephalopathy in neonates and can be used as a basis for determining mortality and improving access to therapeutic hypothermia in the region.

According to WHO, in 2017 some 2.5 million children died in their first month of life. This is approximately 7000 newborns each day, 1 million in the first day of life and nearly 1 million in the following 6 days.[11] Globally, the leading direct causes of neonatal death are preterm birth (28%), severe infections (26%) and asphyxia (23%). [12] These three causes account for three quarters of neonatal mortality worldwide.[13]

HIE is one of the leading causes of neonatal death and permanent disability, and its contribution to the health burden is high, in terms of years of life lost and years lived with disability. In addition to the important contribution of asphyxia to perinatal mortality, it is estimated that more than one million newborns who survive it annually develop cerebral palsy, epilepsy, learning disabilities and other developmental problems.[6–8] The risk of major disability in those who survive is high. Without TH, the risk of death or major disability with moderate HIE is 52% and with severe HIE approximately 78%.[10]

In the 20th century, no specific therapeutic interventions were performed to prevent or ameliorate brain damage associated with HIE perinatal aggression. Neonates with moderate and severe HIE constitute a therapeutic challenge due to the associated risk of death or neurological sequelae. The medical, social and legal implications associated with this devastating condition are of consequence and represent an important social and health problem.[14] In Latin America, composed of low- and middle-income countries, perinatal asphyxia is a major problem, and

it can be assumed that thousands of newborns do not receive adequate care. While precise information is available regarding the extent of this problem and its impact in Europe, Canada and the United States, reliable information is not available for Latin American countries; with the exception of Cuba, where there are recent reports.[15]

The scarce published data for Latin America describe single-center experiences in large cities, with small patient numbers.[1] These data estimate HIE incidence at 4%–6.2% of live newborns and risk of death at 10%–20% in neonates with moderate HIE, and >60% in those with severe HIE.[1] However, these data almost assuredly underestimate the reality of the current situation.

The SIBEN Network brings together various Latin American neonatology units for information sharing and collaboration in research and patient care. The units maintain their autonomy while participating in a joint effort aimed at a common objective: promote continuous improvements in the quality of care offered by each. The Network thus facilitates comparative evaluation among participating units and centers, collaborating to implement good clinical practices that may influence care throughout the region. Network participation is free for SIBEN members. Currently, 45 neonatal intensive care units (NICUs) in 9 Latin American countries belong.

It is essential and urgent to improve the quality and accessibility of information on HIE's magnitude in Latin America in order to: 1) characterize perinatal care in the region; 2) obtain objective data that allow for monitoring changes over time; 3) understand healthcare needs generally and for specific geographic areas, to develop plans for improvement and to correct inequalities in the care of newborns with perinatal asphyxia-HIE; and 4) systematize and rationalize efforts aimed at improving care for asphyctic neonates who develop HIE.

The objective of this study was to determine the prevalence of HIE in neonates at ≥ 36 weeks of gestational age (GA) admitted to NICUs that participated in the SIBEN Network registry in 2019, and to understand related mortality rates and the use of therapeutic hypothermia.

METHODS

The 45 units comprising the SIBEN Network are in the public sector. All were invited to participate in this study. However, since only 33 units in 6 countries (Argentina, Brazil, Ecuador, Peru, the Dominican Republic and Venezuela) report data on newborns at ≥ 36 weeks GA, we used data exclusively from these units. There were great disparities in numbers of centers reporting (and thus the numbers of newborns included per country): 18 from Argentina, 11 from the Dominican Republic, and 1 each from Ecuador, Peru, Brazil and Venezuela. Newborns with major congenital malformations were excluded from our research. The study population thus included 2876 newborns (at ≥ 36 weeks GA) admitted to 33 neonatal intensive care units from January 1, 2019 through December 31, 2019.

A clinical care guide was distributed to each of the participating units, accompanied by a list of requested data, both based on the therapeutic recommendations from the 7th SIBEN Clinical Consensus for Neonatal HIE.[1] Accordingly, HIE severity was

classified in three grades: mild, moderate and severe. In addition to neurological dysfunction after delivery, HIE diagnosis was established when the newborn had a history of potential hypoxic ischemic aggression during delivery (e.g., a sentinel event or alteration of the fetal cardio-topographic record) and/or alteration of status at birth (Apgar < 5 at 10 minutes, pH in the first hour ≤ 7.0 , or the need for advanced cardiopulmonary resuscitation).[1]

Study variables We collected the following:

- Apgar score at 1 minute and 5 minutes
- HIE severity by grade
- use of advanced cardiopulmonary resuscitation (CPR) when the newborn required endotracheal intubation
- fraction of inspired oxygen (FiO_2) during resuscitation
- presence of seizures
- use of TH (body or brain)
- mortality during hospitalization (death of the newborn before discharge and death of the newborn attributable to HIE)

We analyzed the data using descriptive statistics, summary measures, frequency tables and graphs.

This study complies with the internationally accepted ethical recommendations established by the Declaration of Helsinki, in its current version.[16]

RESULTS

2876 newborns admitted to neonatal intensive care units in 33 healthcare institutions in 6 countries were reported to the SIBEN Network from January 1, 2019 through December 31, 2019 (Table 1). Due to the large differences in the number of reports by geographic location, the newborns were analyzed as a group, without making comparisons among NICUs or countries.

Frequency and severity of HIE reported to the SIBEN Network Data was not reported on HIE for 27 of the 2876 newborns. Among the remaining 2849 newborns with available data, 146 cases of HIE (5.1%) were reported, classified according to severity (Table 2). Severity was not reported for 40 (27.4%), and thus these are not included in Table 2, although they are added for the total count. The absolute frequencies and percentages corresponding to the Apgar categories at one minute and five minutes, clinical seizures, advanced resuscitation, TH use and mortality are also reported.

Apgar score Out of the cohort of 2876 newborns, 275 (9.6%) with an Apgar score ≤ 3 in the first minute of life and 258 (8.6%)

Table 1: Case data supplied to SIBEN Network

Country	Number of NICUs reporting	Number of newborns reported
Dominican Republic	11	1839
Argentina	18	1002
Ecuador	1	14
Peru	1	10
Brazil	1	7
Venezuela	1	4
Total	33	2876

NICU: neonatal intensive care unit

Table 2: Apgar score, advanced resuscitation, seizures, therapeutic hypothermia use, and mortality by HIE severity

	HIE						Total* (N = 146)	
	Mild (N = 27)		Moderate (N = 36)		Severe (N = 43)			
	n	%	n	%	n	%	n	%
Apgar score (minutes)								
≤3	15	55.6	33	91.7	35	81.4	111	76.0
>3	12	44.4	3	8.3	8	18.6	35	24.0
Apgar score (minutes)								
≤5	11	40.7	33	91.7	33	76.7	103	70.5
>5	16	59.3	3	8.3	10	23.3	43	29.5
Advanced resuscitation								
Yes	8	29.6	20	55.6	27	62.8	74	50.7
No	19	70.4	16	44.4	16	37.2	72	49.3
Seizures								
Yes	10	37.0	29	80.6	30	69.8	98	67.1
No	17	63.0	7	19.4	13	30.2	48	32.9
TI use	2	7.4	4	11.1	8	18.6	19	13.0
Mortality	3	11.1	14	38.9	26	60.5	61	41.8

* Includes cases in which HIE severity was not reported during hospitalization.
n: number of cases %: percentage with respect to total cases
HIE: hypoxic ischemic encephalopathy TH: therapeutic hypothermia

with a score ≤5 at 5 minutes were reported. Of the 146 newborns who presented with HIE, 111 (76%) had an Apgar score of ≤3 at 1 minute of life and 103 (70.5%) ≤5 at 5 minutes of life. Low Apgar scores were much more common in the moderate and severe forms of HIE (Table 2).

Seizures Of the 146 newborns with HIE, 98 (67.1%) experienced seizures. Seizures were also much more common in moderate and severe forms of HIE (Table 2).

Resuscitation according to HIE severity Advanced resuscitation was necessary in 74 newborns with HIE (51%) (Table 2). The likelihood of advanced resuscitation obviously increased with HIE severity. Of the 20 newborns with moderate HIE who received advanced CPR, 9 (45%) required cardiac massage and 4 (20%) required vasoactive medication. Of the neonates with severe HIE, 27 (63%) required advanced CPR, of which 22 (81%) required cardiac massage and 11 (41%) required medication. Only 11% of newborns were resuscitated with 21% FiO₂ and 40% were resuscitated with 100% oxygen. FiO₂ data was not reported for the remaining 49%.

Therapeutic hypothermia Only 19 of the 146 newborns with HIE (13%) were treated with TH (mild HIE: 2, moderate HIE: 4, severe HIE: 8, with unknown severity: 5) (Table 2). Of those treated with TH, 75% received body cooling and 25% received selective brain cooling. It is obvious that, regardless of the severity of HIE, TH use is infrequent.

Mortality Among the 2876 newborns, mortality reported was 11% (310 newborns) while mortality in the 146 newborns with HIE was 42% (61/146), which is positively correlated with HIE severity. Of the 61 newborns with HIE who died, 37 cases (60.7%) were directly attributable to HIE, regardless of severity. In the remaining 24 (39.3%), death was attributed to sepsis, meningitis, respiratory failure, hypoxemia, kernicterus and other causes.

DISCUSSION

HIE is a neonatal condition that results in high mortality and severe neurological sequelae.[1–3] In this study, HIE prevalence in newborns at ≥36 weeks GA admitted to SIBEN Network centers was 5.1% with a mortality rate of 42%, almost four times that of non-HIE newborns at the same GA reported to the Network. Although HIE severity was not reported for all newborns, in 54% of reported cases it was either moderate or severe. These data do not represent all of Latin America nor the reality of each country, as our sample corresponds to voluntary reporting made by only some of the neonatal units within the region. However, even with the aforementioned limitations of our sample, these data reflect a situation demanding urgent action.

TH has proven benefits for newborns with HIE,[10,15,17–23], among which the reduction in mortality or neurodevelopmental alterations at 18 months stands out with a relative risk (RR) of 0.75, 95% CI (0.68–0.83).[17] TH has few side effects and its implementation is relatively simple. However, TH was only used in a small number of newborns with HIE in this sample, and it remains unavailable in many centers throughout the region. In the SIBEN Network during the study period, 87% of neonates who presented with HIE did not receive TH, and of the 79 reported with moderate or severe HIE, only 12 (15%) had access to TH. It is highly probable that the mortality rate in these newborns would have been lower if TH had been available and applied. Even though we do not know the neurological evolution of these newborns after discharge, evidence shows that TH leads to reduced rates of major disability associated with HIE and therefore better long-term neurological outcomes.[17]


As is the case with other health indicators, no Latin American countries present national data on prevalence and clinical evolution of newborns with HIE, with the exception of Cuba, where HIE frequency in 2017 and 2018 was comparable to rates in high-income countries. HIE mortality rates in Cuba of 12% and 17% (for 2017 and 2018, respectively) cannot be stratified by HIE severity since, as of this writing, the Cuban national registry has not yet recorded this data for later analysis. Unlike Latin America, other regions have working groups that track information related to HIE incidence, its severity, conditions available for comprehensive care and the TH implementation. [24,25] In a cross-sectional study conducted in 57 Spanish hospitals, 95% of those surveyed used servo-controlled total body cooling and had established protocols specific to HIE patient care.[26]

This study does not include an analysis of the use of oxygen in advanced resuscitation procedures. The universal recommendation is to use ambient air (21% FiO₂). However, this was the case in only 11% of newborns resuscitated in this sample. Some 40% were resuscitated with 100% oxygen, despite ample evidence advising against this practice and the damage the hypoxia-reperfusion-hyperoxia cycle can have on the brain. [27–31]

Any process aimed at improving quality of care for newborns with HIE must be based on reliable information. This is the first study involving Latin American countries that provides data on this important problem. Comprehensive care of newborns affected by HIE is multi-faceted and must include the

availability of adequate resuscitation with trained personnel in the delivery room, avoiding inappropriate use of oxygen; rapid clinical diagnoses; the ability to assess HIE severity, and use of previously validated care protocols. Timely care for families is essential, as is TH provision in the NICU or potential for patient referral to a center capable of providing TH within the first six hours of life. Finally, given the consequences HIE has for neurodevelopment and quality of life for both children and their families, specialized followup programs should be established to identify and treat neurodevelopmental issues in a timely manner, and offer support and guidance to families.[32]

CONCLUSIONS

Hypoxic ischemic encephalopathy is a neonatal condition responsible for high mortality rates and severe neurological sequelae. HIE prevalence in this study was 5.1%, with an overall mortality rate of 42%. Despite the fact that HIE was graded as either moderate or severe in 54% of cases, therapeutic hypothermia was not performed on 87% of neonates presenting with HIE. This is the first study published containing multicenter data on HIE in Latin America, and it demonstrates an urgent need for the implementation of programs to improve the quality of care available for newborns with neonatal encephalopathy. 

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