Original Article

Perinatal Events and Outcomes Associated with Hypoxic-Ischemic Encephalopathy in Thailand: A Multicenter, Observational Study

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Background: Risk factors for perinatal hypoxic-ischemic encephalopathy (HIE) differ across high- and low- or middle-income countries. Recent evidence from a randomized trial of therapeutic hypothermia (TH) suggests that the intervention should not be offered in the aforementioned countries because of higher mortality rates and associated morbidity.

Objective: To investigate characteristics of infants of 35 weeks or more gestational age (GA) born with HIE and determine the short-term outcomes of recipients of TH.

Materials and Methods: A multicenter, retrospective, chart review was conducted of infants with 5-minute Apgar scores of 5 or less admitted to the four tertiary centers in Thailand between 2013 and 2020. Events associated with perinatal hypoxia and outcomes were extracted.

Results: The incidence of perinatal HIE was 0.8 per 1,000 livebirths. Among 225 HIE infants, 46.2% had metabolic acidosis, 58.1% experienced hypoxic events, and 92.8% required advanced resuscitation. Among 123 infants who met TH criteria, 83 (67.5%) were treated. The overall HIE-related mortality rate was 24.9%. TH recipients had a lower mortality rate than untreated infants at 32.5% versus 52.5%, respectively (p=0.03) with a relative risk of 0.62 (95% CI 0.40 to 0.95). The findings were comparable to the reports from high-income countries.

Conclusion: To correctly select neonates for TH, increased HIE awareness, mandatory cord blood gas analysis, and country-wide dissemination of eligible criteria are necessary for timely intervention.

Keywords: Middle-income country; Encephalopathy; Risk factors; Hypoxic-ischemia; Therapeutic hypothermia

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Perinatal asphyxia is the leading cause of death in newborns, mostly in low- and middle-income countries (LMIC)[1-3]. In the middle-income countries, however, the incidence of intrapartum-related encephalopathy and neonatal mortality is declining[3,4], but the number with long-term neurological impairment remains problematic[3].

Therapeutic hypothermia (TH) is proven to improve outcomes in late preterm and term infants with moderate or severe hypoxic-ischemic encephalopathy (HIE)[5,6]. Robust meta-analyses of TH, conducted in high-income countries indicate a significant reduction in the combined outcome of mortality or neurological disability[6]. The recent randomized controlled HELIX trial conducted in South Asian countries, using modern devices and well-equipped supportive care, surprisingly found a significantly higher mortality rate in the TH group compared to the normothermia arm, without improvement in death or disabilities at 18 to 22 months[7]. These findings suggest that differences in demographic characteristics or sentinel intrapartum

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events among infants in LMIC could influence both the effectiveness of therapy and respective outcomes. Additionally, knowledge of the demographic characteristics of infants at-risk for HIE particularly in Southeast Asia (SEA) or other countries that have similar LMIC economic and health care systems is needed, to substantiate the incidence of HIE and factors associated with perinatal hypoxia.

The present study objectives were to evaluate the maternal demographic and intrapartum characteristics of infants 35 weeks and older gestational age (GA) who had low Apgar scores with associated HIE and determine short-term, hospital-related outcomes among TH recipients.

Materials and Methods

The present study was a retrospective, multi-center, observational study. The study protocol was approved by the Siriraj Institutional Review Board (CoA no. Si 586/2018 and Si 490/2021) and the local research ethics board of each institution participated in the study (the Institutional Review Board of Chonburi Hospital, no. 65/62/R/h1; the Lampang Human Ethics Research Subcommittee, no. 34/62, and the Ethic Committee of Sunpasitthiprasong Hospital, no.014/64C). Individual chart reviews were conducted on infants of 35 weeks or older GA with birth asphyxia based on the ICD-10 World Health Organization definition[8] admitted to a referral neonatal intensive care unit (NICU) over eight years, between January 1, 2013, and December 31, 2020. The institutions included The Siriraj Hospital in Bangkok in the Center of Thailand, and each represented one of the three tertiary regional centers of Lampang Hospital in the North, Sunpasitthiprasong Hospital in the Northeast, and Chonburi Hospital in the East of Thailand. The centers had established TH at different time points during the study period. The four hospitals accepted outborn infants and provided care for both low- and high-risk neonates. TH candidates were transferred to cooling centers by a referral team in the respective facilities. All infants of 35 weeks or older GA who had 5-minute Apgar scores of 5 or less were included in the present study[9,10]. Exclusion were infants whose complete medical records could not be retrieved and those with major congenital anomalies, to avoid bias in the latter at the level of administered care and related outcomes[11].

Definitions

Perinatal HIE was defined as infants with a 5-minute Apgar score of 5 or less combined with signs of encephalopathy graded by the Sarnat-Sarnat classification[12]. Incidences were estimated using the number of infants of 35 weeks or more GA who were liveborn at each of the study centers as a denominator[13]. The four study centers used the same inclusion criteria for TH adapted from the ICE trial and comprised 1) GA of 35 weeks or more and birth weight of 1,800 g or more, 2) signs of moderate or severe encephalopathy, and 3) at least two perinatal hypoxic-ischemic events as 10-minute Apgar score of 5 or less or two or more persistently low Apgar scores, positive-pressure ventilation after more than 10 minutes, umbilical cord or early blood gas at less than one hour after birth with metabolic acidosis, or intrapartum sentinel events[10].

Data of pre-specified antenatal and intra-partum risk factors associated with neonatal encephalopathy[14-16], physical examinations, and outcomes were extracted from the individual charts by the respective hospital co-investigators (NT, RA, UT, and TW), using a customized template.

Statistical analysis

Descriptive data was presented as frequency and percentage for categorical variables and as mean ± standard deviation (SD) or median [25th percentile (P25), 75th percentile (P75)] for continuous data according to the data distribution. Missing values were excluded from each variable analysis. Variables were compared using chi-square or Fisher's exact test for categorical variables, two-independent sample t-tests or Mann-Whitney U test for continuous variables. All statistical analyses were performed using PASW Statistics, version 18.0 (SPSS Inc., Chicago, IL, USA). A p-value of less than 0.05 was considered statistically significant.

Results

Over the eight years period, 176,087 infants were born at 35 weeks or older GA at the present study hospitals. Four hundred twenty-three infants had a 5-minute Apgar scores 5 or less or 2.4 per 1,000 live births, with a range of 1.6 to 4.1 per 1,000 live births, across the hospitals enrolled in the present study. After exclusion of 82 infants due to major anomalies and 149 infants with incomplete/unavailable medical records, 310 infants, including 192 inborn or 61.9% and 118 outborn or 38.1%, were included in the present study. Figure 1 outlines the recruitment for the present study. Clinical encephalopathy was documented in 225 infants, among which 137 infants or 60.9% were inborn. The incidence of perinatal HIE

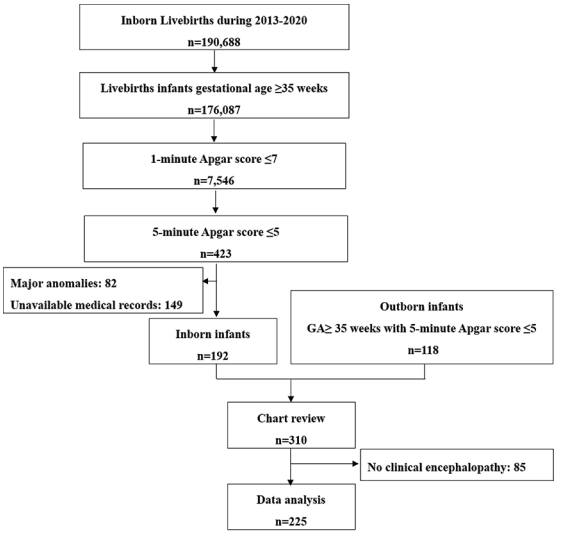

Figure 1. Flow chart of patient recruitment.

in infants born at 35 weeks or older GA, was 0.8 per 1,000 livebirths.

Table 1 and 2 shows the maternal and infants' demographic characteristics. Most mothers (88.8%) were Thai and 10.8% were from other SEA countries as Lao, Myanmar, and Cambodia. Thirty-six infants or 16% and 189 or 84% were 35 to 36 weeks and 37 weeksor older GA, respectively. Median [P25, P75] 5-minute Apgar scores were 4 [2, 5] and 97.3% were intubated during resuscitation at the time of birth.

Table 3 shows the characteristics and respective outcomes of infants that experienced perinatal HIE. One-hundred seventy-five infants (78.1%) had moderate or severe encephalopathy. Of noted, umbilical cord blood or early postnatal blood gas analysis was available in only 182 infants or 80.9%. Median [P25, P75] age of NICU admission was 1 [1, 2] and 3 [2, 4] hours for inborn and outborn infants, respectively. One-hundred twenty-three infants or 54.7%, met the present study eligibility criteria for TH, and it was provided in 83 or 67.5% infants.

Table 4 shows the characteristics of infants who met eligibility criteria for TH during the study period. Although TH was not available at every study center throughout the present study period, the overall characteristics of infants received or did not receive TH were similar, except for the 5-minute Apgar score (p=0.03), body length (p=0.002), and age of NICU admission (p<0.001). Protocol deviations for the receipt of TH occurred in 22 of the 105 infants was less than 1,800 g birth weight for one infant, mild degree of encephalopathy for five infants, no documented grade of encephalopathy for six infants, and less than three perinatal hypoxic events for ten

Table 1. Maternal demographic characteristics of infants with 5-minute Apgar score of ≤5 and clinical signs of encephalopathy across the four recruiting hospitals (n=224)

Factor	n (%)
Age (years); median [P25, P75]	28 [22, 33]
Nationality	
Thai	198/223 (88.8)
Other SEA countries	24/223 (10.8)
Received antenatal care	216/223 (96.9)
Primigravida	118/223 (52.9)
Multiple pregnancy	11/224 (4.9)
Pregnancy complications	
Diabetes	31/222 (14.0)
Hypertension	25/222 (11.2)
Antepartum hemorrhage	14/222 (6.3)
Intrapartum complications	
Abnormal fetal heart rate	95/222 (42.8)
Meconium-stained amniotic fluid	50/222 (22.5)
Shoulder dystocia	28/222 (12.6)
Rupture of membranes >18 hours	8/222 (3.6)
Maternal temperature >38°C	2/222 (0.9)
Intraamniotic infection	1/222 (0.5)
Emergency cesarean section	114/221 (51.6)
Non-emergency cesarean section	7/221 (3.2)

SEA=South-East Asian

Table 2. Demographic characteristics of infants 35-weeks' gestation or more with 5-minute Apgar score ≤5 and clinical signs of encephalopathy (n=225)

Factor	
Gestational age (weeks); mean±SD	38.1±1.6
Sex: male; n (%)	130/225 (57.8)
Inborn; n (%)	137/225 (60.9)
Age at NICU admission (hours); median [P25, P75]	1.5 [1, 3]
Birthweight (g); median [P25, P75]	3,000 [2,561.3, 3,325]
Small-for-gestational age; n (%)	26/224 (11.6)
Large-for-gestational age; n (%)	18/224 (8.0)
Body length (cm); median [P25, P75]	50 [48, 52]
Head circumference (cm); median [P25, P75]	33 [32, 34]
Apgar scores; median [P25, P75]	
1-minute	1 [0.25, 2]
5-minute	4 [2, 5]
10-minute	5 [4, 7]
Birth resuscitation; n (%)	
Positive-pressure ventilation	220/221 (99.5)
Intubation	215/221 (97.3)
Chest compressions	113/221 (51.1)
Medication(s)	88/221 (39.8)
Death; n (%)	56/225 (24.9)

SD=standard deviation; NICU=neonatal intensive care unit

Table 3. Characteristics and outcomes of infants 35-weeks' gestation or more with 5-minute Apgar score ≤5 and clinical signs of encephalopathy (n=225)

Factor	n (%)
Inborn	137/225 (60.9)
Birth weight ≥1,800 g	221/224 (98.7)
Perinatal hypoxic events	
Require positive-pressure ventilation >10 minutes	207/223 (92.8)
Sentinel events	125/215 (58.1)
Apgar score ≤5 at 10 minutes	120/216 (55.6)
Severe metabolic acidosis (pH <7.0 or base deficit >16)	84/182 (46.2)
Clinical signs of encephalopathy	
Alteration of consciousness	156/223 (70.0)
Hypotonia	156/223 (70.0)
Abnormal primitive reflexes	142/223 (63.7)
Seizures	111/225 (49.3)
Degree of encephalopathy	
Mild	33/224 (14.7)
Moderate	83/224 (37.1)
Severe	92/224 (41.1)
NICU admission within 6 hours	203/216 (94.0)
Clinical outcomes	
Non-invasive ventilation	30/221 (13.6)
Intubation	213/221 (96.4)
Intracranial hemorrhage	11/223 (4.9)
Therapeutic hypothermia	105/225 (46.7)
Length of hospital stay (days); median [P25, P75]	13 [7, 22]
Death	56/225 (24.9)

NICU=neonatal intensive care unit

infants. Of note, the mortality rate of infants that received TH was 32.5%, compared to 52.5% who did not (p=0.03) and the relative risk (95% CI) was 0.62 (0.40 to 0.95).

Discussion

The true national incidence, severity, and outcomes of infants with perinatal HIE is uncertain due to the lack of a uniform reporting system in Thailand and the continuous migration into the country. In the present study, the incidence of perinatal HIE was 0.8 per 1,000 live births, which was lower than the range reported by the developed countries that was 1 to 8 per 1,000 live births[3,13]. Although the authors recognized that the HIE incidence was underestimated due to inherent bias, the present study incidence is much lower than the 14.9 per 1,000 live births of the sub-Saharan Africa or the 10.4 per 1,000 livebirths in South Asia[3].

Overall demographic characteristics of the enrolled subjects were similar to clinical trials of TH in the developed countries. The present study rates of major complications were comparable to the control group of the National Institute of Child Health and Human Development trial[17], maternal age of 28 versus 27 years, maternal hypertension at 11.2% versus 13%, diabetes at 14% versus 8%,

Table 4. Characteristics of infants who were eligible and received therapeutic hypothermia (n=83) compared to non-recipients (n=40)

	Total (n=123)	No hypothermia therapy (n=40)	Hypothermia therapy (n=83)	p-value
Gestational age (weeks); mean±SD	38.0±1.7	38.3±1.61	37.9±1.7	0.22
Sex: male; n (%)	65/123 (52.8)	18/40 (45.0)	47/83 (56.6)	0.23
Inborn; n (%)	82/123 (66.7)	31/40 (77.5)	51/83 (61.4)	0.08
Age at NICU admission (hours); median [P25, P75]	2 [1, 3.5]	1 [0.6, 2.3]	2 [1, 3.5]	<0.001*
Birthweight (g); mean±SD	3,004.0±613.4	3,028.5±592.7	2,992.2±626.3	0.76
Small-for-gestational age; n (%)	11/123 (8.9)	1/40 (2.5)	10/83 (12.0)	0.09
Large-for-gestational age; n (%)	10/123 (8.1)	3/40 (7.5)	7/83 (8.4)	0.87
Body length (cm); median [P25, P75]	49.5 [48, 52]	50 [50, 53]	49 [47, 51]	0.002*
Head circumference (cm); median [P25, P75]	33 [32, 34]	34 [32, 34.5]	33 [32, 34]	0.21
Apgar scores; median [P25, P75]				
1-minute (n=123)	1 [0, 2]	1 [0, 1.8]	1 [0, 2]	0.23
5-minute (n=123)	3 [0, 4]	1.5 [0, 4]	3 [1, 5]	0.03*
10-minute (n=120)	4 [1.3, 6]	4 [0, 6]	5 [3, 6]	0.08
Birth resuscitation; n (%)				
Positive-pressure ventilation	122/122 (100)	40/40 (100)	82/82 (100)	-
Intubation	121/122 (99.2)	40/40 (100)	81/82 (98.8)	0.67
Chest compressions	75/122 (61.5)	27/40 (67.5)	48/82 (58.5)	0.34
Medication(s)	64/122 (52.5)	26/40 (65.0)	38/82 (46.3)	0.05
Severe encephalopathy; n (%)	77/123 (62.6)	26/40 (65.0)	51/83 (61.4)	0.703
Death before discharge; n (%)	48/123 (39.0)	21/40 (52.5)	27/83 (32.5)	0.03*

SD=standard deviation; NICU=neonatal intensive care unit

Criteria of therapeutic hypothermia included: 1) BW ≥1,800 g; 2) At least 2 out of the 3 criteria of intrapartum compromise (10-minute Apgar score ≤5 or positive-pressure ventilation at 10 minutes, severe acidosis, or sentinel events); 3) Seizures or signs of moderate to severe encephalopathy

* p<0.05, statistical significance

and antepartum hemorrhage at 6.3% versus 10 to 19%. The present study rate of maternal fever or intraamniotic infection was 1.4%, which was low compared to the clinical trials of TH with a range of 1.8% to 12%[10,17,18]. Meconium-stained amniotic fluid occurred in 22.5% of the present study subjects, while it was reported up to 29% in the neo.nEURO network randomized trial[19]. When compared to the HELIX trial, however, maternal characteristics in the present study cohort were different. The present study had higher rates of common pregnancy complications at 27.9%. In addition, the rates of meconium-stained amniotic fluid and maternal fever were lower in the present study at 22.5% versus 27% and 0.9% versus 2%, respectively, but the rate of cesarean section was much higher at 54.8% versus 23%.

Apart from maternal factors, the median infant birthweight was 3,000 g, which 11.6% were small for GA. This is comparable to the study from SEA[19], but slightly lower than approximately 3300g in studies[10,17,20]. Pertinent demographic characteristics were similar except for the number of inborn infants, which was one of the interesting factors related to the outcome[21]. Overall, 61% of the infants in the present study were inborn similar to the ICE and neo. nEURO network trials and higher than in the HELIX trial at 30%. The median time to NICU admission in the present study was 1.5 hours, and 94% of outborn infants were admitted to the referral hospitals within six hours of life. This is well within the golden, recommended period of six hours to initiate TH and positively influences the outcomes[21,22]. Although, it is difficult to accurately compare the incidence of risk factors associated with perinatal HIE across the countries due to variable study definitions, the overall baseline maternal and infant characteristics relating to outcomes show a similar trend between high- versus middle-income countries, but not similar to the HELIX trial.

Only 67.5% of the eligible infants in the present study cohort received TH, but this reflected a real-world, eight-year perspective. Nevertheless, the rate of TH in eligible infants has subsequently improved from 59.1% (58/88 infants), between 2013 and 2017 to 88.6% (31/35 infants) between 2018 and 2020 ($p<0.001$). General characteristics of the infants who met the eligible criteria for TH were not different between the groups who received and did not receive the treatment. The authors postulate that one reason for not receiving TH was unavailability immediately following birth rather than selective bias based on the infant's characteristics. Of note, more than 90% of the enrolled subjects who had abnormal neurological signs were clinically evaluated for TH. Umbilical cord or early blood gas analysis was performed in 182 infants or 80.9% of the present study cohort because it was inconsistently available[19], which had implications for the diagnosis of HIE. It is likely that offering TH to potential infants based on clinical status without biologic evidence of metabolic acidosis could lead to overuse of TH in the country. Eligible infants who received TH had a significantly lower risk of death before hospital discharge with a relative risk of 0.62 (95% CI 0.40 to 0.95), which was different from the HELIX trial. However, the difference in mortality favoring TH was due to the high mortality rate in non-TH recipients at 52.5%, which was 2-fold higher than the control group at 24% in the HELIX trial[7], while the mortality rate of TH recipients was similar at 32.5% versus 36%. The higher mortality rate in the present study was potentially due to disease severity at 65% versus 19% in the control group in the HELIX trial. The high proportion of cases with severe encephalopathy raises concern about whether physicians in the rural hospitals are aware that both moderate and severe degrees of encephalopathy qualify for TH. The authors speculate that the high mortality rate among infants who did not receive TH could be from early withdrawal of supportive treatment in infants with severe encephalopathy, but this awaits confirmation.

The present study average frequency of HIE across the four institutions is comparable to the Malaysian registry and the high-income countries. However, the range suggests that in parts of Thailand, the incidence is higher, and the availability of TH could lower mortality and long-term adverse sequelae and should not be prematurely abandoned as suggested by the authors of the HELIX trial[23-25] but needs conformation in well-executed prospective studies.

Individual chart review by neonatologists using specific definitions for each variable relevant in current practice, ensures internal validity of the present study results. Additionally, the authors included major referral hospitals in various parts of Thailand to minimize selection bias and afford country-wide generalizability of the findings. Nevertheless, limitations related to the retrospective chart review merit consideration. First, the authors were unable to identify maternal socioeconomic and nutritional status, which are reported risk factors for neonatal encephalopathy[15]. Second, variables, particularly for intrapartum events in outborn infants

were missing in 3.2%. Third, as previously addressed, an umbilical cord gas or arterial blood gas analysis within the first few hours of life was either unavailable in rural hospitals, or not considered part of the standard practice in most hospitals during the study period. However, the total number of recruited infants and the present study standardized, regional TH entry criteria analogous to the ICE trial, should partially compensate for these limitations and maintain the credibility of the present study results.

Conclusion

Maternal and infant demographic characteristics and intrapartum risk factors for perinatal HIE in Thailand are comparable to the published reports from high-income countries. To improve access to country-wide TH, strategies need to be implemented to raise awareness of the eligibility criteria for the therapy among obstetricians and allied perinatal health-care providers. Umbilical cord blood or early postnatal blood gas analysis should be mandatory to enhance recognition of HIE and facilitate timely transport of potential candidates for TH. Infants who received TH had a significantly lower mortality rate. The benefit of TH versus potential harm in the present study setting needs to be weighed judiciously and evaluated in future studies in high- or middle-income countries based on the recent sub-optimal results of the HELIX clinical trial.

What is already known on this topic?

TH reduces mortality or disability in late preterm and term infants with moderate or severe HIE in high-income countries.

The randomized trial conducted in South Asian countries found a significantly higher mortality rate in infants that received TH compared to the untreated group.

What this study adds?

Infants with moderate or severe HIE in Thailand who received TH had a significantly lower mortality rate. The findings are similar to the results of infants treated with TH in high-income countries.

Maternal and infant demographic characteristics and intrapartum risk factors for perinatal HIE are comparable to the published reports from high-income countries.

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Conflicts of interest

The authors report no conflicts of interest.

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