ORIGINAL ARTICLE

Hypoxic Ischemic Encephalopathy Indicators of Sarnat and Sarnat Scoring in Neonatal Subjects with Perinatal Asphyxia

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Abstract

Objectives

Hypoxic-ischemic encephalopathy (HIE) is still a relevant cause of neonatal mortality and morbidity. HIE severity can predict long-term outcomes. Sarnat staging is one of the most common methods used to evaluate HIE severity. However, an ongoing urge exists to find other accurate and affordable ways to accompany this clinical staging for HIE. This study aimed to evaluate the relationship between cerebral arteries' resistive indices and other hypoxic-ischemic encephalopathy indicators using Sarnat scoring of newborns subjected to perinatal asphyxia.

Materials & Methods

In this retrospective study, 76 neonates with gestational age ≥34 weeks affected with HIE were investigated. The patients were categorized into three groups according to Sarnat staging: I, II, and III. Initially, perinatal data were analyzed to assess the correlation between HIE severity and various factors such as gestational age, type of delivery, Apgar scores, necessity for resuscitation, and requirement for respiratory assistance. Notably, these relationships were significant.

Results

Examining various symptoms in different HIE stages showed that the incidence of coagulopathy was significantly higher in severe HIE neonates than in mild neonates. Eventually, proposedly, cranial arterial Doppler indices, i.e., the anterior cerebral artery's resistive index (RI), significantly differed between HIE stage groups.

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Conclusion

This study represented a combination of available and affordable data to achieve early HIE staging, including perinatal data, clinical symptoms, and a bedside Doppler ultrasonography of cerebral perfusion. Higher cranial artery RI was associated with severe HIE and could be considered for therapeutic hypothermia, which may reduce HIE mortality and morbidity.

Keywords: Cerebral Arteries, Hypoxia-Ischemia, Brain, Asphyxia Neonatorum, Sarnat Scoring
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Introduction

Perinatal asphyxia and its neurological manifestations, i.e., hypoxic - ischemic encephalopathy (HIE) is one of the major causes of neonatal mortality (15%-20%) and morbidity (30%), such as cerebral palsy, epilepsy, intellectual disability, and autism. The incidence of HIE ranges from 1.3 to 1.7 per 1000 live births in developed countries (1). Several risk factors cause perinatal asphyxia, including very young or old mother age, antepartum or intrapartum anemia, prolonged rupture of membranes, meconium-stained amniotic fluid, low birth weight (<2500 grams), multiple births, preeclampsia, fetal malpresentation, and labor augmentation with oxytocin (2, 3). Perinatal asphyxia causes not only neurological sequelae depending on the severity and duration of oxygen or blood flow reduction in the brain tissues but also damage to other organs , such as the kidney (35%), heart (20%), and even gastrointestinal organs (20%) (4). Using criteria to establish the severity of encephalopathy is necessary for evaluating the prognosis and implementing appropriate therapeutic interventions, such as therapeutic hypothermia for moderate to severe cases or supportive care, i.e., adequate ventilation and perfusion, fluid management, hypo- or hyperglycemia prevention, and seizures treatment (5). Therefore, HIE is graded as mild with no serious effects, moderate with 10-50% long-term neurological deficit, or severe with a 25-50% mortality rate and 80% chance of neurologic sequela. This grading mostly depends on brain tissue damage and is commonly achieved through Sarnat staging or Thompson score by assessing different aspects of the neurological examination (6-8). Because neonatal encephalopathy may worsen during the reperfusion phase, serial evaluations are required to determine the maximal degree of involvement. Therefore, this clinical HIE grading combined with other measures, e.g., electroencephalogram (EEG) and neuroimaging, such as brain magnetic resonance imaging (MRI), is used for estimating the severity and risk of adverse neurodevelopmental outcomes (9). Although these assessments are critical for clinical decision-makingand counseling parents,

the prognostic value of these measures may be modest, and most importantly, challenging to access, implement, or interpret. Hence, an affordable, accessible, portable, and quick method with no radiation exposure, such as cranial ultrasound, is the best initial investigation of choice in HIE, which could display distinguishing findings such as periventricular leukomalacia (PVL) and germinal matrix hemorrhage (GMH), or parasagittal watershed infarcts between anterior/middle cerebral artery and middle/ posterior cerebral artery in mild to moderate HI injury, and deep gray matter involvements, such as ventrolateral thalami, hippocampi, brainstem, corticospinal tracts, and sensorimotor cortex as metabolically active tissues in severe hypoxic-ischemic (HI) injury. Besides, progressive necrosis results in loss of periventricular white and passive ventriculomegaly (10). However, some of the limitations of cranial sonography are low sensitivity for detecting cortical lesions in severe cases and operator dependency.

On the other hand, considering the decrease of the resistive index (RI) , i.e., peak systolic minus end-diastolic velocity/peak systolic velocity as a measure of cerebral flow patterns — with increasing gestational age in normal neonates, transcranial Doppler ultrasound could help identify the increased RI of the middle cerebral artery (MCA) or anterior cerebral artery (ACA) as an indicator of intracranial pressure and brain death in severe HIE (11). Following asphyxia consequences, e.g., hypoxemia, hypercapnia, and acidosis, over the first few days of life, the brain blood flow velocity would change due to RI alterations as a compensatory response relating to poor neurological outcomes (12). However, as a vascular dynamics prognostic tool in HIE, RI sensitivity and specificity must be obtained through its relation with other hypoxic ischemic encephalopathy indicators. Therefore, this study aimed to evaluate the relationship between ACA RI values or other hypoxic-ischemic encephalopathy with Sarnat scores in newborns who experienced asphyxia at Qom Izadi Hospital throughout the study.

Materials & Methods

Study population

This retrospective cross-sectional study was based on the recorded files of the patients admitted to Izadi Educational Hospital, Qom University of Medical Sciences in Iran, for thirty months. The population of interest consisted of all neonates born at this center who suffered from asphyxia during birth, with inclusion criteria of diagnostic criteria for HIE, as follows neonates with abnormal neurologic behaviors, such as seizure, decreased muscle tone and altered state of consciousness that started during first hours of life, signs of multiple organ involvements (e.g., kidney, lungs, liver, heart, intestines) due to HIE, 1st or 5th minute after birth Apgar score ⩽5 or continued need for resuscitation and neonatal metabolic acidosis (umbilical artery or neonatal blood pH within the first hour after birth <7 and BE(base excess) less than .

The exclusion criteria were any neonatal pathologies: neonates with any chromosomal, congenital anomalies, congenital infections, hemolytic diseases, suspected metabolic diseases, hydrops fetalis, and severe sepsis with

hemodynamic disturbances.

Data collection and analysis

The data were collected from all the cases' files and summaries via retrospective chart review using particular forms that were designed for this purpose, including demographic data, e.g., sex, gestational age, birth weight, delivery method, perinatal death, resuscitation or mechanical ventilation requirement, Apgar scores at 1 and 5 minute, neonatal neurologic signs (e.g., seizures, altered state of consciousness, hypotonia), multiple organ involvement (e.g., kidney, lungs, liver, heart, and adrenal gland) consistent with laboratory data, e.g., blood gas evaluation, liver enzyme test, or echocardiographic reports, and other imaging findings (abdominal and brain ultrasonographic data on adrenal hemorrhage and cerebral edema or hemorrhage, respectively). Besides, RI values were collected using Doppler ultrasound.

Sarnat and Sarnat staging (modified one used shortly after birth) was applied to evaluate HIE severity, providing the best correlation with long-term outcomes. This clinical method described three stages of encephalopathy based on several examinations as follows: level of consciousness, muscle tone, simple stretch reflexes or complex reflexes such as sucking and Moro autonomic function, i.e., pupil status (mydriasis or miosis) or heart rate, breathing pattern, gastrointestinal motility, e.g., diarrhea, and seizures. Infants who continue in the Sarnat stage I generally recover with normal neurologic function within a day or two. Sarnat stage II may last up to two weeks of age with a 20% to 35% risk of neurologic deficits later on. Sarnat stage III may last hours to weeks, with a high mortality rate and neurologic impairments in nearly all survivors.

Data were analyzed using SPSS V25 and R-4.1.0 software. T-test and Chi-square test were used to compare the variables between study groups. ROC curve and AUC were used to assess the accuracy of RI compared to Sarnat staging. This study used the Youden index to find the optimal threshold.

Results

In this analytical cross-sectional study, 76 newborns with HIE and gestational age≥35 weeks admitted to Qom Izadi Hospital during 30 months were categorized into three groups according to Sarnat clinical staging for HIE: stage I, II, and III with 35, 32, and nine newborns in each group, respectively. The overall incidence of HIE in the years under study was 34.43 per 10,000 live births. Due to the small number of newborns in the 3rd stage group, most statistical comparisons were performed between the first and second stages.

Table 1 demonstrates no significant difference between birth weight and HIE severity staging using a t-test (P= 0.706). Similarly, the gestational age difference was insignificant among HIE stage groups (P=0.124).

Table 2 represents gender and type of delivery distribution among newborns with HIE. According to the chi-square test, there was no significant difference in the context of the percentage boys versus girls with the HIE stage (P=0.515). Likewise, there was no significant relation between the HIE stage and type of delivery (p=0.628). Of the three newborns in the third group, two were born by emergency cesarean section, and one was born by NVD.

Table 1: Birth weight and gestational age in different Sarnat stages of HIE patients (N=76). These quantitative data are presented as mean ± standard deviations.

Variable	HIE stage	Number	Mean	Std. Deviation	P-value
Birthweight (gram)	Stage I	35	3175.71	654.86	0.706
	Stage II	32	3029.22	796.15	
	Stage III	9	3188.89	1055.57	
Gestational age (week)	Stage I	35	38.20	2.29	0.124
	Stage II	32	37	3.45	
	Stage III	9	36	5.22	

Table 2: Gender and type of delivery distribution in different HIE stage groups. NVD= normal vaginal delivery

HIE stage Male Female			Sex		Delivery			
			NVD	Vaginal with instrument	Elective cesarean	Emergency cesarean section		
	Stage I	Count	21	14	12	2	8	13
		Percent	60%	40%	34.3%	5.7%	22.9%	37.1%
	Stage II	Count	21	11	8	4	8	12
		Percent	65.6%	34.4%	25.0%	12.5%	25.0%	37.5%
	Stage III	Count	4	5	5	0	2	2
		Percent	44.4%	55.6%	55.6%	0.0%	22.2%	22.2%
Total		Count	46	30	19	6	13	25
Percent		60.5%	39.5%	30.2%	9.5%	20.6%	39.7%	
P-value			0.515		0.628			

Table 3: First and 5th minutes after birth Apgar score and resistance index based on different HIE severity groups. These data are presented as mean and standard deviations.

Variable	Stage	N	Mean	Std. Deviation	p-value
Apgar1	I	34	6.76	1.970	0.003
	II	29	5.172	2.139	
Apgar5	I	34	8.29	1.243	0.008
	II	29	7.24	1.805	
RI	I	34	0.68	.080	0.015
	II	29	0.74	.084	

Table 4: Comparison of the outcomes and symptoms in different HIE stage groups

Variable		Stage						p-value
	I		II		III			
	Count	Percent	Count	Percent	Count	Percent		
Resuscitation	No	17	48.6%	6	18.8%	0	0	0.003
	Yes	18	52.9%	26	81.3%	9	100	
Ventilation support	No	10	28.6%	5	15.6%	0	0	0.118
	Yes	25	71.4%	27	84.4%	9	100	
Adrenal hemorrhage	No	35	100.0%	27	84.4%	7	77.8	0.031
	Yes	0	0.0%	5	15.6%	2	22.2	
Elevated liver transaminase	No	26	76.5%	17	54.8%	3	33.3	0.033
	Yes	8	23.5%	14	45.2%	6	66.7	
Renal failure	No	32	91.4%	30	93.8%	3	33.3	<0.001
	Yes	3	8.6%	2	6.3%	6	66.7	
Tricuspid valve regurgitations	No	11	57.9%	13	43.3%	4	44.4	0.591
	Yes	8	42.1%	17	56.7%	5	55.6	
Thrombocytopenia	No	28	80%	25	78.1%	2	22.2	0.002
	Yes	7	20%	7	21.9%	7	77.8	
Prolonged PT, PTT	No	23	95.8%	18	66.7%	3	33.3	<0.001
	Yes	1	4.2%	9	33.3%	6	66.7	
Brain edema	No	18	51.4%	9	28.1%	1	11.1	0.033
	Yes	17	48.6%	23	71.9%	8	88.9	
Brain hemorrhage	No	34	97.1%	28	87.5%	6	66.7	0.026
	Yes	1	2.9%	4	12.5%	3	33.3	

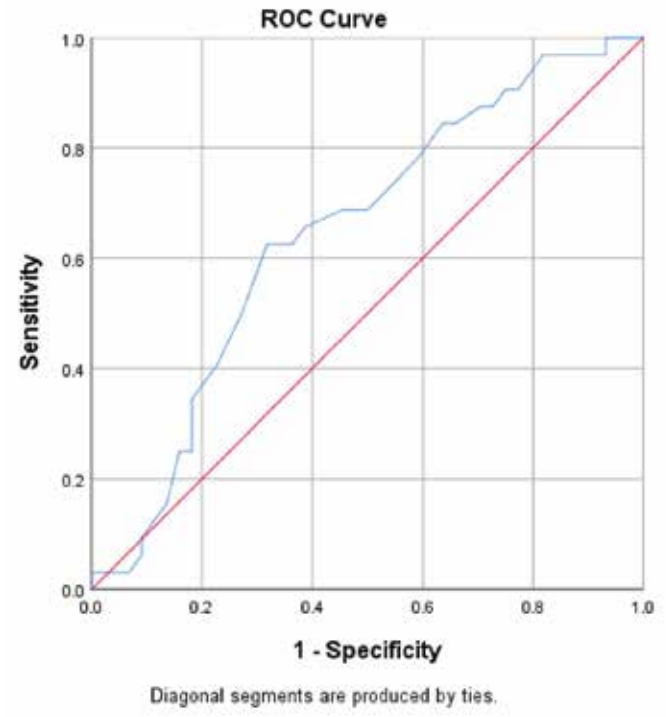

Fig 1. *ROC curve of the cranial arterial resistive index for the discriminating between grade I and grade II of HIE.*

Table 3 implies Apgar scores 1 and 5 minutes after birth in study groups, which both were significantly different in neonates with various HIE stages, according to the t-test (P=0.003 and 0.008, respectively). Additionally, the study groups' cerebral flow patterns and intracranial pressure were assessed using the ACA RI, collected via cranial Doppler ultrasound within the first three days after birth. T-test shows a significant RI difference among HIE severity stage groups (P=0.015). The mean of the first and 5th minutes of Apgar score in the third group were 5.8±2.32 and 7.74±1.65, respectively. The resistive index in the third group was 0.65±0.116.

Table 4 illustrates other outcomes and symptoms in different HIE stage groups. These symptoms included seizure, internal organ damage such as adrenal hemorrhage, renal failure, tricuspid valve insufficiency, and hepatic damage detected by increased liver enzymes, i.e., AST and ALT (aspartate and alanine aminotransferase) or hepatic dysfunction leading to coagulopathy traced by prolonged PT and PTT (prothrombin and partial thromboplastin time) and even hemostatic defects e.g. thrombocytopenia. A significant difference was observed in the need for resuscitation among HIE stage groups, according to the chi-square test. Also, brain imaging data collected by head ultrasound in the first three days after birth shows that cerebral edema incidence significantly varies in different HIE severity groups. However the need for ventilation support and tricuspid valve regurgitations did not significantly change in different HIE stages.

This study performed ROC curve analysis to assess how well the RI can discriminate between grade I and grade II of HIE (Fig 1). The area under the curve was 0.646 (95% CI, 0.521-0.771). Based on the Youden index, the best cutoff point for RI was 0.725. The best cutoff of 0.725 gave a sensitivity of 62.5%, a specificity of 74.3%, an accuracy of 68.7%, a positive predictive value of 68%, and a negative predictive value of 68.4% with nine false positives and 12 false negatives.

Based on multiclass ROC analysis, the area under the curve of RI for the discriminating between grades I to III of HIE was 0.608.

Discussion

The present study represents 76 newborns with HIE admitted to Qom Izadi Hospital, categorized according to the Sarnat HIE scoring system.

At first, we investigate the relationship between some perinatal data and Sarnat scoring in our study population. There was no significant difference in birth weight, gestational age, delivery methods, or gender among different HIE groups. However, the relationship between HIE severity and Apgar score or need for resuscitations was significant. HIE happens mostly in premature neonates who are delivered by instrument through NVD or the ones with low Apgar scores in need of neonatal resuscitation. Consistent with these data, lower gestational ages are supposed to be accompanied by increased suboptimal neurodevelopmental incidences (13). Besides, newborns who went through ventouse and forceps delivery were more susceptible to HIE versus C/S delivered babies (14). In a study on Apgar scoring in determining HIE, all stage III neonates had a 1st-minute Apgar score of 0-3, whereas stage I neonates had a 4-5 score (15). Contrary to this study, male HIE-induced

mouse models have shown larger infarct size and brain tissue loss and more behavioral deficits than females during the chronic phase of HIE, not in the primary injury phase (16). On the other hand, investigating HIE risk factors in a US birth cohort study, there is no report on the relationship between birth weight and HIE severity (17).

Secondly, the current study examines and record various symptoms in different HIE stages. Incidence of Adrenal hemorrhage was significantly higher in severe HIE neonates compared to mild ones. However, the percent of tricuspid valve regurgitations did not significantly change in different HIE stages.

The present study shows that, in assessing the neurological status of HIE babies, the ischemic damage to kidneys, known as acute renal failure rate, was higher in greater ischemic encephalopathy degrees. Correspondingly, Serum creatinine levels correlate with the severity of HIE of neonates according to Sarnat scoring and brain imaging results (18). Contrary to the obtained results, previous studies show that tricuspid valve regurgitation as a marker of myocardial ischemia during cardiovascular disturbances in severe hypoxia was found to be in correlation with HIE severity and even mortality (19).

As shown in this study, liver functional defects leading to coagulopathies related to prolonged PT, PTT, or thrombocytopenia may be in correlation with HIE severity. However, elevated liver transaminase as evidence of hepatocyte injury was irrelevant to HIE severity. In contrast to these findings, studies have detected that elevation of liver aspartate and alanine transaminases, i.e., ASTand ALT in perinatal asphyxia, was proportional to the severity of hypoxia (20).

Ultimately, brain imaging data using head ultrasound have shown that intracranial hemorrhage (ICH) incidence significantly varies in different HIE severity groups. ICH is due to rupture of the germinal matrix fragile capillaries, whereas hypoperfusion may cause infarction of the boundary zones between different arterial territories within the periventricular white matter. According to the obtained results, studies suggest that all hemorrhages except cephalhematoma increased with the severity of HIE staging (21). However some literature has found that brain edema associated with HIE happens apart from hypoxia severity (22, 23). Moreover, the cranial Doppler ultrasound findings demonstrated significant RI difference as a measure of cerebral flow pattern and intracranial pressure among HIE severity stage groups. Consistent with the present results, using Doppler sonography or even MRI, RI indices were reported to be higher in severe HIE cases (24). Some literature even introduced color Doppler ultrasound as an early diagnostic tool for HIE staging (24). They suggest that cranial arterial Doppler indices are more associated with HIE severity and neuromotor outcomes than cranial ultrasonographic data (25), which is in line with the present study's findings.

In Conclusion

we represent some perinatal data and symptoms along with a targeted bedside measure of cerebral perfusion as available and affordable ways of early HIE staging. Using this handy method assessing RI of cerebral arteries along with consideration of Sarnet staging (based upon clinical symptoms)

may help early detection of severe cases in need of therapeutic hypothermia and hopefully would lessen HIE mortality and morbidities.

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Author's Contribution

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Conflicts of interest

The authors have no conflicts of interest to declare.

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