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Evaluation of Cardiovascular and Pulmonary Dysfunction in Hypoxic Ischemic Encephalopathy Neonates

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Abstract: ***Background:*** Perinatal asphyxia is one of the leading causes of neonatal mortality and morbidity worldwide and the outcomes of hypoxic ischemic encephalopathy (HIE) are devastating and permanent, making it a major burden for the family and society. ***Objective:*** To assess cardiovascular and pulmonary function in hypoxic ischemic encephalopathy neonates. ***Materials and methods:*** This cross-sectional type of descriptive study was conducted in the Department of Pediatrics at Rajshahi Medical College Hospital, Rajshahi over a period of 2years from July 2021 to June 2023. The study was conducted after obtaining ethical clearance from the Institutional Review Board (IRB) of Rajshahi Medical College and consent from the guardian of patients. Based on predefined eligibility criteria, a total number of 70 neonates with HIE stage II and III were included in this study. ***Results:*** Out of 70 hypoxic ischemic encephalopathy neonates, 55.70% neonates had stage-II and 44.30% had stage-III hypoxic ischemic encephalopathy. Mean age of the neonates was 10.81±8.08 hours, about 68.60% were male and 31.40% were female. Most of the neonates 71.43% had pulmonary dysfunction, 57.10% had cardiovascular dysfunction. ***Conclusion:*** There was statistically significant cardiovascular and pulmonary dysfunction ($p< 0.001$) as well as significant difference between the stage II and stage III hypoxic ischemic encephalopathy neonates in terms of cardiovascular and pulmonary ($p< 0.05$) dysfunctions.

Keywords: Hypoxic ischemic encephalopathy, pulmonary function, cardiovascular system.

Original Research Article

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Article at a glance:

Study Purpose: *To assess cardiovascular and pulmonary function in hypoxic ischemic encephalopathy neonates.*

Key findings: *Out of 70 HIE neonates, 57.10% required inotrope and 42.90% did not require inotrope. These 40 (57.10%) neonates required inotrope for > 24 hours to maintain blood pressure within the normal range. On the other hand, 60.00% required O2 via nasal plus head box, 28.57% required O2 only via nasal and 11.43% required O2 via CPAP. Most (71.43%) of the neonates had pulmonary dysfunction, 57.10% had cardiovascular dysfunction.*

Newer findings: *Consistent with previous studies but relationship between age of neonates on admission and stage of hypoxic ischemic encephalopathy was found statistically highly significant $p < 0.001$). Delay in admission potentiates organ dysfunctions.*

Abbreviations: *HIE- Hypoxic ischemic encephalopathy, CPAP- Continuous Positive Airway Pressure.*

INTRODUCTION

Neonate is a baby from birth to first 28 days of life. Out of the 8.2 million under-five child deaths per year, about 2.4 million occur during the neonatal period globally. The majority (almost 3 million of these) die within 1st week .[1] Perinatal asphyxia is a notable cause of mortality in

newborns and causes neurodevelopmental disability in infancy and childhood, especially in low-income and middle-income countries. [2] When hypoxia is the cause of neonatal encephalopathy, a clinical syndrome has been described known as hypoxic ischemic encephalopathy (HIE). [3] HIE is a type of neonatal encephalopathy caused by systemic hypoxemia and/or reduced cerebral blood flow resulting from an acute peripartum or intrapartum event. It is a condition that can cause significant mortality and long-term morbidity. HIE can be a clinical consequence of prenatal, birth and/or postnatal asphyxia. [4] HIE in term neonate occurs at a rate of about three per thousand live-born neonates in developed countries, but the rate is estimated to be higher in the developing world. [5] Low APGAR score (AS) that is an indirect clinical marker for hypoxic-ischemic events and low cord blood pH which if present either alone or in combination with features of encephalopathy are taken to imply the occurrence of HIE.[4]

Perinatal hypoxic ischemic encephalopathy insults are frequently accompanied by multiorgan system involvement. Although cerebral injury is the most concerning consequence, myocardial dysfunction may also contribute to postnatal neurological impairment and exacerbate other organ damage.[6] The cardiovascular determinants of cellular homoeostasis rely on the distinctive interface between myocardial performance, end-organ perfusion and tissue oxygen delivery and consumption. Perturbations to the cardiovascular system in neonates with hypoxic ischemic encephalopathy (HIE) can include myocardial damage, right ventricular (RV) dysfunction and altered transitional circulation.[7] The pulmonary effects of hypoxic ischemic encephalopathy include increased pulmonary vascular resistance, pulmonary hemorrhage, pulmonary edema secondary to cardiac failure and possibly failure of surfactant production with secondary hyaline membrane disease. Chest X-ray is used to define as any one of the following features pulmonary infiltrates, patchy hyperinflation and atelectasis, air leaks, loss of lung volume, ground glass appearance or white out lungs. In this situation ventilatory support is needed to maintain oxygen requirement > 40% for at least the first 4 hours after birth.[8] The study might be helpful for general physicians and pediatricians in their day-to-day management of hypoxic ischemic encephalopathy neonates.

Objective

To assess cardiovascular and pulmonary function in hypoxic ischemic encephalopathy neonates.

METHODOLOGY

This was a cross-sectional type of descriptive study done in the Special Care Newborn Unit (SCANU) and neonatal unit in Department of Pediatrics, Rajshahi Medical College Hospital, Rajshahi. This study was conducted over a period of 2 years from July 2021 to June 2023. Neonates with hypoxic ischemic encephalopathy (stage-II and stage-III) aged up to 48 hours were included in the study. Full term neonates whose gestational age ranged from 37 to 42 weeks, 0 to 48 hours of age, birth weight ≥ 1800 gm., HIE stage-II and stage-III neonates according to Modified Sarnat and Sarnat staging were included. Exclusion criteria were neonates with major congenital anomalies or clinical condition (dysmorphism, Meconium aspiration syndrome, TORCH infection, Imperforated anus, inborn error of metabolism), any major illness other than hypoxic ischemic encephalopathy, hospitalization due to birth injury, mother or father of neonate who did not give consent to participate in the study. Sample size was determined using single proportion estimate formula (Hague, 2009) and minimum sample size at 5% level of significance. Purposive sampling technique was employed to include the required number of stage II and stage III hypoxic ischemic encephalopathic neonates. Before the starting of the study, a questionnaire was prepared according to the objectives of the study. Data related to the maternal medical history, obstetric history, intrapartum details, details history of the resuscitation were recorded. Through physical examinations of the newborn were carried out and findings were noted on the questionnaire. The neurological conditions of the infant were examined and recorded soon after arrival at the hospital. The initial and subsequent neurological data included level of consciousness, presence of spontaneous movements and coma, altered muscle tone, the age at onset of seizures (subtle or tonic-clonic) and number and dosage of anticonvulsants

received were recorded. This information along with a clinical description of the attending team was considered for determination of the degree of encephalopathy which was classified according to the criteria by Modified Sarnat and Sarnat within 48 hours of birth. Data were collected using a semi-structured questionnaire (research instrument) and analyzed by using the 'Statistical Package for Social Sciences (SPSS) software, 24-version. Categorical variables were summarized by using numbers and percentages while continuous variables were summarized by means and standard deviation (SD). A chi-square test was used to see the relationship of organ dysfunctions between stage II and stage III hypoxic ischemic encephalopathy neonates. A p-value < 0.05 was considered statistically significant for all tests.

RESULTS

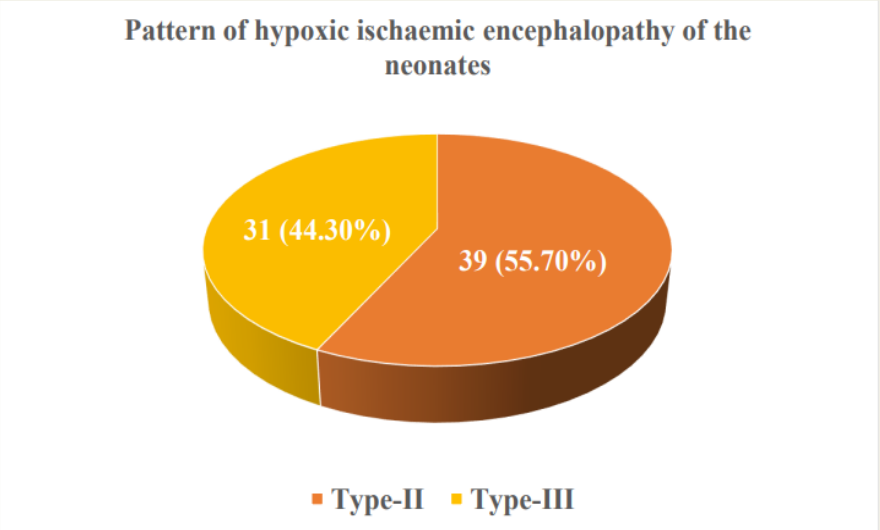

Figure 1: Pattern of hypoxic ischemic encephalopathy of the neonates (n=70)

More than half (55.70%) of the neonates were type-II and 44.30% were type-III hypoxic ischemic encephalopathy neonates (Figure 3).

Table 1: Organ dysfunctions of hypoxic ischemic encephalopathy neonates (n=70)

Organ dysfunction	Category	Frequency	Percentage
Cardiovascular dysfunction	Present	40	57.10%
	Absent	30	42.90%
Pulmonary dysfunction	Present	50	71.43%
	Absent	20	28.57%

Most (71.43%) of the neonates had pulmonary dysfunction, 57.10% had cardiovascular dysfunction

Table 2: Distribution of hypoxic ischemic encephalopathy neonates by their cardiovascular function (n=70)

Cardiovascular Function	Category	Frequency	Percentage
Requirement of inotrope	Yes	40	57.10%
	No	30	42.90%
Total		70	100%
Duration of inotrope use > 24 hours		40	57.10%

Out of 70 hypoxic ischemic encephalopathy neonates, 57.10% required inotrope and 42.90% did not require inotrope. These 40 (57.10%) neonates required inotrope for > 24 hours to maintain blood pressure within the normal range (Table 1).

Table 3: Distribution of hypoxic ischemic encephalopathy neonates by their pulmonary dysfunction (n=70)

Pulmonary Function	Frequency	Percentage
O2 requirement via only nasal	20	28.57%
O2 requirement via nasal and head box	42	60.00%
O2 requirement via CPAP	08	11.43%

Out of 70 HIE neonates, 60.00% required O2 via nasal plus head box, 28.57% required O2 only via nasal and 11.43% required O2 via CPAP (Table 3)

Table 4: Relationship of cardiovascular and pulmonary dysfunctions between stage II and stage III hypoxic ischemic encephalopathy neonates (n=70)

Organ dysfunctions		Group			
		HIE stage II	HIE stage III	p value	Significant level
		Frequency			
Cardiovascular dysfunction	Present	13 (33.30%)	27 (87.10%)	<0.001	S
	Absent	26 (66.70%)	4 (12.90%)		
Pulmonary dysfunction	Present	20 (40.00%)	30 (96.80%)	<0.001	S
	Absent	19 (48.70%)	1 (3.20%)		

Among stage II hypoxic ischemic encephalopathy neonates 33.30 and 40.00% developed cardiovascular and pulmonary dysfunctions respectively. On the other hand, among stage III hypoxic ischemic encephalopathy neonates, 87.10 and 96.80% developed cardiovascular and pulmonary dysfunctions respectively. There was statistically significant difference between the stage II and stage III hypoxic ischemic encephalopathy neonates in terms of cardiovascular, pulmonary dysfunctions ($p < 0.001$ for each organ)

Table 5: Relationship between age of neonates on admission and stage of hypoxic ischemic encephalopathy (n=70)

Age of neonates on admission	Pattern of hypoxic ischaemic encephalopathy		Total Frequency (%)
	Stage II Frequency (%)	Stage III Frequency (%)	
< 24 hours	38 (97.40%)	20 (64.50%)	58 (82.90%)
≥ 24 hours	1 (8.30%)39 (55.70%)	11 (91.70%)	12 (17.10%)
Total	39 (55.70%)	31 (44.30%)	70 (100%)

$\chi^2 = 13.18$, df=1, $p < 0.001$

Among 58 neonates who came in hospital < 24 hours, 97.40% developed stage II and 64.50% developed stage III hypoxic ischemic encephalopathy. On the other hand, among 12 neonates who came in hospital ≥ 24 hours, 91.70% developed stage III and 8.30% developed stage II hypoxic ischemic encephalopathy.

DISCUSSION

Hypoxic ischemic encephalopathy (HIE) is a serious neurological complication that may develop in asphyxiated infants. Severity of encephalopathy may vary and concurrent multiple organ dysfunctions are commonly observed. The aim of this study was to evaluate immediate organ dysfunction in hypoxic ischemic encephalopathy neonates. In this study (Fig.1), more than half (55.70%) of the neonates were type-II and 44.30% were type-III hypoxic ischemic encephalopathy neonates. Nearly similar findings were found in a study done by Ashraf, (2017) where 66.7% were stage-II and 33.3% were stage-III hypoxic ischemic encephalopathy neonates (Ashraf, 2017).[9] But our findings were not similar with a study done by Shah et al., (2014), where 27.58% belonged to HIE grade II out of 56.8% of babies with HIE. [10]

Dissimilar findings were found with the study done by Debnath et al., (2021).[11] In this study, there was statistically significant difference between the stage II and stage III hypoxic ischemic encephalopathy neonates in terms of cardiovascular, pulmonary dysfunction ($p < 0.05$).
In the present study (Table-1), 57.10% of the neonates had cardiovascular dysfunction. Similar finding was found in a study done by Pattar et al., (2015) where cardiovascular involvement was in 54.3% neonates.[12] Similar findings were also found with the studies done by Singh and Sengar, (2016), Michniewicz et al., (2021) and Shah et al., (2004).[13, 14, 15] But this finding was not similar with a study done by Ashraf, (2017) where 25.60% neonates had cardiovascular dysfunction.

Dissimilar findings were also found with the studies done by Vemuri et al., (2015) and Hankins et al., (2002).[16, 17] Pulmonary dysfunctions found in 71.43% of the neonates. This finding was similar with the study done by Ashraf, (2017) where 71.8% neonates had pulmonary dysfunction. Similar findings were also found with the studies done by Shah et al., (2014), Linderkamp et al., (1978) and Shah et al., (2004).[10,13,18] But findings were not similar 62 with a study done by Singh and Sengar, (2016) where respiratory system was affected in 44.2% asphyxiated neonates [14]. Dissimilar findings were also found with the studies. [8, 19, 20]
Cardiovascular dysfunction reflects in 57.10% required inotrope and 42.90% did not require inotrope. These neonates required inotrope for > 24 hours to maintain blood pressure within the normal range (Table-2). Pulmonary dysfunction reflects in 60.00% required O_2 via nasal plus head box, 28.57% required O_2 only via nasal and 11.43% required O_2 via CPAP (Table-3) to maintain SPO_2 at >94%. The cardiovascular response to asphyxia involves redistribution of cardiac output to maintain oxygen delivery to critical organs such as the adrenal gland, heart and brain, at the expense of other organs such as the gut, kidneys and skin. This results in reduced perfusion and localized hypoxia/ischemia in these organs, which if severe, can result in multi-organ failure. Current clinical therapies need to be considered together with therapeutic hypothermia and cardiovascular recovery.

Table 5 showed the relationship between age of neonates on admission and stage of hypoxic ischemic encephalopathy. Among 58 neonates who came in hospital < 24 hours, 97.40% developed stage II and 64.50% developed stage III hypoxic ischemic encephalopathy. On the other hand, among 12 neonates who came in hospital ≥ 24 hours, 91.70% developed stage III and 8.30% developed stage II hypoxic ischemic encephalopathy. So, the relationship between age of neonates on admission and stage of hypoxic ischemic encephalopathy was found statistically highly significant $p < 0.001$).

CONCLUSION

Neonates with HIE commonly present with perinatal asphyxia and have long-term consequences and multiple organ dysfunctions. Results of the study indicated that pulmonary and cardiovascular systems were commonly affected. There was statistically significant relationship of age on admission and development of multi organ dysfunction of neonates with stage of hypoxic ischemic encephalopathy ($p < 0.001$ and $p < 0.01$, respectively). The spectrum of multiple organ dysfunctions emphasized the need of immediate management of asphyxiated neonates. Early assessment of clinical and biochemical profile would be helpful in managing the condition, reducing severity and improving the outcome of illness.

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Authors' contributions

BT, BA, RP: Concept and design, data acquisition and interpretation, drafting and final approval. MBH, IH, MS: Data acquisition, interpretation, drafting, final approval and agree to

be accountable for all aspects of the work. SA: Co guide, BU: Principal guide.

Declarations

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Conflict of interest

There was declared no conflict of interest of the authors.

Ethical approval

Ethical approval of the study was obtained from the Ethical Review Committee, BSMMU, Dhaka. The ethical issues were informed and addressed for future development of management to the participants' parents. Verbal consent had been given by the parents of the affected children.

Consent for publication: Taken.

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