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Original Research Article

Biochemical Markers of Birth Asphyxia in Neonates and Its Outcome

Prahlad Prasad Gupta[1*], Amrita[2], Sude Kumar Singh[3]

[1]Associate Professor, Department of Biochemistry, Darbhanga Medical College & Hospital, Laheriasarai, Bihar

[2]Tutor, Department of Biochemistry, Darbhanga Medical College & Hospital, Laheriasarai, Bihar

[3]Professor and Head of Department, Department of Biochemistry, Darbhanga Medical College & Hospital, Laheriasarai, Bihar

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Corresponding Author: Dr. Sude Kumar Singh

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Abstract:

Background: Due to unattended deliveries in rural regions, perinatal asphyxia contributes for over 29% of newborn mortality in developing countries. Even with following the recommended standards, the majority of deliveries have unsatisfactory results. This study aims to investigate the various clinical manifestations of birth asphyxia and associated biochemical derangements.

Methods: This prospective study, which included 58 term neonates admitted to the neonatal intensive care unit with definite histories suggestive of perinatal hypoxic insult, was carried out from February 2023 to July 2023 in the Department of Biochemistry in collaboration with the Department of Pediatrics, DMCH, Laheriasarai, Bihar. Microsoft Excel Ver. 20 software was used to analyze the collected history, clinical characteristics, and pertinent investigations (random blood sugar, serum creatinine, blood urea, and serum electrolytes).

Results: In every stage, vaginal births were more prevalent. All newborns, with the exception of those with hypoxic-ischemic encephalopathy (HIE) I, had abnormal neonatal reflex. All HIE II neonates had convulsions, primarily multifocal seizures, whereas only 22.2% of HIE III babies experienced seizures. HIE III patients had oliguria (77.8%) and congestive heart failure (55.17%), and 22 cases (37.9%) experienced acute kidney damage. As the degree of hypoxia increased, hypoglycemia was seen (HIE III 26.67 ± 2.78). In HIE III, serum urea, creatinine, and potassium increased considerably whereas sodium and calcium decreased.

Conclusion: Clinical and supporting laboratory markers together can be utilized to monitor patients and direct early intervention to reduce morbidity and mortality.

Keywords: Birth asphyxia, Biochemical markers, Hypoxic ischemic encephalopathy, Neonates.

Introduction

One of the main causes of newborn morbidity and mortality in underdeveloped nations is perinatal asphyxia, often known as birth asphyxia[9]. In addition to saving neonates' lives, effective neonatal resuscitation also helps to avoid long-term neurological consequences. In India, perinatal asphyxia accounts for 45.1% of stillbirths and 28.8% of neonatal deaths [5].

Hypoxia (lack of oxygen) or inadequate perfusion (ischemia) to different organs in the fetus or infant is the results of perinatal asphyxia. A combination of hypoxia, hypercarbia, and metabolic acidosis brought on by placental insufficiency during pregnancy, obstruction of the umbilical arteries, or inadequate breathing following delivery is known as birth asphyxia [4,7]. It causes a variety of functional and/or physiological alterations in the fetus or baby, either during the antepartum, intrapartum, or both periods. The most frequent avoidable cause of harm to the central nervous system (CNS) in newborns is birth asphyxia, which shields them from long-term neurological abnormalities and disabilities [6].

In poor nations, an estimated 3.6 million newborns have mild to severe birth asphyxia. Approximately 840,000 infants (23%) pass away or may experience severe neurological consequences [10]. When it comes to prenatal asphyxia, prevention is more crucial than treatment. Neonatal asphyxia is largely caused by maternal causes, such as protracted labor, gestational diabetes, antepartum hemorrhage, hypertension, and multiple pregnancies [9]. Approximately 60% of HIEs are caused by the protracted second stage of labor, which can be avoided with proper institutional design, access to trained medical staff, and facilities for operational deliveries when needed [1,8]. Post-dates, chord around the neck, oligohydramnios, meconium-stained amniot-

ic fluid (MSAF), malpresentation, etc. are some of the neonatal risk factors for birth asphyxia (HIE) [8].

The outcome of these HIE newborns is significantly influenced by the serum electrolyte level. Any variation from the standard electrolyte (sodium, potassium, and calcium) levels can cause shock, convulsions, and other metabolic disorders. A baby's prognosis is negatively impacted by perinatal asphyxia because it causes anaerobic metabolism, decreased adenosine triphosphate (ATP) production, ion pump impairment, and the buildup of intracellular sodium, chloride, water, calcium, and extracellular potassium, which results in an electrolyte imbalance[2,3]. The kidneys are the most hypoxic organs outside of the central nervous system[3]. Asphyxia at birth causes ischemia to the proximal tubule, which leads to acute renal failure and tubular necrosis. Serum urea and creatinine rise as a result of this [3]. Therefore, careful control of blood sugar, electrolytes, and body temperature as well as the provision of the right amount of oxygen may lessen the severity of the ischemic insult.

Materials and Methods

This study was conducted in the Department of Biochemistry and with collaboration of Department of Pediatrics at Darbhanga Medical College and Hospital, Laheriasarai, Bihar from February 2023 to July 2023. The experienced pediatrician evaluated and registered as cases 58 term infants who were hospitalized to the neonatal intensive care unit and met the recommended criteria for perinatal hypoxic insult. The study excluded newborns having a history of congenital or acquired serious infections, respiratory distress syndrome, neonates receiving or receiving antibiotics, congenital anomalies or tumors, and any kind of birth injury.

(1) Umbilical cord pH of less than 7.0 (mixed or metabolic); (2) Apgar score of 0–5 for more than five minutes; (3) Neurologic problems, such as hypotonia, convulsions, and coma; and (4) multiorgan dysfunction were the criteria used to define birth asphyxia. Once upon a time, the diagnostic criteria for birth asphyxia, jointly published by ACOG and AAP [16], were generally accepted. In actuality, diagnoses made using these criteria encompass multiorgan failure and HIE in addition to hypoxia.

The incidence of missed diagnoses, according to clinical practices, ranges from 79 to 88%[17, 18]. As a result, it is clear that the aforementioned criteria cannot be applied in a clinical setting. In order to support the diagnosis of birth asphyxia and HIE, we used the Apgar score, clinical characteristics in accordance with the Sarnat and Sarnat staging [19], and appropriate lab tests in our study. According to the Sarnat and Sarnat categorization, newborns with HIE were divided into many Stages (I, II, and III) [19]. A standard Performa was used to record the patient's complete medical history, clinical observations, and pertinent investigations (random blood sugar, serum creatinine, blood urea, and serum electrolytes). Upon admission, all infants had peripheral venous samples taken in sterile tubes, which were then kept at -20°C until standard biochemical techniques could be applied to test them. To save time and reagents, the samples were evaluated weekly and stored at −20°C as per the lab's standard methodology for research sample storage. SPSS software version 20 was used to analyze all of the results, and $p < 0.05$ was deemed significant.

Results

Eight cases (13.79%), sixteen instances (13.79%), and nine cases (27.58%) were distributed among the three HIE stages (I, II, and III), respectively. Of the 25 cases (43.1%) in the asphyxiated non-HIE group, none had any neurological symptoms. Even though birth weight gradually decreased as severity increased, it did not reach the necessary level of significance. Across all stages, vaginal delivery was more common; 43 (74.13%) of the neonates were delivered via vaginal delivery, whereas 15 (25.86%) were delivered by lower segment cesarean section (LSCS). An asphyxiated baby's mean Apgar score was 3.62 at one minute and 5.12 after five minutes. As the severity of HIE increased, the Apgar score trended downward. 4.56 in non-HIE compared to 3.12 in HIE III after one minute, and 5.84 in non-HIE compared to 4 in HIE III at five minutes. In comparison to the non-HIE group (4.56 and 5.84), the APGAR score at 1 minute and 5 minutes was extremely low, especially in HIE III (3.12 and 4).

Primitive reflexes were absent in all infants with HIE III but aberrant in 50% of HIE II neonates. In the HIE II group, convulsions are still a common occurrence, however in the HIE III group, only 22.2% of neonates experienced seizures. The most typical presentation (75% in HIE II) was a multifocal seizure. One infant in the HIE I group displayed mild lip-smacking and lip-chewing seizures. Of the newborns, 25 (44.8%) had oligouria (urine output < 1 ml/kg/h); the majority of these babies (77.8%) had severe birth asphyxia. Kidney damage or abrupt renal shutdown occurred in 22 newborns (37.9%). Of newborns that were asphyxiated, 55.17% had congestive heart failure (HIE III-88.89%). The severity of HIE was correlated with an increasing trend in neonatal death (Table 1).

Table 1: Perinatal factors and clinical profile of birth asphyxia

Variables (n=58)	Non-HIE (n=25)	HIE I (n=8)	HIE II (n=16)	HIE III (n=9)
Gestational age (weeks)	38.6	39.6	38.25	39.0
Birth weight (Kg)	2.74	2.58	2.56	2.43
Vaginal delivery (%)	18(72%)	5(62.5%)	13(81.25%)	7(77.77%)
Caesarian section (%)	7(28%)	3(37.5%)	3(18.75%)	2(22.22%)
Apgar – 1 min.	4.56	4.37	4.0	3.12
Apgar – 5 min.	5.84	5.75	5.62	4.0
Fetal heart rate <120/min (%)	12(48%)	2(25%)	10(62.5%)	8(88.89%)
Abnormal reflexes	0	0	8(50%)	9(100%)
Convulsion	0	0	16(100%)	2(22.22%)
Convulsion type				
• Subtle	0	1(12.5%)	2(12.5%)	0
• Multifocal	0	0	12(75.0%)	0
Oliguria (%)	7(28%)	3(37.5%)	8(50%)	7(77.78%)
Acute kidney injury (%)	7(28%)	2(25%)	6(37.5%)	7(77.78%)
Mortality within 7 days (%)	2(8%)	1(12.5%)	2(12.5%)	5(55.56%)

As the hypoxia severity increased, hypoglycemia was noted; the mean hypoglycemia in HIE III was 26.67 ± 2.78 mg/dl, which was low enough to cause symptoms. In HIE III, serum urea, creatinine, and potassium dramatically rose while sodium and calcium significantly decreased (Table 2). Within seven days of birth, five (55.56%) newborns in the HIE III group passed away from multiple organ failure, whereas other groups had an overall mortality rate of 8–12%.

Table 2: Biochemical parameters in different stages of HIE

Parameters	HIE I	HIE II	HIE III	Non-HIE
Random Blood sugar (RBS) [mg/dl]	60.12±13.43	46.5±17.76	26.67±2.78*	62.76±14.87
Urea [mg/dl]	31.37±14.39	37.87±11.89	71.77±22.12*	30.72±15.48
Creatinine [mg/dl]	1.1±0.40	1.4±0.62	2.86±1.04*	1.0±0.42
Serum Na [mmol/l]	134±4.34	133.75±3.90	130.3±3.39*	135.92±3.72
Serum K [mmol/l]	4.7±0.53	4.91±0.26*	5.3±0.47*	4.21±0.64
Serum Ca [mmol/l]	1.04±0.14	0.97±0.06*	0.89±0.07*	1.14±0.08

*p<0.05 when compared with the non-HIE babies, HIE: Hypoxic-ischemic encephalopathy, RBS: Random blood sugar.

Discussion

In the current study, 25 infants (43.1%) showed no signs of central nervous system involvement, while 33 babies (56.8%) developed HIE. Of the newborns, 27.58% are in group HIE II. Gupta and colleagues have noted a comparable engagement trend[14]. Nonetheless, Nicole et al. found HIE in 75.86% of patients, with the majority of those falling into the classification of moderate HIE (65.4%) [20]. In asphyxiated neonates, Goodwin et al. found a decreased incidence of HIE (31%) [29]. because only term neonates were included in the study, gestational age was comparable across all groups. Asphyxiated HIE and asphyxiated none-HIE newborns had mean birth weights of 2.52 and 2.74 kg, respectively; nevertheless, there was a diminishing pattern with increasing severity in all groups, which was not statistically significant.

While Singh et al. observed a birth weight of 2.4 kg and 2.8 kg in asphyxiated babies and healthy control babies [21], Gupta et al. had reported comparable results [14]. Compared to babies delivered by LSCS, babies delivered vaginally 43 (74.13%) had a higher likelihood of developing HIE in all three categories. It is reasonable to expect that a difficult vaginal birth could result in hypoxia and other difficulties. According to a study by Finer et al., infants delivered vaginally had a higher rate of hypoxia (65%) than those delivered with LSCS (35%). As a cause of birth damage and hypoxia in newborns, Chandra et al. found that factors such as a protracted second stage of labor, vaginal breach delivery, pregnancy-induced hypertension, and intrauterine growth restriction were closely related [15].

As the severity of HIE increased, the Apgar score trended downward. Nicole et al. have previously reported findings similar to these [20]. It has been demonstrated that babies with an Apgar score of 0–4 have significantly lower pH and greater CO2 partial pressure [23]. The relevance of the score increases with the length of time it stays low. The mortality rate for a newborn with a score of 0–3 at 1 minute is 5–10%; if the score stays in the 0–3 range after 20 minutes, it increases to about 53% [12]. Drug use, trauma, hypovolumia, infection, and abnormalities should all be ruled out as causes of low Apgar scores. A 5-minute Apgar score of less than six is considered asphyxia proof. But it could not always be a sign of suffocation because it could be the result of maternal analgesia. In

addition to the Apgar score, MacDonald et al. used the criteria of needing more than one minute of positive pressure ventilation as an indication of asphyxia in a study involving 38,405 neonates. This allowed them to exclude infants who were depressed from maternal analgesia and who did not require prolonged resuscitation despite having a low Apgar score [24]. The Apgar score is less meaningful in preterm neonates, and the likelihood of receiving a lower Apgar score despite normal cord blood pH increases with prematurity.

If the Apgar score stays below 3 for ten minutes or more, there is a greater chance of multiple organ failure. Birth asphyxia affects several organs, with one or more organs being injured in 82% of newborns[13].

The organ injury rate climbed steadily from 0.39% to 13.62% when the umbilical cord arterial pH value declined from 7.20 to <7.00. Conversely, as the base excess value decreased from ≥−10 mmol/L to <−20 mmol/L, the organ injury rate increased from 1.24% to 9.05% [30]. Furthermore, clinical experience shows that if the Apgar score stays below 3 for ten minutes or more, there is an increased chance of multi-organ failure.

Birth asphyxia's cardiac problems are a result of myocardial hypoxia injury. In our investigation, we discovered that 32 out of 58 (55.17%) asphyxiated neonates had a reduced fetal heart rate, with a high proportion of 88.88% in HIE III. Fetal heart rates of less than 120 beats per minute were seen in 96% of babies with severe asphyxia and 75% of babies with mild asphyxia, according to Gary et al. [25]. While all kids in HIE III exhibited absentee or reduced neonatal reflexes, suggesting a higher degree of injury, convulsions were a consistent sign in HIE II neonates. In our investigation, the most frequent type of seizure observed (75% in HIE II) was a multifocal seizure.

It is difficult to explain why only 2 out of 9 newborns (22.2%) experienced seizures in HIE III; most likely due to evolution. Similar results have also been reported by Shah et al. [11].

Birth trauma, elevated cerebral permeability, oxidative stress, brain edema, and metabolic issues are all linked to central nervous system difficulties [26]. Additionally, compared to moderate asphyxia, Karlowicz and Adelman discovered that severe birth asphyxia was associated with a higher frequency of convulsions and impaired reflexes [25].

As HIE severity increased, so did the metabolic disturbances such as hypoglycemia, hypocalcemia, hyponatremia, and hyperkalemia. Serum K and Ca levels in HIE II and III babies were also markedly abnormal, as were blood glucose and sodium levels in HIE III patients. In comparison to the control group, newborns with birth asphyxia had lower sodium and equivalent potassium levels, according to a study by Gupta et al.[14]. According to findings by Gary et al., severe acidosis, hyperkalemia, and hypocalcemia were linked to worse outcomes, and hyponatremia was observed in 38% of cases [25]. With considerably lower serum Ca (1.05 ± 0.1 mmol/l) in HIE than in the control group (1.22 ± 0.07), Yoneda observed a worse outcome [27].

Because the newborn kidney's ability to reabsorb sodium is limited, as the sodium load increases and reaches the distal tubules, more of it is excreted in the urine, resulting in hyponatremia. Simultaneously, SIADH contributes to perinatal asphyxia and partial aldosterone resistance [31]. Hyponatremia alone may cause the intravascular volume to constrict, further impairing renal function [28].

In HIE I, II, and III, renal failure was noted in 25%, 37.5%, and 77.8% of cases, respectively. 28% of the asphyxiated non-HIE newborns experienced renal shutdown, most likely as a result of their increased sensitivity to changes in the amount of oxygen supplied. According to Gary et al., up to 61% of kids with severe birth asphyxia had an elevated prevalence of renal failure [25]. Neonatal mortality was higher in cases of severe HIE, accounting for 17.24% of the 58 newborns that died within 7 days due to the severity of multiple systems' involvement.

Conclusion

The primary cause of newborn illness and mortality, especially in developing nations, is birth asphyxia, which also leads to future multi-organ dysfunction. The three stages of HIE cause changes in a number of clinic biochemical markers; close monitoring of these parameters will aid in early diagnosis, timely intervention, and better illness prognosis.

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