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Evaluation of alteration in renal parameters and serum electrolyte levels in cases of birth asphyxia

Dr. Baiju Kumar[1], Dr. NP Gupta[2*]
[1] Senior Resident, Department of Pediatrics, Darbhanga Medical College & Hospital, Laheriasarai, Bihar, India
[2] Associate Professor, Department of Paediatrics, Darbhanga Medical College and Hospital, Darbhanga, Bihar, India
[*] Corresponding Author: Dr. NP Gupta

Abstract
Hypoxic ischemic brain injury is the most important consequence of perinatal asphyxia. Sodium, potassium and calcium are the major electrolytes in human body, and any deviation from their normal levels in blood might cause convulsions, shock and other metabolic abnormalities. Calcium is an important second messenger in our body and also helps carrying out muscle function and acts as cofactor for several enzymatic activities. Body should maintain optimum level of these electrolytes in blood. Initial hypoglycemia is an important risk factor for perinatal brain injury. Hyperuricemia indirectly shows the severity of tissue injuries. Hyponatremia, hypocalcaemia, hypoglycemia, hyperuricemia are risk factors for perinatal brain injury. Knowledge of these abnormalities to the clinician is very valuable as it is an important variable affecting perinatal mortality. Immediate aggressive treatment of these abnormalities could modify the entire outcome of the babies. Hence based on above findings the present study was planned for Evaluation of Alteration in Renal Parameters and Serum Electrolyte Levels in Cases of Birth Asphyxia.
The Present study was planned in Department of Pediatrics, Darbhanga Medical College & Hospital, Laheriasarai, Bihar. Total 50 cases were enrolled in the present study. The Group I consist of 25 cases diagnosed with the Birth asphyxia. The Group II consist of normal cases of newborns. Cord blood sample will be drawn in the labour room and sent for analysis of serum electrolytes, serum calcium, serum uric acid levels & serum creatinine levels. Calcium will be estimated by A25 autoanalyser of biosystems by arsenazo, uricase peroxidase & glucose oxidase method respectively. Serum electrolytes will be analyzed by ST-100 autoanalyser. The relevant parameters are recorded as per the preforma which include the identification data & Demographic characteristics.
Perinatal asphyxia is an important cause of neonatal renal failure. Monitoring of blood levels of urea, serum creatinine, serum calcium and urine output helps in the early diagnosis and management of renal failure in birth asphyxia. However, in birth asphyxia, since non oliguric renal failure is common, monitoring only urine output does not help in the diagnosis of acute renal failure, the biochemical parameters in both blood and urine should be monitored. Hyponatremia, hypoglycaemia, hypocalcaemia, hyperuricaemia are the risk factors for perinatal brain injury. Knowledge of these abnormalities is very valuable to the paediatrician and immediate treatment of these abnormalities could help us in decreasing the perinatal mortality and morbidity.

Keywords: renal parameters, serum electrolyte levels, birth asphyxia, etc

Introduction
Perinatal asphyxia (also known as neonatal asphyxia or birth asphyxia) is the medical condition resulting from deprivation of oxygen to a newborn infant that lasts long enough during the birth process to cause physical harm, usually to the brain. It is also the inability to establish and sustain adequate or spontaneous respiration upon delivery of the newborn. It remains a serious condition which causes significant mortality and morbidity. It is an emergency condition and requires adequate and quick resuscitation measures.
Perinatal asphyxia is also an oxygen deficit from the 28th week of gestation to the first seven days following delivery. It is also an insult to the fetus or newborn due to lack of oxygen or lack of perfusion to various organs and may be associated with a lack of ventilation.
In accordance with WHO, perinatal asphyxia is characterised by- Profound metabolic acidosis, with a PH <7.20 on umbilical cord arterial blood sample, Persistence of an APGAR score of 3 at the 5th minute, Clinical neurologic sequelae in the immediate neonatal period, Evidence of multiorgan system dysfunction in the immediate neonatal period.
Hypoxic damage can occur to most of the infant's organs (heart, lungs, liver, gut, kidneys), but brain damage is of most concern and perhaps the least likely to quickly or completely heal. In more pronounced cases, an infant will survive, but with damage to the brain manifested as either mental, such as developmental delay or intellectual disability, or physical, such as spasticity.
It results most commonly from antepartum causes like a drop in maternal blood pressure or some other substantial interference with blood flow to the infant's brain during delivery. This can occur due to inadequate circulation or perfusion, impaired respiratory effort, or inadequate ventilation. Perinatal asphyxia happens in 2 to 10 per 1000 newborns that are born at term, and more for those that are born prematurely [1]. WHO estimates that 4 million neonatal deaths occur yearly due to birth asphyxia, representing 38% of deaths of children under 5 years of age [2].

Perinatal asphyxia can be the cause of hypoxic ischemic encephalopathy or intraventricular hemorrhage, especially in preterm births. An infant suffering severe perinatal asphyxia usually has poor color (cyanosis), perfusion, responsiveness, muscle tone, and respiratory effort, as reflected in a low 5 minute Apgar score. Extreme degrees of asphyxia can cause cardiac arrest and death. If resuscitation is successful, the infant is usually transferred to a neonatal intensive care unit.

There has long been a scientific debate over whether newborn infants with asphyxia should be resuscitated with 100% oxygen or normal air [3]. It has been demonstrated that high concentrations of oxygen lead to generation of oxygen free radicals, which have a role in reperfusion injury after asphyxia [4]. Research by Ola Didrik Saugstad and others led to new international guidelines on newborn resuscitation in 2010, recommending the use of normal air instead of 100% oxygen [5, 6].

There is considerable controversy over the diagnosis of birth asphyxia due to medicolegal reasons [7, 8]. Because of its lack of precision, the term is eschewed in modern obstetrics [9].

Despite major advances in monitoring technology and knowledge of fetal and neonatal pathologies, hypoxic-ischemic encephalopathy (HIE) remains a serious condition that causes significant mortality and long-term morbidity. HIE is characterized by clinical and laboratory evidence of acute or subacute brain injury due to asphyxia (ie, hypoxia, acidosis). Most often, the exact timing and underlying cause remain unknown. The American Academy of Pediatrics (AAP) and American College of Obstetrics and Gynecology (ACOG) published guidelines to assist in the diagnosis of severe hypoxic-ischemic encephalopathy [10, 11].

Brain hypoxia and ischemia due to systemic hypoxemia, reduced cerebral blood flow (CBF), or both are the primary physiologic processes that lead to hypoxic-ischemic encephalopathy (HIE). The initial compensatory adjustment to an asphyxial event is an increase in CBF due to hypoxia and hypercapnia. This is accompanied by a redistribution of cardiac output to essential organs, including the brain, heart, and adrenal glands. A blood pressure (BP) increase due to increased release of epinephrine further enhances this compensatory response.

In adults, CBF is maintained at a constant level despite a wide range in systemic BP. This phenomenon is known as the cerebral autoregulation, which helps maintain cerebral perfusion. The physiologic aspects of CBF autoregulation has been well studied in perinatal and adult experimental animals. In human adults, the BP range at which CBF is maintained is 60-100 mm Hg.

Limited data in the human fetus and the newborn infant suggest that CBF is stable over much narrower range of BPs [12, 13]. Some experts have postulated that, in the healthy term newborn, the BP range at which the CBF autoregulation is maintained may be only between 10-20 mm Hg (compared with the 40 mm Hg range in adults noted above). In addition, the autoregulatory zone may also be set at a lower level, about the midpoint of the normal BP range for the fetus and newborn. However, the precise upper and lower limits of the BP values above and below which the CBF autoregulation is lost remain unknown for the human newborn.

In the fetus and newborn suffering from acute asphyxia, after the early compensatory adjustments fail, the CBF can become pressure-passive, at which time brain perfusion depends on systemic BP. As BP falls, CBF falls below critical levels, and the brain injury secondary to diminished blood supply and a lack of sufficient oxygen occurs. This leads to intracellular energy failure. During the early phases of brain injury, brain temperature drops, and local release of neurotransmitters, such as gamma-aminobutyric acid transaminase (GABA), increase. These changes reduce cerebral oxygen demand, transiently minimizing the impact of asphyxia.

At the cellular level, neuronal injury in HIE is an evolving process. The magnitude of the final neuronal damage depends on the duration and severity of the initial insult, combined with the effects of reperfusion injury, and apoptosis. At the biochemical level, a large cascade of events follow hypoxic-ischemic injury.

Excitatory amino acid (EAA) receptor overactivation plays a critical role in the pathogenesis of neonatal hypoxia-ischemia. During cerebral hypoxia-ischemia, the uptake of glutamate the major excitatory neurotransmitter of the mammalian brain is impaired. This results in high synaptic levels of glutamate and EAA receptor overactivation, including N-methyl-D-aspartate (NMDA), amino-3-hydroxy-5-methyl-4 isoxazole propionate (AMPA), and kainate receptors. NMDA receptors are permeable to Ca++ and Na+, whereas AMPA and kainate receptors are permeable to Na+. Accumulation of Na+ coupled with the failure of energy dependent enzymes such as Na+/ K+ - ATPase leads to rapid cytotoxic edema and necrotic cell death. Activation of NMDA receptor leads to intracellular Ca++ accumulation and further pathologic cascades activation.

EAAs accumulation also contributes to increasing the pace and extent of programmed cell death through secondary Ca++ intake into the nucleus. The pattern of injury seen after hypoxia-ischemia demonstrate regional susceptibility that can be largely explained by the excitatory circuity at this age (putamen, thalamus, perirolandic cerebral cortex). Finally, developing oligodendroglia is uniquely susceptible to hypoxia-ischemia, specifically excitotoxicity and free radical damage. This white matter injury may be the basis for the disruption of long-term learning and memory faculties in infants with hypoxic-ischemic encephalopathy.

Intracellular Ca++ concentration increases following hypoxia-ischemia as a result of (1) NMDA receptor activation, (2) release of Ca++ from intracellular stores (mitochondria and endoplasmic reticulum [ER]), and (3) failure of Ca++ efflux mechanisms. Consequences of increases intracellular Ca++ concentration include activation of phospholipases, endonucleases, proteases, and, in select neurons, nitric oxide synthase (NOS). Activation of phospholipase A2 leads to release of Ca++ from the ER via activation of phospholipase C. Activation of proteases and endonucleases results in cytoskeletal and DNA damage.

During the reperfusion period, free radical production increases due to activation of enzymes such as cyclooxygenase, xanthine oxidase, and lipoxygenase. Free radical damage is further exacerbated in the neonate because of immature antioxidant defenses. Free radicals can lead to lipid peroxidation as well as DNA and protein damage and can trigger apoptosis. Finally, free radicals can combine with nitric oxide (NO) to form peroxynitrite a highly toxic oxidant.

NMDA receptor activation results in activation of neuronal

NOS vias PSD-95 and results in the early and transient rise in NO concentration observed in the initial phase of hypoxia. Inducible NOS is expressed in response to the marked inflammation secondary to cerebral ischemia and results in a second wave of NO overproduction that can be prolonged for up to 4-7 days after the insult.

This excessive NO production plays an important role in the pathophysiology of perinatal hypoxic-ischemic brain injury. NO neurotoxicity depends in large part on rapid reaction with superoxide to form peroxynitrite [14]. This, in turn, leads to peroxynitrite-induced neurotoxicity, including lipid peroxidation, protein nitration and oxidation, mitochondrial damage and remodeling, depletion of antioxidant reserve, and DNA damage.

Inflammatory mediators (cytokines and chemokines) have been implicated in the pathogenesis of hypoxic-ischemic encephalopathy and may represent a final common pathway of brain injury. Animal studies suggest that cytokines, particularly interleukin (IL)-1b contributes to hypoxic-ischemic damage. The exact mechanisms and which inflammatory mediators are involved in this process remains unclear.

Following the initial phase of energy failure from the asphyxial injury, cerebral metabolism may recover following reperfusion, only to deteriorate in a secondary energy failure phase. This new phase of neuronal damage, starting at about 6-24 hours after the initial injury, is characterized by mitochondrial dysfunction, and initiation of the apoptotic cascade. This phase has been called the "delayed phase of neuronal injury."

The duration of the delayed phase is not precisely known in the human fetus and newborn but appears to increase over the first 24-48 hours and then start to resolve thereafter. In the human infant, the duration of this phase is correlated with adverse neurodevelopmental outcomes at 1 year and 4 years after insult [15].

In severe HIE, the mortality rate is reportedly 25-50%. Most deaths occur in the first days after birth due to multiple organ failure or redirection of care to comfort measures as a result of the grim prognosis. Some infants with severe neurologic disabilities die in their infancy from aspiration pneumonia or systemic infections.

The incidence of long-term complications depends on the severity of HIE. As many as 80% of infants who survive severe HIE develop serious complications, 10-20% develop moderately serious disabilities, and as many as 10% are healthy. Among the infants who survive moderately severe HIE, 30-50% may have serious long-term complications, and 10-20% have minor neurologic morbidities. Infants with mild HIE tend to be free from serious CNS complications.

Two therapeutic hypothermia trials provided updated information on mortality and the incidence of abnormal neurodevelopmental outcomes infants with moderate to severe HIE [16, 17]. In these trials, 23-27% of infants died prior to discharge from the neonatal intensive care unit (NICU), whereas the mortality rate at follow-up 18-22 months later was 37-38%.

The neonatal period, unquestionably is the most hazardous period of life, never again in life individual is confronted with more dramatic changes than in transition from dependent intrauterine existence to independent post natal life. Perinatal asphyxia one of the most common primary cause of mortality and morbidity among neonates in India and is the commonest cause of stillbirths. Birth asphyxia is an important cause of static neurological developmental handicap both in term and preterm infants.

Hypoxic ischemic brain injury is the most important consequence of perinatal asphyxia. Sodium, potassium and calcium are the major electrolytes in human body, and any deviation from their normal levels in blood might cause convulsions, shock and other metabolic abnormalities. Calcium is an important second messenger in our body and also helps carrying out muscle function and acts as cofactor for several enzymatic activities. Body should maintain optimum level of these electrolytes in blood. Initial hypoglycemia is an important risk factor for perinatal brain injury. Hyperuricemia indirectly shows the severity of tissue injuries. Hyponatremia, hypocalcaemia, hypoglycemia, hyperuricemia are risk factors for perinatal brain injury. Knowledge of these abnormalities to the clinician is very valuable as it is an important variable affecting perinatal mortality. Immediate aggressive treatment of these abnormalities could modify the entire outcome of the babies.

Hence based on above findings the present study was planned for Evaluation of Alteration in Renal Parameters and Serum Electrolyte Levels in Cases of Birth Asphyxia.

Methodology

The Present study was planned in Department of Pediatrics, Darbhanga Medical College & Hospital, Laheriasarai, Bihar. Total 50 cases were enrolled in the present study. The Group I consist of 25 cases diagnosed with the Birth asphyxia. The Group II consist of normal cases of newborns. Cord blood sample will be drawn in the labour room and sent for analysis of serum electrolytes, serum calcium, serum uric acid levels & serum creatinine levels. Calcium will be estimated by A25 autoanalyser of biosystems by arsenazo, uricase peroxidase & glucose oxidase method respectively. Serum electrolytes will be analyzed by ST-100 autoanalyser. The relevant parameters are recorded as per the preforma which include the identification data & Demographic characteristics.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion Criteria: Term newborns with Apgar scores less than 7 at 1 minute of birth with birth weight 2.5kg or more.

Exclusion Criteria: Babies with congenital malformations, Suspected metabolic disease, Those born to mothers having hypertension, diabetes mellitus, treated with diuretics, receiving general anesthesia, pethidine, phenobarbitone, magnesium sulphate and other drugs likely to cause depression in babies. Mothers with history of febrile attack within 2 weeks before delivery were excluded from the study.

Results & Discussion

Early recognition of renal failure is important in babies with Hypoxic ischemic encephalopathy to facilitate appropriate fluid and electrolyte management as a stable electrical milieu is vital. Diagnosis of renal failure is difficult in this group as many clinical and biochemical parameters are unreliable in this age group. Hence this study was done to determine the incidence of acute renal failure in asphyxiated

babies and correlate the severity with Hypoxic ischemic encephalopathy grading with emphasis on early diagnosis of acute renal failure which may be of particular benefit for asphyxiated newborns at risk of developing renal failure [18]. Birth asphyxia is associated frequently with metabolic changes like hypoglycemia, hypocalcaemia, hyponatremia, hyperphosphatemia and metabolic acidosis. Calcium is an important second messenger in our body and also helps out muscle function and acts as a co-factor for several enzymatic activities. During pregnancy, calcium is transferred actively from the maternal circulation to the fetus by a transplacental Ca pump regulated by the parathyroid hormone-related peptide. The majority of fetal Ca accretion occurs in the third trimester. This process results in higher plasma Ca concentration in fetus than in the mother and leads to fetal hypocalcaemia with total and ionized Ca concentration of 10-11 mg/dl and 6 mg/dl in umbilical cord blood at term. After birth due to the abrupt cessation of placental transfer of calcium hence, levels starts falling to 8-9 mg/dl and ionized calcium to 4.4-5.4 mg/dl at 24 h of age. Serum calcium then starts rising to reach levels comparable to older children and adults by 2 weeks of age [19].

Gupta *et al.* showed lower serum sodium levels among asphyxiated babies as compared to the control group and no statistically significant difference in the serum potassium levels between cases and controls. Jajoo *et al.* showed a significant low serum calcium levels in asphyxiated babies than controls. They have not mentioned whether the reduced sodium and calcium levels were in proportion to the severity of asphyxia or they were randomly decreased.

All studies showed that non-oliguric renal failure being most common in asphyxiated neonates. Non-oliguric renal failure can be explained due to decreased pituitary release of vasopressin or reduced responsiveness of renal to vasopressin and heterogeneous response of individual nephrons to the tubular epithelium that results in anatomical damage in majority of nephrons, leading to reduction in single nephron GFR and decreased tubular fluid. But if damage to tubular epithelium is less severe, there is a decrease in fractional reabsorption which exceeds the decrease in single nephron GFR leading to polyuria in non oliguric renal failure. The mean blood urea levels were higher among cases as compared to controls which were statistically significant but there was no significant difference among groups with severity of asphyxia.

Table 1: Basic Characteristic

Cases of	Group I	Group II
No. of Cases	**25**	**25**
Gestation weeks	35 – 38	34 – 39
Weight gm	2150 – 2890	2210 – 3240
Caesarean Delivery	15	18
Respiratory Distress	10	7
Sex		
Male	17	20
Females	8	5

Table 2: Renal Parameters

Cases of	Group I	Group II
No. of Cases	**25**	**25**
BUN	21.4 – 25.4	18.4 – 25.3
Serum Creatinine	1.32 – 1.81	0.79 – 1.29
Urine Sodium	31.4 – 43.8	13.4 – 18.5
Urine Creatinine	19.4 – 35.2	14.4 – 25.4

Table 3: Serum Electrolytes

Cases of	Group I	Group II
No. of Cases	**25**	**25**
Serum Sodium (mEq/L)	128.4 – 134.5	137.4 – 142.8
Serum Potassium (mEq/L)	4.4 – 8.3	3.9 – 6.6
Serum Calcium (mEq/L)	7.1 – 8.3	8.7 – 10.8

Table 4: Renal Failure

Renal Failure	Birth Asphyxia		
	Mild	Moderate	Severe
Renal Failure	4	16	5
No Renal Failure	24	1	0

Hypoxic ischemic brain damage is the most important consequence of perinatal asphyxia. Basu P *et al.* found significant positive correlations between the serum sodium level and the Apgar score. Mean serum calcium level was found lower in asphyxiated newborns compared to normal newborns [20]. Gupta *et al.* showed lower serum sodium levels among asphyxiated babies as compared to the control group and no statistically significant difference in the serum potassium levels between cases and controls [21]. Jajoo *et al.* showed a significant low serum calcium levels in asphyxiated babies than controls [22]. Basu P *et al.* found a significant correlation between hypoglycemia, uric acid levels and tissue damage in birth asphyxia [23].

Hypoglycemia in perinatal asphyxia is demonstrated in different animal models and is documented in leading text books of neonatology [24]. Bader *et al.* [25] in one study and Chen *et al.* [26] in another observed that increased plasma and urinary concentration of purine degradation products were induced by sustained preceding hypoxic state. Erdag and Vitrinel also found that one of the ATP degradation products, such as uric acid, can be a valuable chemical indicator of tissue hypoxia [27].

In the present study it was found that there was significant decrease in extracellular sodium and calcium levels in the asphyxiated babies and the decrease was directly proportional to the degree of asphyxia. Although the serum potassium levels were within normal limits both in asphyxiated and control babies, the potassium levels among cases were higher than the levels in controls and were statistically significant. Also the values of serum potassium among the asphyxiated babies were directly proportional to the severity of asphyxia or inversely proportional to the Apgar scores. It was also found that rise in the serum potassium level was not of clinical significance, and its changes in the serum levels were not at par with the decrease in the levels of other two electrolytes. Also this hyponatremia and hypocalcemia, which developed perinatally, proportionally contribute to the development of more and more severe asphyxia if not rectified immediately.

Conclusion

Perinatal asphyxia is an important cause of neonatal renal failure. Monitoring of blood levels of urea, serum creatinine, serum calcium and urine output helps in the early diagnosis and management of renal failure in birth asphyxia. However, in birth asphyxia, since non oliguric renal failure is common, monitoring only urine output does not help in the diagnosis of acute renal failure, the biochemical parameters in both blood and urine should be monitored. Hyponatremia, hypoglycaemia, hypocalcaemia, hyperuricaemia are the risk factors for perinatal brain injury.

Knowledge of these abnormalities is very valuable to the paediatrician and immediate treatment of these abnormalities could help us in decreasing the perinatal mortality and morbidity.

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