International Journal of Medical and Health Research
ISSN: 2454-9142
Received: 30-12-2018; Accepted: 20-01-2019
www.medicalsciencejournal.com
Volume 5; Issue 2; February 2019; Page No. 151-155

Clinical assessment of newborns with birth asphyxia with respect to renal parameters and serum electrolytes level

Dr. Umesh Kumar[1], Dr. B.B Singh[2*]
[1] Senior Resident, Department of Paediatrics, ANMMCH, Gaya, Bihar, India
[2] HOD, Department of Paediatrics, ANMMCH, Gaya, Bihar, India
[*] Corresponding Author: Dr. B.B Singh

Abstract
The duration of the delayed phase is not precisely known in the human fetus and new born 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. When a neonate suffers asphyxia, series of clinical and biochemical alterations occur which can adversely affect the outcome. While treating hyponatremic seizures, correction of the electrolyte disturbance is more effective than using anticonvulsants. Hyper kalemia is associated with cardiac dysfunction and death. Hypocalcaemia is associated with jitteriness, cardiac dysfunction and seizure. Further the degree of electrolyte imbalance may vary according to the severity of birth asphyxia. Hence present study was planned for clinical assessment of new borns with birth asphyxia with respect to renal parameters and serum electrolytes level.
The study was conducted in Department of Paediatrics, ANMMCH, Gaya, bihar from Jan 2016 to Aug 2016. The 50 cases if the new born were enrolled in the present study. The 25 new borns were enrolled in Group A as cases of birth asphyxia and 25 new borns were enrolled in Group B as control patients. Detailed antenatal, natal and postnatal history and clinical examination was done and findings were recorded on predesigned pro forma. Serum electrolytes (sodium, potassium and calcium) were analysed using ion selective electrode by automated machine.
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. Hyponatremia, hyper kalemia and hypocalcaemia occur in neonates with birth asphyxia which may cause increased morbidity and mortality. More severe hyponatremia should be suspected if there is severe birth asphyxia and vice versa. Hence its level should be more regularly monitored to prevent the problems associated with it.

Keywords: perinatal hypoxia, hie, APGAR score, serum electrolytes levels, renal parameters. etc

1. Introduction
Neonatal asphyxia or birth asphyxia now preferably regarded as Perinatal asphyxia is the medical condition resulting from deprivation of oxygen to a new born infant that lasts long enough during the birth process to cause physical harm, usually to the brain. Perinatal asphyxia is a greek word meaning stopping of pulse. It is also the inability to establish and sustain adequate or spontaneous respiration upon delivery of the new born. 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 1st 7days following delivery. It is also an insult to the fetus or new born due to lack of oxygen, lack of perfusion to various organs and may be associated with 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 new borns 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 new born 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 new born 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.

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) [10]. 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 new born infant suggest that CBF is stable over much narrower range of BPs [11]. Some experts have postulated that, in the healthy term new born, 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 new born. 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 new born.

In the fetus and new born 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 [12]. 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 as phyxial 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 new born 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 [13]. When a neonate suffers asphyxia, series of clinical and biochemical alterations occur which can adversely affect the outcome. While treating hyponatremic seizures, correction of the electrolyte disturbance is more effective than using anticonvulsants. Hyper kalemia is associated with cardiac dysfunction and death. Hypocalcaemia is associated with jitteriness, cardiac dysfunction and seizure. Further the degree of electrolyte imbalance may vary according to the severity of birth asphyxia. Hence present study was planned for clinical assessment of new borns with birth asphyxia with respect to renal parameters and serum electrolytes level.

Methodology

The study was conducted in Department of Paediatrics, ANMMCH, Gaya, Bihar from Jan 2016 to Aug 2016. The 50 cases if the new born were enrolled in the present study. The 25 new borns were enrolled in Group A as cases of birth asphyxia and 25 new borns were enrolled in Group B as control patients. Detailed antenatal, natal and postnatal history and clinical examination was done and findings were recorded on predesigned pro forma. Serum electrolytes (sodium, potassium and calcium) were analysed using ion selective electrode by automated machine.

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 new borns born and appropriate for gestational age (those babies falling between 10th to 90th percentile of weight for their gestational age i.e. weight between 2.5 to 4 kg) with Birth asphyxia as per WHO definition- “failure to initiate and sustain breathing at birth” and based on Apgar score as an Apgar score of < 7 at 5 min of life even after receiving resuscitation according to Neonatal Resuscitation Program (NRP) guidelines were included in the study.

Exclusion criteria: Preterm and IUGR (intrauterine growth retardation) babies, babies with gross congenital malformations, suspected metabolic diseases, cases receiving medications except vitamin K prior to collection of blood samples, those born to mothers with diabetes mellitus, mothers on antiepileptic, mothers with suspected or confirmed.

Results and Discussion

Perinatal asphyxia is a common neonatal problem and adds significantly to neonatal morbidity and mortality. Infants with asphyxia had lower sodium and pH in the umbilical cord arterial blood, umbilical cord arterial potassium though found to be in normal range but their values were in the higher range of normal, blood urea and creatinine were found to be in the higher in asphyxiated neonates then non-asphyxiated and the findings were statistically significant, glucose levels were found low in mild, moderate and severely asphyxiated neonates, but the values were within normal range.

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.

The difference between the results were probably because of difference in the timing of collection of samples, as we collected blood sample as early as possible no later than one hour of life, so chance of correction of electrolyte by body’s internal milieu was less. Basu *et al*. [14] found increased severity of hyponatremia, hyper kalemia and hypocalcaemia with increased severity of birth asphyxia. The pattern of hyponatremia and hyper kalemia was similar to our study. Similarly in case control study by Jajoo *et al*. [15], Rai [16] *et al*. and Schedewie *et al*. [17] showed that asphyxiated new borns had lower serum calcium level compared to their controls.

The treatment of hyponatremia in such condition is by fluid restriction rather increasing sodium load for reasons mentioned in background section. So fluid should be restricted in cases of birth asphyxia till normalization of serum sodium with close monitoring of weight and serum sodium. Serum potassium and Electrocardiography (ECG) monitoring should be done to avoid the deadly complications of hyper kalemia. Apart from other treatment measures, correction of acidosis and use of potassium free fluid are the most useful measures to correct hyper kalemia.

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.

Table 1: Sex of New Borns

Groups	Group A	Group B
Cases of	Birth Asphyxia	Control Cases
Males	19	22
Females	6	3
Total	25	25

Table 2: Renal Parameters

Groups	Group A	Group B
Cases of	Birth Asphyxia	Control Cases
BUN	19.3 – 34.9	19.2 – 24.6
Serum Creatinine	1.23 – 1.79	0.86 – 1.32
Urine Sodium	29.8 – 44.5	12.6 – 17.8
Urine Creatinine	18.6 – 34.8	13.4 – 24.1

Table 3: Serum Electrolytes

Groups	Group A	Group B
Cases of	Birth Asphyxia	Control Cases
Serum Sodium (mEq/L)	129.5 – 138.7	135.9 – 140.7
Serum Potassium (mEq/L)	4.3 – 6.1	4.1 – 4.5
Serum Calcium (mEq/L)	7.5 – 8.6	8.9 – 9.3

In our study the mean serum sodium concentration was lower among the cases as compared to controls which were comparable with other studies which was statistically significant. The serum sodium levels were lower in neonates with severe birth asphyxia; the mean serum sodium is higher in our study as compared to Misra *et al*. [18] study in which the study population is small with most neonates belonging to either stage II or stage III which indicates either moderate or severe degree of asphyxia. Pallab Basu and colleagues [19] study does not mention the distribution of cases in with different severity of asphyxia. The mean serum potassium level was higher in cases than the controls which is comparable with other studies. In Misra *et al*. [18] study the mean serum potassium level was higher than the other studies in which only 7 neonates have been studied and majority had severe birth asphyxia.

The mean serum calcium level in our study was lower as compared to controls, which was noticed after 24-48 hrs, as only few patients belong to severe birth asphyxia. The mean serum calcium level is not reduced to as low as in Pallab Basu [19] study in which they have not considered regarding the distribution of cases. As most neonates were on calcium supplementation, hypocalcaemia of < 7 was not seen in any neonates.

Deepak jajoo [20] and colleagues came to a conclusion that serum calcium levels were significantly lower in term appropriate for gestational age infants who had history of birth asphyxia, they were of the opinion that hypoxia impairs the functions of parathyroid gland resulting in lower calcium levels.

Alphonsus in his study showed that serum calcium levels at 12 hrs. were significantly lower in asphyxiated neonates as compared to non-asphyxiated neonates, this conclusion is in concordance with our study where the serum calcium levels were found to be significantly lower in cord arterial blood in asphyxiated neonates when compared to non- asphyxiated neonates [21].

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. Hyponatremia, hyperkalemia and hypocalcaemia occur in neonates with birth asphyxia which may cause increased morbidity and mortality. More severe hyponatremia should be suspected if there is severe birth asphyxia and vice versa. Hence its level should be more regularly monitored to prevent the problems associated with it.

References

1. Truwit CL, Barkovich AJ. "Brain damage from perinatal asphyxia: correlation of MR findings with gestational age -- Barkovich and Truwit American Journal of Neuroradiology. American Journal of Neuroradiology. 1990; 11(6):1087–1096. Retrieved 2008-03-27.
2. Aslam Hafiz Muhammad, Saleem Shafaq Afzal, Rafia Iqbal Umair, Saleem Sehrish Muhammad, Shaikh Muhammad Waqas Abid, *et al*. "Risk factors of birth asphyxia". Italian Journal of Pediatrics. 2014; 40:94. doi: 10.1186/s13052-014-0094-2. ISSN 1824-7288. PMC 4300075. PMID 25526846.
3. Davis PG, Tan A, O'Donnell CPF, Schulze A. "Resuscitation of newborn infants with 100% oxygen or air: a systematic review and meta-analysis. The Lancet. 2004; 364(9442):1329–1333. doi: 10.1016/ S0140-6736(04)17189-4. PMID 15474135.
4. Kutzsche S, Ilves P, Kirkeby OJ, Saugstad OD. "Hydrogen peroxide production in leukocytes during cerebral hypoxia and reoxygenation with 100% or 21% oxygen in newborn piglets". Pediatric Research. 2001; 49(6):834–842. doi: 10.1203/00006450-200106000-00020. PMID 11385146.
5. ILCOR. Neonatal Resuscitation Guidelines, 2010.
6. Norwegian paediatrician honoured by University of Athens, Norway.gr
7. Blumenthal I. "Cerebral palsy—medicolegal aspects". Journal of the Royal Society of Medicine. 2001; 94 (12):624–7. doi: 10.1177/014107680109401205. PMC 1282294. PMID 11733588.
8. Dhar KK, Ray SN, Dhall GI. "Significance of nuchal cord". Journal of the Indian Medical Association. 1995; 93(12):451–3. PMID 8773129.
9. ACOG. "Committee Opinion, Number 326, December 2005: Inappropriate Use of the Terms Fetal Distress and Birth Asphyxia". Retrieved, 9, 2010.
10. Ferriero DM. Neonatal brain injury. N Engl J Med. 2004; 4, 351(19):1985-95
11. Rosenkrantz TS, Diana D, Munson J. Regulation of cerebral blood flow velocity in nonasphyxiated, very low birth weight infants with hyaline membrane disease. J Perinatol. 1988; 8(4):303-8.
12. Pacher P, Beckman JS, Liaudet L. Nitric oxide and peroxynitrite in health and disease. Physiol Rev. 2007; 87(1):315-424.
13. Roth SC, Baudin J, Cady E, Johal K, Townsend JP, Wyatt JS. Relation of deranged neonatal cerebral

oxidative metabolism with neurodevelopmental outcome and head circumference at 4 years. Dev Med Child Neurol. 1997; 39(11):718-25.
14. Basu P, Das H, Choudhuri N. Electrolyte status in birth asphyxia. Indian J Pediatr. 2010; 77(3):259–62.
15. Jajoo D, Kumar A, Shankar R, Bhargava V. Effect of birth asphyxia on serum calcium levels in neonates. Indian J Pediatrics. 1995; 62(4):455–9.
16. Rai S, Bhatiyani KK, Kaur S. Effect of birth asphyxia on serum calcium and glucose level: A prospective study. Int J Sci Stud. 2015; 3(7):3–6.
17. Schedewie HK, Odell WD, Fisher DA, Krutzik SR, Dodge M, Cousins L, Fiser WP. Parathormone and perinatal calcium homeostasis. Pediatr Res. 1979; 13(1):1–6.
18. Misra PK, Kumar A, Natu SM, Kapoor RK, Srivatsava KL, Das K. Renal failure in symptomatic perinatal asphyxia. Indian Pediatrics. 1991; 28:1147-51. PMid:1797666
19. Basu P, Som S, Das H, Chaudhuri N. Electrolyte status in birth asphyxia. Indian Journal of Pediatrics. 2010; 77:259–62. https://doi.org/10.1007/s12098-010-0034-0 PMid:20177828
20. Deepak Jajoo, Ashok Kumar R, Shankar V Bhargava. Effect of Birth Asphyxia on Serum Calcium Levels in Neonates. Indian J Pediatr. 1995; 62:455-459.
21. Alphonsus N. Onyiriuka. Prevalence of neonatal hypocalcaemia among full-term infants with severe birth asphyxia. Pacific Journal of Medical Sciences, 2011, 8(1).