Original Article

Clinico biochemical profile of birth asphyxia in neonates of western Odisha

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Abstract

Background: Perinatal asphyxia contributes to almost 29% of neonatal deaths in developing countries as most of the deliveries occur in rural areas and are unattended. The outcome of most of the deliveries is not encouraging in spite of standard guidelines. **Objectives:** To study the different spectrum of clinical presentation of birth asphyxia and its biochemical derangements. **Materials and Methods:** This was a prospective, hospital-based study conducted from September 2005 to March 2008 comprising of 58 term neonates admitted to neonatal intensive care unit with definite history suggestive of perinatal hypoxic insult. Compilation of history, clinical features, and relevant investigations (random blood sugar, serum creatinine, blood urea and serum electrolytes) were done, and the results were analyzed by using Medcalc software version 12. **Results:** Vaginal delivery was more common across all the stages. Abnormal neonatal reflex was a common feature in all babies except hypoxic-ischemic encephalopathy (HIE) I. Convulsion, mostly multifocal seizures was present in all HIE II babies where as only 22.2% babies had seizure in HIE III. Congestive heart failure (55.17%) and Oliguria was present in HIE III (77.8%) and 22 cases (37.9%) developed acute kidney injury. Hypoglycemia was observed with increasing severity of asphyxia (HIE III 26.67 ± 2.78). Serum urea, creatinine and potassium increased significantly in HIE III whereas calcium and sodium were decreased. **Conclusion:** The combination of clinical and supportive laboratory parameters can be used for monitoring of patients to guide early intervention to decreases morbidity and mortality.

Key words: *Birth asphyxia, Biochemical markers, Hypoxic ischemic encephalopathy, Neonates*

Birth asphyxia is one of the leading cause of perinatal death and a recognizable cause of brain damage in newborn. Hypoxic-ischemic encephalopathy (HIE) prevalence ranges from 0.1% to 0.5% of total live births and is the cause of around 23% of neonatal death worldwide [1]. Of total, ninety eight percent of neonatal deaths occur in developing countries only [2]. As per WHO, approximately 4 million babies die each year within 1 month of life [3-5]. Perinatal asphyxia and birth injuries together contribute about 29% of these deaths [4]. 82% of neonates with a history of birth asphyxia develop injury to one or more organs [6]. The common complications of asphyxia are cerebral palsy, irreversible renal cortical necrosis, persistent pulmonary hypertension of the newborn, hypotension, cardiogenic shock or heart failure [6-8]. Birth asphyxia is one of the most common causes of renal failure in newborn [9]. A number of metabolic complications like impaired thermoregulation, lactic acidosis, hypoglycemia, hyponatremia, hypocalcemia may also coexist and alters the course of the disease process [6].

On the basis of patho physiological mechanisms involving brain and kidney damage in HIE, a number of metabolic parameters have been studied to provide an early and reliable marker of tissue damage for both diagnostic and prognostic purposes. The biochemical abnormalities which are associated with poor outcome in birth asphyxia are, fluctuating level of sugar, hyperuricemia, hyperkalemia, hypocalcemia, hyponatremia and increased creatinine level [10]. In spite of the standard guidelines outlined by the American Academy of Pediatrics (AAP) and American College of Obstetrics and Gynecology (ACOG), the outcome of most of the deliveries is not encouraging [11]. Therefore, to reduce the burden of birth asphyxia related morbidity in rural areas, one should focus on the spreading the awareness of the cause and effect of birth asphyxia in the reproductive population. This research points out the different spectrum of clinical presentation of birth asphyxia and its biochemical derangements leading to increased morbidity and mortality.

MATERIALS AND METHODS

The present study was a prospective, observational, hospital based study conducted in the Department of Biochemistry and Pediatrics at VSSMC and Hospital, Burla, Sambalpur from September 2006 to March 2008. The study was approved by Institutional Ethical Committee and informed consent was obtained from the parents. A total of 58 term neonates admitted to neonatal intensive care unit fulfilling the suggested criteria

of perinatal hypoxic insult were examined by the trained pediatrician and were enrolled as cases. Neonates with history of maternal drug addiction or analgesia, severe infection (congenital or acquired), respiratory distress syndrome, babies received or receiving antibiotics, congenital anomaly or tumors and any type of birth injury were excluded from the study.

Birth asphyxia was defined by (1) umbilical cord pH of <7.0 (mixed or metabolic) (2) Apgar score of 0-5 for longer than 5 min (3) Neurologic complications including hypotonia, convulsion, coma and (4) multiorgan dysfunction [11]. The diagnostic criteria jointly released by ACOG and AAP [11], were once widely accepted for the diagnosis of birth asphyxia. In fact, diagnoses based on these criteria include not only asphyxia but also HIE and multiorgan dysfunction. However, clinical practices have shown that the rate of missed diagnosis reaches 79-88% [12,13] and so obviously, the above criteria is not feasible for clinical application. In our study we have used Apgar score, clinical features as per the (Sarnat and Sarnat staging) [14] and necessary lab investigations to support the diagnosis of birth asphyxia and HIE.

Neonates with HIE were grouped in different Stages (I, II, III) as per Sarnat and Sarnat classification [14]. Detailed history, clinical findings, and relevant investigations (random blood sugar, serum creatinine, blood urea and serum electrolytes) were recorded in a standard Performa. Peripheral venous sample from all the neonates were collected in sterilized tubes at the time of admission and stored at −20°C until analyzed by standard biochemical methods. The samples were kept at −20°C as a routine research sample storage protocol adopted in lab and were analyzed on weekly basis to save time and reagents. All the results were analyzed by using Medcalc software version 12.1 $p < 0.05$ were considered significant.

RESULTS

Distribution of cases across the three stages of HIE (I, II, III) were 8 (13.79%), 16 (13.79%) and 9 (27.58%) respectively. 25 cases (43.1%) belonged to asphyxiated non-HIE group who did not have any neurological manifestations. Birth weight though showed a gradual decrease with increasing severity, it failed to reach the level of significance. Vaginal delivery was more common across all the stages, and 15 neonates (25.86%) were delivered by lower segment cesarean section (LSCS) against 43 (74.13%) by the vaginal route. The mean Apgar score in asphyxiated babies was 3.62 and 5.12 at 1 min and 5 min. The Apgar score showed a decreasing trend with the increasing severity of HIE. 4.56 in non-HIE versus 3.12 in HIE III at 1 min and 5.84 in non-HIE versus 4 in HIE III at 5 min. APGAR score at both 1 min and 5 min was very low, more so in HIE III (3.12 and 4) as compared to non-HIE group (4.56 and 5.84).

50% neonates with HIE II had abnormal or absent primitive reflexes while it was absent in all the neonates of HIE III. Convulsion remains a constant presentation in HIE II group where as only 22.2% babies had seizure in HIE III. Multifocal seizure was most common presentation (75% in HIE II). One baby in HIE I group had subtle seizure in the form of smacking and chewing movements of lips. Oliguria (urine output less than 1 ml/kg/h) was present in 25 (44.8%) babies with more number of cases belong to babies with severe birth asphyxia (77.8%). 22 babies (37.9%) developed acute renal shutdown/kidney injury. Congestive heart failure was found in 55.17% of asphyxiated babies (HIE III-88.89%). Neonatal mortality showed an increasing trend with the severity of HIE (Table 1).

Hypoglycemia was observed with increasing severity of asphyxia and mean the hypoglycemia in HIE III was 26.67 ± 2.78 mg/dl, which was sufficiently low to produce symptoms. Serum urea, creatinine and potassium increased significantly in HIE III whereas calcium and sodium decreased significantly (Table 2). 5 (55.56%) babies in HIE III group died of multi organ failure within 7 days of life while overall 8-12% mortality was observed in other groups.

DISCUSSION

In the present study, 33 babies (56.8%) developed HIE whereas 25 (43.1%) did not show any involvement of central nervous system. 27.58% babies belong to group HIE II. Gupta et al. has observed a similar pattern of involvement [7]. However, Nicole et al. observed HIE in 75.86% of cases with maximum cases in moderate HIE (65.4%) subcategory [15]. Goodwin et al. reported a lower incidence (31%) of HIE in asphyxiated newborns [9]. In our study, gestational age was similar in all the groups as term neonates were enrolled for the study. Mean birth weight was 2.52 and 2.74 kg in asphyxiated HIE and asphyxiated none-HIE babies; however, across the groups it showed a declining pattern with increasing severity, which was again not statistically significant. Gupta et al. had reported similar findings [7], whereas Singh et al. reported a birth weight of 2.4 kg and 2.8 kg in asphyxiated babies and healthy control babies [16]. The babies who were delivered by vaginal route 43 (74.13%) showed an increased chance of development of HIE in all three groups in comparison to those born by LSCS. It may be assumed that vaginal delivery if difficult may cause asphyxia and subsequent complications due to it. Study by Finer et al. reported greater incidence of asphyxia in infants born by vaginal delivery (65%) than by LSCS (35%) [17]. Chandra et al. observed that the associated factors like prolonged second stage of labor, vaginal breach delivery, pregnancy-induced hypertension and intrauterine growth restriction to be closely associated as a cause of birth injury and asphyxia in newborn [10].

The Apgar score showed a decreasing trend with the increasing severity of HIE. Similar findings had been reported by Nicole et al. [15]. Babies with a Apgar score of 0-4 are shown to have significant lower pH and higher partial pressure

Table 1: Perinatal factors and clinical profile of birth asphyxia

Characteristics (*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
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	3.12
Apgar - 5 min	5.84	5.75	5.62	4
FHR <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	0	1 (12.5)	2 (12.5)	0
Subtle	0	0	12 (75.0)	0
Multifocal				
Oliguria (%)	7 (28)	3 (37.5)	8 (50)	7 (77.78)
AKI (%)	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)

FHR: Fetal heart rate, AKI: Acute kidney injury

Table 2: Biochemical parameters in different stages of HIE

Parameters	HIE I	HIE II	HIE III	Non-HIE
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**

of CO_2 [18]. The longer the score remains low, the greater is its significance. An infant with a score of 0-3 at 1 min has a mortality rate of 5-10%, which rises to approximately 53% if that score remains in the range of 0-3 at 20 min [3]. Low Apgar score can be due to drugs, trauma, hypovolumia, infection or anomalies which should be excluded. For 5 min Apgar score, a score of <6 is regarded as evidence of asphyxia. However, it may not always indicate the asphyxia as it can be due to maternal analgesia. MacDonald et al. in a study conducted on 38,405 neonates used the criteria as need of more than 1 min of the positive pressure ventilation as indication of asphyxia in addition to Apgar score, to exclude the infants depressed from maternal analgesia, who do not require prolonged resuscitation despite low Apgar score [19]. In preterm infants, the Apgar score is of lesser value, and greater the prematurity more is the chance of getting a lower Apgar score despite normal cord blood pH. The risk of multi organ failure increases once the Apgar score remains under 3 for 10 min or longer. Multiple organs are affected in birth asphyxia with 82% neonates incurring injury to one or more organ [6].

As the umbilical cord arterial pH value decreased from 7.20 to <7.00, the organ injury rate gradually rose from 0.39% to 13.62%, in contrast, with the base excess value dropped from ≥−10 mmol/L to <−20 mmol/L, the organ injury rate gradually increased from 1.24% to 9.05% [20]. Moreover, clinical experience reveals that the risk of multi-organ failure increases once the Apgar score remains under 3 for 10 min or longer.

The cardiac complications of birth asphyxia reflect hypoxic injury to the myocardium. In our study, we found fetal heart rate to be depressed in 32 of 58 (55.17%) asphyxiated babies with a maximum percentage of 88.88% in HIE III. Gary et al. reported fetal heart rate lower than 120 beats/min in 96% of severely asphyxiated babies and 75% in moderately asphyxiated babies [21]. Convulsion was a constant feature in HIE II babies whereas all babies in HIE III showed depressed or absent neonatal reflexes indicating greater degree of damage. Multifocal seizure was the most common type of seizure (75% in HIE II) observed in our study. Only 2 of 9 babies (22.2%) had seizures in HIE III which is difficult to explain, probably in the process of evolution. Shah et al. has also reported similar findings [2]. Complications associated with the central nervous system are attributed to oxidative stress, increased cerebral permeability, brain edema, birth trauma and metabolic complications [22]. Karlowicz and Adelman also reported a

higher frequency of convulsion and altered reflexes in severe birth asphyxia in comparison to moderate asphyxia [21].

The metabolic derangements like hypoglycemia, hypocalcemia, hyponatremia and hyperkalemia were more pronounced with the increasing severity of HIE. For serum sodium and blood glucose levels, it was significantly deranged in HIE III and for serum K and Ca levels in HIE II and III babies. Study by Gupta et al. reported lower sodium and comparable potassium in birth asphyxia babies as compared to control group [7]. As per observations by Gary et al., hyponatremia was reported in 38% cases and hyperkalemia, hypocalcaemia and severe acidosis was associated with poorer outcome [21]. Yoneda reported poorer outcome with significantly low serum Ca (1.05 ± 0.1 mmol/l) in HIE than in control group (1.22 ± 0.07) [23]. The capacity for sodium re-absorption is limited in neonatal kidney and so with increasing sodium load reaching the distal tubules, more of it is excreted in the urine leading to hyponatremia, with simultaneous contribution by SIADH secondary to perinatal asphyxia and partial resistance to aldosterone [24]. Hyponatremia per se may lead to contraction of intravascular volume further reducing the renal function [25].

Incidences of renal failure in asphyxiated babies as reported by different authors are mentioned in Table 3. Renal failure was observed in 25%, 37.5% and 77.8% in HIE I, II and III respectively. In asphyxiated non-HIE babies, 28% developed renal shutdown probably because of higher sensitiveness to fluctuating level of O_2 supply. Gary et al. reported an increased incidence of renal failure in severe birth asphyxia babies, as high as 61% [21]. Out of 58, 17.24% babies died within 7 days owing to the severity of involvement of multiple systems, increased with the severity of HIE and thus neonatal mortality too was more in the severe HIE.

CONCLUSION

Birth asphyxia is the leading cause of neonatal morbidity and mortality and subsequent multi organ dysfunction, particularly in third world countries. Several clinic biochemical parameters are altered across the three stages of HIE, intensive monitoring of these parameters will help in prompt diagnosis, timely intervention and improving the outcome of the disease.

Table 3: Incidence of renal failure in different studies

Research authors	Incidence (%)
Pammi et al. (2000) [26]	72
Aggarwal et al. [27]	56
Jenik et al. (2000) [28]	55
Jayashree et al. (1991) [29]	43
Gary et al. (1995) [21]	30.30
Present study	37.93

REFERENCES

1. Bryce J, Boschi-Pinto C, Shibuya K, Black RE, WHO Child Health Epidemiology Reference Group. WHO estimates of the causes of death in children. Lancet. 2005;365(9465):1147-52.
2. Shah GS, Agarwal J, Mishra OP, Chalise S. Clinicobiochemical profile of neonates with birth asphyxia in eastern Nepal. J Nepal Paediatr Soc. 2012;32(3):206-9.
3. Adcock LM, Papile LA. Perinatal asphyxia. In: Cloherty PJ, Eichenwald EC, Stark AR, editors. Manual of Neonatal Care. 6th ed. New Delhi: Wolters Kluwer; 2008. p. 518-23.
4. Costello AM. Perinatal health in developing countries. Trans R Soc Trop Med Hyg. 1993;87(1):1-2.
5. World Health Organization. Child health and development: Health of the newborn. Geneva: WHO; 1991.
6. Klein JM, Zlatnik FJ, Hein HA. Multiorgan system failure from perinatal asphyxia. Iowa Perinat Lett. 2005;XXVI(1):1-4.
7. Gupta BD, Sharma P, Bagla J, Parakh M, Soni JP. Renal failure in asphyxiated neonates. Indian Pediatr. 2005;42(9):928-34.
8. Sergeyeva RA, Ismagilov MF. Cerebral palsy. Etiology and pathogenesis. Neurol Bull. 1998:1-2.
9. Goodwin TM, Belai I, Hernandez P, Durand M, Paul RH. Asphyxial complications in the term newborn with severe umbilical acidemia. Am J Obstet Gynecol. 1992;167(6):1506-12.
10. Chandra S, Ramji S, Thirupuram S. Perinatal asphyxia: Multivariate analysis of risk factors in hospital births. Indian Pediatr. 1997;34(3):206-12.
11. Use and abuse of the Apgar score. Committee on Fetus and Newborn, American Academy of Pediatrics, and Committee on Obstetric Practice, American College of Obstetricians and Gynecologists. Pediatrics. 1996;98(1):141-2.
12. Korst LM, Phelan JP, Wang YM, Martin GI, Ahn MO. Acute fetal asphyxia and permanent brain injury: A retrospective analysis of current indicators. J Matern Fetal Med. 1999;8(3):101-6.
13. Murphy-Kaulbeck L, Bland E, Oppenheimer L. Neonatal encephalopathy and asphyxia: Revisiting diagnostic criteria. Otawa: Canadian OB/GYN Society; 2000.
14. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. Arch Neurol. 1976;33(10):696-705.
15. Nicole N, Komen W, Ko KH, Mullar C, Obladen M. Early biochemical indicators of hypoxic ischemic encephalopathy after birth asphyxia. Pediatr Res. 2001;49(4):502-6.
16. Singh KS, Rua T, Tandon A, Kumari S, Ray G, Barta S. Status of lipid peroxidation and antioxidant enzymes in hypoxic ischemic encephalopathy. Indian Pediatr. 1999;36(6):561-566.
17. Finer NN, Robertson CM, Richards RT, Pinnell LE, Peters KL. Hypoxic-ischemic encephalopathy in term neonates: Perinatal factors and outcome. J Pediatr. 1981;98(1):112-7.
18. Dutta S, Narang A. Birth asphyxia. Chandigarh: PGIMER; 2003. p. 1-7, 51-55, 72-81.
19. MacDonald HM, Mulligan JC, Allen AC, Taylor PM. Neonatal asphyxia. I. Relationship of obstetric and neonatal complications to neonatal mortality in 38,405 consecutive deliveries. J Pediatr. 1980;96(5):898-902.
20. Collaborative Study Group of Neonatal Umbilical Cord Blood Gas Parameters. Multicenter clinical study on umbilical cord arterial blood gas parameters for diagnosis of neonatal asphyxia. Zhonghua Er Ke Za Zhi. 2010;48(9):668-73.

21. Karlowicz MG, Adelman RD. Nonoliguric and oliguric acute renal failure in asphyxiated term neonates. Pediatr Nephrol. 1995;9(6):718-22.
22. Shah S, Goel AK, Padhy M, Bhoi S. Correlation of oxidative stress biomarker and serum marker of brain injury in hypoxic ischemic encephalopathy. Int J Med Appl Sci. 2014;3(1):106-15.
23. Yoneda S. Low adjusted serum ionized calcium concentration shortly after birth predicts poor outcome in neonatal hypoxic ischemic encephalopathy. J Obstetr Gynaecol Res. 2005;31(1):57-64.
24. Adelman RD, Solhand MJ. Pathophysiology of body fluid. In: Behrman RE, Kliegman RM, Jension HB, editors. Nelson Text Book of Paediatrics. 16th ed. Philadelphia: WB Saunders Co.; 2000. p. 93-9.
25. Aldana Valenzuela C, Romaro Maldonado S, Vargas Origel A, Hemandes Arriga J. Acute complications in full term neonates with severe neonatal asphyxia. Gynecol Obstetr. 1995;63:123-7.
26. Pammi V, Pragnya M. Renal insult in Asphyxia neonatorum. Indian Pediatr. 2000;37:1102-6.
27. Aggarwal A, Kumar P, Chowdhury G, Majumdar S, Narang A. Evaluation of renal functions in asphyxiated newborns. J Trop Pediatr. 2005;51(5):295-9.
28. Jenik AG, Ceriani Cernadas JM, Gorenstein A, Ramirez JA, Vain N, Armadans M, et al. A randomized, double-blind, placebo-controlled trial of the effects of prophylactic theophylline on renal function in term neonates with perinatal asphyxia. Pediatrics. 2000;105(4):E45.
29. Jayashree G, Dutta AK, Sarang MS, Saili A. Acute renal failure in asphyxiated newborns. Indian Pediatr. 1991;28(1):19-23.

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