Original Article

Biochemical profile of term neonates with perinatal asphyxia and their correlation with severity of asphyxia

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Abstract

Background: Birth asphyxia is a major cause of neonatal mortality and neurological morbidity. This study was aimed to determine biochemical (sodium, potassium, and calcium) abnormalities and their correlation across different severities of perinatal asphyxia in term neonates. **Methods:** This observational analytical study was conducted in term neonates with perinatal asphyxia admitted at the neonatal intensive care unit of a tertiary care centre for a period of 18 months. Blood collection was done at baseline, 24 hours, and 48 hours of treatment to evaluate electrolyte abnormalities. The abnormality in serum electrolytes was correlated across different stages of hypoxic ischaemic encephalopathy (HIE) as per severity and at different time intervals. **Results:** A total of 74 neonates were included in the study and classified into HIE stage 1 (n = 37), stage 2 (n = 18), and stage 3 (n = 19). At baseline, hyponatremia, hyperkalaemia, and hypocalaemia were observed in 36.5% (n = 27), 20.3% (n = 15), and 10.8% (n = 8), respectively. The difference between mean serum sodium (p: 0.007), potassium (P: 0.004), and calcium levels (p: 0.001) at baseline in stage 1 and stage 3 was statistically significant. The degree of hyponatremia and hyperkalaemia was more and statistically significant as per increasing severity of HIE. All the deaths (n = 6.8.1%) belonged to stage 3 of HIE. **Conclusion:** The degree of hyponatremia, hypocalaemia, and hyperkalaemia in the asphyxiated newborns correlated with the severity of birth asphyxia. The mortality rate was greater in asphyxiated neonates with severe HIE and electrolyte abnormality. Effective perinatal care and meticulous management of dyselectrolytemia are crucial for improving neonatal outcomes.

Keywords: Asphyxia, dyselectrolytemia, hypoxic-ischaemic encephalopathy

Introduction

Perinatal asphyxia accounts for 34-52% of preventable cause of under-5 child mortality in low- and middle-income countries.[1,2] The neurologic consequences of perinatal hypoxia are referred to as neonatal hypoxic-ischaemic encephalopathy.[3,4] The majority of cases of perinatal asphyxia occur intrapartum.[5-7] Perinatal asphyxia leads to anaerobic metabolism and various biochemical abnormalities, which can have a negative impact on the outcome. Depending on the severity of birth asphyxia, the degree of electrolyte imbalance may vary.[8,9]

This study was initiated with the goal of examining the electrolyte abnormalities and their correlation with severity of perinatal asphyxia.

Material and Methods

This observational and analytical study was conducted at the NICU facility of a tertiary care centre, completed within 18 months. The aim and objective of the study was

1. To describe biochemical abnormalities in neonates with perinatal asphyxia.
2. To find out correlation of level of sodium, potassium, and calcium with different severities of perinatal asphyxia.

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Received: 23-04-2024 **Revised:** 19-06-2024
Accepted: 01-07-2024 **Published:** 18-11-2024

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_676_24

How to cite this article: Bhoye SV, Bhongale ND, Thorat RM, Wade PA. Biochemical profile of term neonates with perinatal asphyxia and their correlation with severity of asphyxia. J Family Med Prim Care 2024;13:5108-12.

Study design: Observational and analytical study

Sample size: Sample size was determined using the expected proportion of event/outcome in each group, values of which were estimated from the literature.[10] A total of 74 participants were enrolled after fulfilling the inclusion criteria.

Ethical clearance was taken from the Institutional Ethics Committee as per the institutional requirements.

Inclusion criteria

Term babies appropriate for age (babies in between 10th and 90th percentiles of weight for their gestational age) with birth asphyxia were delivered at tertiary care. Neonates were identified of having perinatal asphyxia when[11]:

a. Prolonged (1 hour) antenatal acidosis
b. Fetal heart rate < 60 beats per minute
c. APGAR score ≤3 at ≥10 minutes
d. Need for positive pressure ventilation for >1 minute or first cry delayed >5 minutes
e. Seizure within 12 to 24 hours of birth

Exclusion criteria

1) Congenital anomalies which are picked up on clinical examination.
2) Babies born to mother treated with diuretics, general anaesthesia, antihypertensives, and magnesium sulphate.
3) Parents not giving consent.

Methodology

After fulfilling inclusion criteria, 74 neonates were enrolled for the study after obtaining informed consent from parents and caretakers. Detailed history was taken and noted. Clinical assessment of babies along with basic investigation was done. Clinical grading for HIE was done using Sarnat and Sarnat.

To rule out biochemical abnormalities in perinatal asphyxia, blood collection was done initially at baseline (2–6 hours) and then at 24 hours and 48 hours of treatment.

Serum sodium and potassium were estimated in ion-selective electrodes in an electrolyte analyser, which is based on the principle of potentiometry. Serum total calcium was estimated in an auto-analyser by the end point colorimetric (O Cresolpthalein Complexone or OCPC) method. It was done at the Biochemistry laboratory of a tertiary care centre.

The normal level for serum electrolytes was taken as serum sodium 135–145 meq/l, serum potassium 3.5–5.5 meq/l, and serum calcium 7 mg/dl–11 mg/dl.[12-14]

Statistical analysis

Data collected were compiled onto an MS Office Excel worksheet and were subjected to statistical analysis using an appropriate package like SPSS software. Descriptive statistics like frequency (n) and percentage (%) of categorical data, mean, and standard deviation of numerical data in each group/subgroup were depicted. Frequency (n) and percentage (%) of various categories in each group/subgroup were compared using Chi square test.

Normality of numerical data was checked using Shapiro–Wilk test or Kolmogorov–Smirnov test. Depending on the normality of data, statistical tests were determined. For numerical continuous data following a normal distribution, inter-group comparison (two groups) was done using *t*-test; else, a non-parametric substitute like Mann–Whitney U-test was used.

For a numerical continuous data following a normal distribution, inter-group comparison (>2 groups) was done using one-way analysis of variance (ANOVA) test; else, a non-parametric substitute like Kruskal–Wallis ANOVA test was used.

Keeping the alpha error at 5%, the beta error at 20%, and the power at 80%, $P < 0.05$ was considered statistically significant.

Results

Data of 74 asphyxiated term neonates were collected, out of which 70% (n = 52) were male and 30% (n = 22) female. Twenty-three (31.1%) neonates were born of LSCS, and 51 (68.9%) by normal delivery. The number of asphyxiated neonates was more in multigravida women (n = 44) compared to primiparous women (n = 30). The most common maternal and obstetrics risk factors observed were premature rupture of membranes (20.2%), hypertension (18.91%), severe anaemia (9.4%), and diabetes mellitus (6.8%).

Other observed neonatal clinical conditions were (36.5%), apnoea (18.9%), hyper-bilirubinaemia (13.5%), shock (12.6%), meconium aspiration syndrome (6.8%), hypoglycaemia (4.1%), sepsis (4.1%), and acute renal failure (1.4%). Distribution of neonates as per HIE staging based on Sarnat and Sarnat classification and their outcome is shown in Table 1. At baseline, hyponatremia, hyperkalaemia, and hypocalaemia were observed in 36.5% (n = 27), 20.3% (n = 15), and 10.8% (n = 8), respectively [Table 2]. The difference between mean serum sodium ($P = 0.007$), potassium ($P = 0.004$), and calcium levels ($P = 0.001$) at baseline in stage 1 and stage 3 was statistically significant [Table 2]. The highest mean sodium level (136.07 ± 2.28 meq/l) was found in Sarnat and Sarnat stage 1 patients, while the lowest (127.71 ± 0.95 meq/l) was seen in stage 3 patients [Table 3]. The degree of hyponatremia significantly increased at 48 h compared to 24 h in both stage 2 and stage 3 ($P = 0.001$) [Table 4]. Serum potassium levels were significantly different between stage 1 and stage 3 at baseline ($P = 0.006$) with a high normal level in stage 1 and hyperkalaemia in stage 3 (4.99 ± 0.37 and 5.53 ± 0.76 meq/l), respectively [Table 5]. At baseline, the lowest mean serum calcium level was observed in stage 3 (7.35 ± 0.85 mg/dl). The difference was significantly lower ($P = 0.001$). No statistically significant

difference was observed in mean calcium levels at baseline and at interval of 24 h and at 48 h [Table 6]. Out of 74 patients under study, 6 (8.1%) patients expired and rest were discharged. All deaths were observed in HIE stage III [Table 1].

Discussion

This study was conducted on full term, appropriate for gestational age, asphyxiated newborns born in a tertiary care hospital; identified the maternal, obstetric, and neonatal risk factors; and compared the pattern of electrolyte disturbances in them at baseline and at 24 h and 48 h of life. The serum electrolyte patterns with severity of HIE stage based on Sarnat and Sarnat classification were correlated. A total of 74 asphyxiated neonates were included in this study with a mean gestational age of 37.7 weeks and a mean weight of 2.76 kg.

In our study, male predominance was noted in asphyxiated neonates constituting 70% of the total study population, which is comparable to other studies.[15-17] The majority of the enrolled neonates were noted to have mild to moderate stages of HIE as per Sarnat and Sarnat classification with 25.7% (n = 18) neonates having a severe stage of HIE. Forty percent neonates belonged to primiparous mothers, while 59.5% belonged to multigravida mothers. The incidence of asphyxia was higher in neonates born by normal vaginal delivery but mostly in mild (58.8%) to moderate (31.3%) stages of HIE. This is similar to previous studies conducted in India and other developing countries.[17] The majority of neonates in this study were born to multigravida mothers in contrast to Babu R *et al.*[16] study, who found incidence of asphyxia was more in primipara mothers in their study population. This can be explained by considering our centre is a tertiary level referral centre and a large number of high-risk and complicated cases coming to the hospital. The long duration of journey in addition to other high-risk factors contributes to more cases of foetal distress and perinatal asphyxia. Amongst the risk factors, premature rupture of membranes (20.2%), hypertension (18.91%), severe anaemia (9.4%), diabetes mellitus (6.8%), and meconium aspiration syndrome (6.8%) were more common. Acharya *et al.*, in their study, demonstrated that prolonged second stage of labour and meconium aspiration syndrome are associated with a severe degree of birth asphyxia. They also observed that these two risk factors were more common in their study group, while other maternal factors like antepartum haemorrhage, gestational diabetes, and preeclampsia had less contribution to the development of HIE (17.3%).[17]

Table 1: Distribution of patients according to Sarnat and Sarnat staging and their outcome

Sarnat and Sarnat Staging	Number	Discharged	Death
Stage 1 (Mild)	37 (50%)	37 (100%)	0
Stage 2 (Moderate)	18 (24.3%)	18 (100%)	0
Stage 3 (Severe)	19 (25.7%)	13 (68.4)	06 (31.6%)
Total	74	68 (91.2%)	06 (8.1%)

Table 2: Electrolytes levels at baseline

Electrolytes level at Baseline	Number	Percentage
Serum Sodium		
Hyponatremia	27	36.5%
Normal	43	58.1%
Hypernatremia	4	5.4%
Serum Potassium		
Hypokalemia	4	5.4%
Normal	55	74.3%
Hyperkalemia	15	20.3%
Serum Calcium		
Hypocalcemia	8	10.8%
Normal	66	89.2%
Hypercalcemia	0	-

We observed the degree of hyponatremia, hyperkalaemia, and hypocalaemia increased with increasing severity of HIE staging at baseline and subsequently. This finding was similar to previous studies.[15-17] Any derangement in these electrolytes can cause seizures and metabolic abnormalities. Calcium is an important second messenger required in many enzymatic activities and muscle and myocardial contraction. Neuronal injury and cerebral oedema caused by hypoxia and ischaemia worsen due to maladaptation to the hyponatremic effect. Prompt and appropriate management of electrolyte derangements can reduce ischaemic penumbra, seizure, further CNS, and other organ injuries with improving outcomes in perinatal asphyxia.[14]

In the present study, 36.5% of the newborns had hyponatremia at baseline, while under stages 2 and 3, the sodium level was found to be significantly lower than the baseline with each consecutive sampling, during each interval of 24 h ($P = 0.033$) and 48 h of life ($P = 0.001$). The degree of hyponatremia was statistically significant ($P = 0.003$) in different stages of HIE with the lowest mean serum sodium observed in stage 3 at 48 h. Pallab Basu *et al.*[15] also reported a significant positive correlation between serum levels of sodium and APGAR score. They studied degree of electrolyte disturbances in asphyxiated and non-asphyxiated newborns and observed that the mean serum sodium level was significantly lower compared to the non-asphyxiated neonates. Babu R *et al.* demonstrated similar findings in their study.[16] However, these studies have compared electrolyte disturbances

Table 3: Mean values of serum electrolytes in different stages of HIE at baseline

Parameters	HIE I	HIE II	HIE III	HIE I vs HIE II	HIE I vs HIE III	HIE II vs HIE III
Serum sodium (mEq/L)±SD	137.19±3.39	137.00±8.18	132.89±2.83	0.990	0.007*	0.034*
Serum potassium (mEq/L)±SD	4.99±0.37	5.11±0.72	5.53±0.76	0.757	0.004*	0.074
Serum calcium (mEq/L)±SD	8.05±0.47	8.13±0.43	7.35±0.85	0.862	0.001*	0.001*

One-way ANOVA test followed by post hoc Tukey test applied. *P<0.05 was taken as statistically significant

Table 4: Comparison of mean sodium levels at different time intervals in relation to Sarnat and Sarnat staging

Sarnat and Sarnat stage	Time Interval	Mean±SD (meq/l)	Baseline to 24 h	24 h-48 h
Stage 1	Baseline	136.07±2.28	0.365 (*n*=15)	
	24 h	135.20±3.17		
Stage 2	Baseline	137.00±8.18	0.004* (*n*=18)	0.001* (*n*=18)
	24 h	132.50±3.03		
	48 h	129.00±0.00		
Stage 3	Baseline	132.31±2.06	0.033* (*n*=13)	0.001* (*n*=13)
	24 h	131.15±0.99		
	48 h	127.71±0.95		

Paired '*t*' test applied. *P*<0.05 was taken as statistically significant, *n*=number of pairs

Table 5: Comparison of mean potassium levels at different time intervals in relation to Sarnat and Sarnat staging

Sarnat and Sarnat Stage	Time Interval	Mean±SD (meq/l)	Baseline to 24 h	24 h-48 h
Stage 1	Baseline	5.03±0.21	0.002* (*n*=15)	--
	24 h	4.87±0.27		
Stage 2	Baseline	5.11±0.72	0.016* (*n*=18)	0.001* (*n*=18)
	24 h	4.84±0.36		
	48 h	4.60±0.00		
Stage 3	Baseline	5.54±0.89	0.033* (*n*=13)	0.114, (*n*=13)
	24 h	5.26±0.63		
	48 h	5.57±0.35		

Paired '*t*' test applied. *P*<0.05 was taken as statistically significant, *n*=number of pairs

Table 6: Comparison of mean calcium levels at different time intervals in relation to Sarnat and Sarnat staging

Sarnat and Sarnat stage	Time Interval	Mean±SD	Baseline to 24 h	24 h-48 h
Stage 1	Baseline	7.96±0.40	0.002* (*n*=15)	--
	24 h	8.46±0.32		
Stage 2	Baseline	8.13±0.43	0.332, (*n*=18)	0.174, (*n*=18)
	24 h	8.44±1.14		
	48 h	6.30±0.00		
Stage 3	Baseline	7.59±0.94	0.707, (*n*=7)	0.257, (*n*=7)
	24 h	7.93±1.69		
	48 h	7.21±0.59		

Paired '*t*' test applied. *P*<0.05 was taken as statistically significant, *n*=number of pairs

in asphyxiated and non-asphyxiated groups, but subsequent electrolyte derangement was not observed in these studies. Asphyxiated newborns are prone to dilutional hyponatremia due to syndrome of inappropriate antidiuretic hormone (ADH) secretion.

There was a statistically significant variation in mean potassium level among the Sarnat and Sarnat staging (P = 0.006). Hyperkalaemia was predominant in stage 3 than in stage 1 at baseline, 24 hours, and 72 hours. The degree of hyperkalaemia increases with the severity of HIE. This is in accordance with other studies conducted by Pallab Basu *et al.* and Babu R *et al.*, who observed similar correlation between serum levels of potassium and severity of asphyxia.[15,16] The higher level of serum potassium in asphyxiated neonates can be explained by shift of potassium from the intra-cellular to extra-cellular compartment resulting from acidosis. Accompanied renal failure can also contribute to hyperkalaemia in asphyxiated neonates.

We observed statistically a significant variation in mean calcium level at baseline among the Sarnat and Sarnat staging (P = 0.001). The mean calcium level at baseline was significantly lower in stage 3 compared to stage 1 (P = 0.001) and stage 2 (P = 0.001). However, no statistically significant difference was observed in mean calcium levels at different time intervals in different stages of HIE. Basu *et al.* and Babu R *et al.* also found decreasing serum calcium levels with increasing severity of asphyxia, showing a positive correlation.[15,16] Similar observations were made by Hasan *et al.*,[18] where it was observed that the serum sodium and potassium levels were statistically significant in relation to the degree of hypoxia, but not the calcium levels.

Of the 74 patients included in the study, 6 (8.1%) patients expired. All the 68 (91.9%) patients in stage 1 and stage 2 HIE were discharged and did not have any focal neurological deficit at the time of discharge. There was a statistically significant association seen between Sarnat and Sarnat staging and the final outcome (P = 0.001), with higher incidence of mortality observed in stage 3 (31.5%). This finding was similar to study conducted by Acharya *et al.*, who also found mortality was higher in severe stage of HIE than mild/moderate. They also noted neurological sequelae was more in moderate and severe stages of HIE.[17]

There were some limitations in our study as this was a single-centre study with no case-control and findings cannot be generalized. The correlation of degree of biochemical abnormalities with severity of asphyxia and at different hours of life has not been reported before from India to the best of our knowledge. The effect of other parameters affecting biochemical abnormalities like acute kidney injury, haemodynamic instability, metabolic acidosis, and also fluid therapy were not considered in our study. Information collected regarding maternal diabetes, fever during pregnancy, the presence of anaemia, and other such factors helped providing a better insight, which can be an advantage of our study. Perinatal asphyxia contributes significantly to the neonatal morbidity and mortality rates globally, with a similar set of circumstances in India.

Conclusion

Asphyxiated babies with severe HIE with electrolyte derangements were found to have severe disease and high mortality in our study group. The risk factors for birth asphyxia can be prevented by proper antenatal care. Prompt identification of risk factors with active and timely intervention/referral to higher centres can decrease incidence of perinatal asphyxia in our country. Neonatal mortality and long-term neurological sequelae can be reduced with effective neonatal resuscitation and quick and timely correction of electrolyte derangements.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Global Health Indicators. Available from: http://www.who.int/gho. [Last accessed on 2022 Jan 18].
2. Sendeku FW, Azeze GG, Fenta SL. Perinatal asphyxia and its associated factors in Ethiopia: A systematic review and meta-analysis. BMC Pediatr 2020;20:135.
3. Perlman JM, Tack ED, Martin T, Shackelford G, Amon E. Acute systemic organ injury in term infants after asphyxia. Am J Dis Child 1989;143:617-20.
4. Perlman JM. Markers of asphyxia and neonatal brain injury. N Engl J Med 1999;341:364-5.
5. Viaroli F, Cheung PY, O'Reilly M, Polglase GR, Pichler G, Schmölzer GM. Reducing brain injury of preterm infants in the delivery room. Front Pediatr 2018;6:290.
6. Enweronu-Laryea CC, Andoh HD, Frimpong-Barfi A, Asenso-Boadi FM. Parental costs for in-patient neonatal services for perinatal asphyxia and low birth weight in Ghana. PLoS One 2018;13:e0204410.
7. Kapaya H, Williams R, Elton G, Anumba D. Can obstetric risk factors predict fetal acidaemia at birth? a retrospective case-control study. J Pregnancy 2018;2018:2195965.
8. Martín-Ancel A, García-Alix A, Cabañas FG, Burgueros M, Quero J. Multiple organ involvement in perinatal asphyxia. J Pediatr 1995;127:786-93.
9. Melkie M, Yigeremu M, Nigussie P, Teka T, Kinde S. Establishing reference intervals for electrolytes in newborns and infants using direct ISE analyzer. BMC Res Notes 2013;6:199.
10. Hankins GD, Speer M. Defining the pathogenesis and pathophysiology of neonatal encephalopathy and cerebral palsy. Obstet Gynecol 2003;102:628-36.
11. Haider BA, Bhutta ZA. Birth asphyxia in developing countries: Current status and public health implications. Curr Probl Pediatr Adolesc Health Care 2006;5:178-88.
12. Lorenz JM, Kleinman LI, Kotagal UR, Reller MD. Water balance in very low-birth-weight infants: Relationship to water and sodium intake and effect on outcome. J Pediatr 1982;101:423-32.
13. Shaffer SG, Meade VM. Sodium balance and extracellular volume regulation in very low birth weight infants. J Pediatr 1989;115:285-90.
14. Tsang RC, Kleinman LI, Sutherland JM, Light IJ. Hypocalcemia in infants of diabetic mothers: Studies in calcium, phosphorus, and magnesium metabolism and parathormone responsiveness. J Pediatr 1972;80:384-95.
15. Basu P, Som S, Das H, Choudhuri N. Electrolyte status in birth asphyxia. Indian J Pediatr 2010;77:259-62.
16. Babu R M, Jerry PK, G H, C S. A comparative study of serum electrolytes in newborns with birth asphyxia and non-asphyxiated newborns. Pediatr Rev 2018;5:407-12.
17. Acharya A, Swain B, Pradhan S, Jena PK, Mohakud NK, Swain A, *et al.* Clinico-biochemical correlation in birth asphyxia and its effects on outcome. Cureus 2020;12:e11407.
18. Hasan BA, Al-Ani MH. Electrolyte disturbance in asphyxiated neonates in maternity hospital in Erbil, Iraq. Med J Babylon 2019;16:331-4.