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Original Article

# Prevalence of Electrolyte Imbalance in Hypoxic-ischemic Encephalopathy: A Hospital-based Prospective Observational Study

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## ABSTRACT

***Background:*** The present study aimed to investigate the prevalence of electrolyte imbalance in hypoxic-ischemic encephalopathy (HIE). Moreover, the correlation of this condition with Apgar score is evaluated.
***Methods:*** This prospective observational hospital-based study was conducted on 75 neonates affected by asphyxiation. Immediately (within ≤ 30 min of stabilization) after resuscitation, basic routine tests along with sodium (Na+), potassium (K+), and calcium (Ca++) were requested from laboratory to be quantitatively estimated. These neonates were clinically examined and classified into various stages of HIE according to recommended staging classification. The values of electrolytes were calculated and compared between various stages of HIE. Furthermore, the correlation between these electrolytes and Apgar score was assessed.
***Results:*** It was observed in our study that HIE is associated with low levels of sodium and calcium. On the other hand, it is correlated with high levels of potassium. As severity of HIE increases, sodium and calcium levels decrease, while potassium level augments. Apgar score was significantly correlated with sodium and potassium. However, the correlation of potassium and sodium with Apgar score was shown to be negative and positive, respectively. Calcium levels did not have a significant correlation with Apgar score.
***Conclusion:*** Electrolyte imbalances, such as hyponatremia, hyperkalemia, and hypocalcemia are common in HIE. Hyponatremia and hyperkalaemia are significantly correlated with Apgar score. Therefore, Apgar score can be used as a determinant to start electrolyte therapy in HIE.

***Keywords:*** HIE, Hyperkalaemia, Hypocalcaemia, Hyponatremia

## Introduction

Perinatal asphyxia is a threat to fetus or newborns due to lack of oxygen and/or perfusion to brain and other organs. It is often associated with multiple pathophysiological consequences, which lead to multiorgan dysfunction (1). Perinatal asphyxia can lead to myocardial dysfunction, rhythm abnormalities, acute renal failure, respiratory failure, necrotizing enterocolitis in preterm neonates, coagulation abnormalities, and metabolic abnormalities, such as hypoglycemia, hyperglycemia, and hypocalcemia (2). In addition, central nervous system as an essential system gets involved in hypoxia.

Decreased perfusion leads to devasting complications both immediate and long-term. Hypoxic–ischemic encephalopathy (HIE) as one of these complications is among the leading causes of neonatal brain injury and neonatal morbidity, as well as mortality (3). Severe HIE can result in deleterious impact on newborns which subsequently leads to cerebral palsy, refractory seizures, pediatric stroke, and paralysis (4).

Intrapartum hypoxic events caused an estimated 717,000 deaths in 2010 (one in five of all neonatal deaths worldwide) (4). Newborns surviving from HIE are at high risk for development of neuropsychological impairments, including psychosis, depressive illness, and cognitive impairment.

Moreover, HIE causes the augmented secretion

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of anti-diuretic hormone which leads to increased retention of water and dilutional hyponatremia (5). Another possible reason for hyponatremia in HIE could be disproportionate sodium reabsorption in collecting tubules resulting in elevated sodium excretion (6).

Hyperkalemia is a common finding in HIE and occurs because of increased acidosis which leads to the shift of intracellular potassium to the extracellular environment (7). In addition, acute kidney injury which is a frequent complication due to HIE can result in hyperkalemia.

Immediately after birth, neonatal calcium level starts to fall and reaches the nadir at 24-28 h (8). In response to this, parathyroid hormone (PTH) level rises and maintains calcium hemostasis. It should be noted that HIE blunts the effect of PTH which can be a potential cause of hypocalcemia (9).

There is limited literature regarding electrolyte disturbance in asphyxiated newborns, especially concerning the correlation between electrolyte imbalance and the severity of asphyxia. Subsequently, the present study aim to investigate electrolytes (i.e., sodium, potassium, calcium) disturbances in asphyxiated newborns representing different severity in the early neonatal period. Furthermore, we assessed the correlation between the severity of perinatal asphyxia and the levels of sodium, potassium, and calcium.

## Methods

This prospective observational study was conducted on 75 term asphyxiated neonates who were born in City Max Hospital and Research Centre, Haryana, India during August 2013-March 2015. The inclusion criteria entailed perinatal asphyxia according to the definition proposed by the World Health Organization as “failure to initiate and sustain breathing at birth”, five-min Apgar score of < 7 even after receiving resuscitation according to the Neonatal Resuscitation Program guidelines.

In this study, sample size of 75 was obtained using Raosoft sample size calculator considering margin of error of 5%, confidence level of 95%, and expecting an annual total perinatal asphyxia cases to be 100 after checking the previous records of our hospital (10). Proper ethical and scientific committee approval and consent from parents were taken for conducting this research.

The exclusion criteria encompassed preterm age of < 36 weeks, intrauterine growth restriction, major congenital abnormalities, hypothermic babies, babies of diabetic mothers, mothers having electrolyte abnormalities, babies of those mothers who are given medicine which disturbs electrolyte balance, such as diuretics and general anesthesia.

All the asphyxiated newborns were resuscitated based on the guidelines of neonatal resuscitation program (NRP) and Apgar score was recorded at one- and five-min. Afterwards, the neonates were shifted to level III nursery care. Priority was given to maintain temperature in all infants because it may affect electrolyte balance in neonates.

In addition to the routine evaluations, sodium ($Na+$), potassium ($K+$), and calcium $Ca++$ were requested from laboratory for all the neonates soon after stabilization which on an average took ≤ 30 min. No child was given therapeutic hypothermia because of the unavailability of this modality in our hospital. Ion electrode method was used to analyze the serum samples for electrolytes by automated machine.

These newborn were examined regularly by senior registrar for clinical symptoms and signs followed by classification into the three stages of HIE according to Sarnat and Sarnat classification of HIE (11) as shown in Table 1.

**Table 1.** Sarnat and Sarnat classification of HIE (11)

| | Stage 1 (Mild) | Stage 2 (Moderate) | Stage 3 (Severe) |
|---|---|---|---|
| Consciousness | Hyperalert | Lethargic or obtunded | Stupor or coma |
| Activity | Normal | Decreased | Absent |
| Neuromuscular control | | | |
| a. Muscle tone | Normal | Mild hypotonia | Flaccid |
| b. Posture | Mild distal flexion | Strong distal Flexion | Intermittent decerebration |
| c. Stretch reflexes | Overactive | Overactive | Decreased or absent |
| Primitive reflexes | | | |
| a. Suck | Weak | Weak or absent | Absent |
| b. Moro | Strong, | Weak incomplete | Absent |
| c. Tonic neck | Slight | Strong | Absent |
| Autonomic function | | | |
| a. Pupils | Dilated | Constricted | Variable, unequal |
| b. Heart rate | Tachycardia | Bradycardia | Variable |

The normal levels of serum sodium, potassium, and ionized calcium were regarded as 130-145 mEq/l, 3.7–5.9 mEq/l, and 1–1.5 mmol/l, respectively (12).

All the data was charted and analyzed using SPSS software version 24 and MedCalc version 18.11. The descriptive statistics included mean and standard deviation. Moreover, analysis of variance (ANOVA) was used with Scheffe's post-hoc test for comparing the groups. The correlation between electrolytes and Apgar score was evaluated by Pearson's correlation test.

## Results

Our study included 75 asphyxiated neonates, out of which 39 were males and 36 were females. Among the participants, 33 were delivered through lower segment cesarean section (LSCS) and 42 through vaginal route. The mean weight of male and female infants was 2.94±1.3 and 2.85±1.1 kg, respectively. The mean gestational age of male infants was 37.5±1 weeks and for females was 37.7±0.8 weeks. There was no statistically significant electrolyte difference when gender, gestational age, and birth weight of the neonates were compared (Table 2).

In the present study, out of 75, 59 (78.7%) newborns showed electrolyte abnormality either, hyponatremia, hyperkalemia, hypocalcemia, or a combination of these conditions. It was shown that 16 (21.3%) neonates which did not develope electrolyte abnormalities were present only in HIE I (N=10, 30%) and HIE II (N=6, 20.7%) stage. All the patients in HIE III developed some electrolyte abnormality. Our study revealed that as the severity of HIE increases electrolyte abnormality also exacerbates (Table 3).

Table 4 indicates the mean electrolyte levels and standard deviations in the various stages of HIE. It was reported that as the severity of HIE increased, sodium concentration decreased and potassium concenrtation elevated. Statistical significance of this occurrence was proved by ANOVA and post-hoc statistical test (Table 5) with the significant P-values of 0.002 and 0 when sodium levels of HIE I were compared with HIE II and HIE III, respectively.

Moreover, comparison of sodium between HIE II and HIE III demonstrated the significant statistical P-value of 0.027. In addition, the comparison of potassium level of between HIE I with HIE II and HIE III showed the P-values of 0 and 0. Comparison of potassium levels between HIE II and HIE III also revealed the significant

**Table 2.** Descriptive statistics of the infants in this study

| | | |
|---|---|---|
| Gender | Male | 39 |
| | Females | 36 |
| Mode of delivery | Vaginal delivery | 33 |
| | LSCS | 42 |
| Mean weight±SD (kg) | Male | 2.94±1.3 |
| | Female | 2.85±1.1 |
| Mean gestational age±SD (weeks) | Male | 37.5±1 |
| | Female | 37.7±0.8 |

**Table 3.** Electrolyte status according to the stage of HIE

| HIE Stage | No. | Hyponatremia | Hyperkalaemia | Hypocalcaemia | No electrolyte abnormality |
|---|---|---|---|---|---|
| I | 33 | 1 (3.03%) | 3 (9.09%) | 5 (15.15%) | 10 (30%) |
| II | 29 | 16 (55.17%) | 19 (65.5%) | 22 (75.86%) | 6 (20.8%) |
| III | 13 | 11 (84.6%) | 9 (69.23%) | 12 (92.3%) | 0 |

**Table 4.** Characteristics of electrolytes in the various stages of HIE

| | | N | Mean | Std. Deviation | Std. Error | 95% Confidence Interval for Mean | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower Bound | Upper Bound |
| Na | HIE I | 33 | 135.1788 | 4.22498 | 0.73547 | 133.6807 | 136.6769 |
| | HIE II | 29 | 131.3276 | 4.30124 | 0.79872 | 129.6915 | 132.9637 |
| | HIE III | 13 | 127.5385 | 4.48359 | 1.24352 | 124.8291 | 130.2479 |
| | Total | 75 | 132.3653 | 5.10139 | 0.58906 | 131.1916 | 133.5391 |
| K | HIE I | 33 | 3.9615 | 0.46198 | 0.08042 | 3.7977 | 4.1253 |
| | HIE II | 29 | 4.5623 | 0.48245 | 0.08959 | 4.3788 | 4.7458 |
| | HIE III | 13 | 5.1862 | 0.77417 | 0.21472 | 4.7183 | 5.6540 |
| | Total | 75 | 4.4061 | 0.69437 | 0.08018 | 4.2463 | 4.5659 |
| Ca | HIE I | 33 | 1.1867 | 0.35762 | 0.06225 | 1.0599 | 1.3135 |
| | HIE II | 29 | 1.0862 | 0.21041 | 0.03907 | 1.0062 | 1.1662 |
| | HIE III | 13 | 0.9677 | 0.35110 | 0.09738 | 0.7555 | 1.1799 |
| | Total | 75 | 1.1099 | 0.31376 | 0.03623 | 1.0377 | 1.1821 |
| APGAR Score | HIE I | 33 | 5.5455 | 1.09233 | 0.19015 | 5.1581 | 5.9328 |
| | HIE II | 29 | 4.6552 | 1.17339 | 0.21789 | 4.2088 | 5.1015 |
| | HIE III | 13 | 3.7692 | 1.16575 | 0.32332 | 3.0648 | 4.4737 |
| | Total | 75 | 4.8933 | 1.30045 | 0.15016 | 4.5941 | 5.1925 |

**Table 5.** ANOVA (post-hoc test) of electrolytes between the two stages of HIE

| Electrolyte | Sarnat and Sarnat | Sarnat and Sarnat | Mean Difference | Significance P-Value | 95% confidence interval | |
|---|---|---|---|---|---|---|
| | | | | | Lower bound | Upper bound |
| $Na^+$ | HIE I | HIE II | 3.85120* | 0.002 | 1.2328 | 6.4696 |
| | | HIE III | 7.64033* | 0 | 4.2717 | 11.0089 |
| | HIE II | HIE III | 3.78912* | 0.027 | 0.3555 | 7.2228 |
| $K^+$ | HIE I | HIE II | -.60080* | 0 | -0.9261 | -0.2755 |
| | | HIE III | -1.22464* | 0 | -1.6432 | -0.8061 |
| | HIE II | HIE III | -0.62384* | 0.002 | -1.0505 | -0.1972 |
| $Ca^{++}$ | HIE I | HIE II | 0.10046 | 0.409 | -0.0869 | 0.2878 |
| | | HIE III | 0.21897 | 0.083 | -0.0221 | 0.4600 |
| | HIE II | HIE III | 0.11851 | 0.484 | -0.1272 | 0.3642 |

**Table 6.** Pearson's correlation between various groups

| Correlation | r | CI for r | Sig P-value |
|---|---|---|---|
| Na+ and Apgar Score | 0.7904 | 0.6866-0.8626 | < 0.001 |
| K+ and Apgar Score | -0.4662 | -0.6268--0.2675 | < 0.001 |
| Ca++ and Apgar Score | 0.1106 | -0.1194-0.3293 | 0.3449 |

r=Pearson's correlation coefficient, CI= Confidence Interval, Sig=Two tailed significance

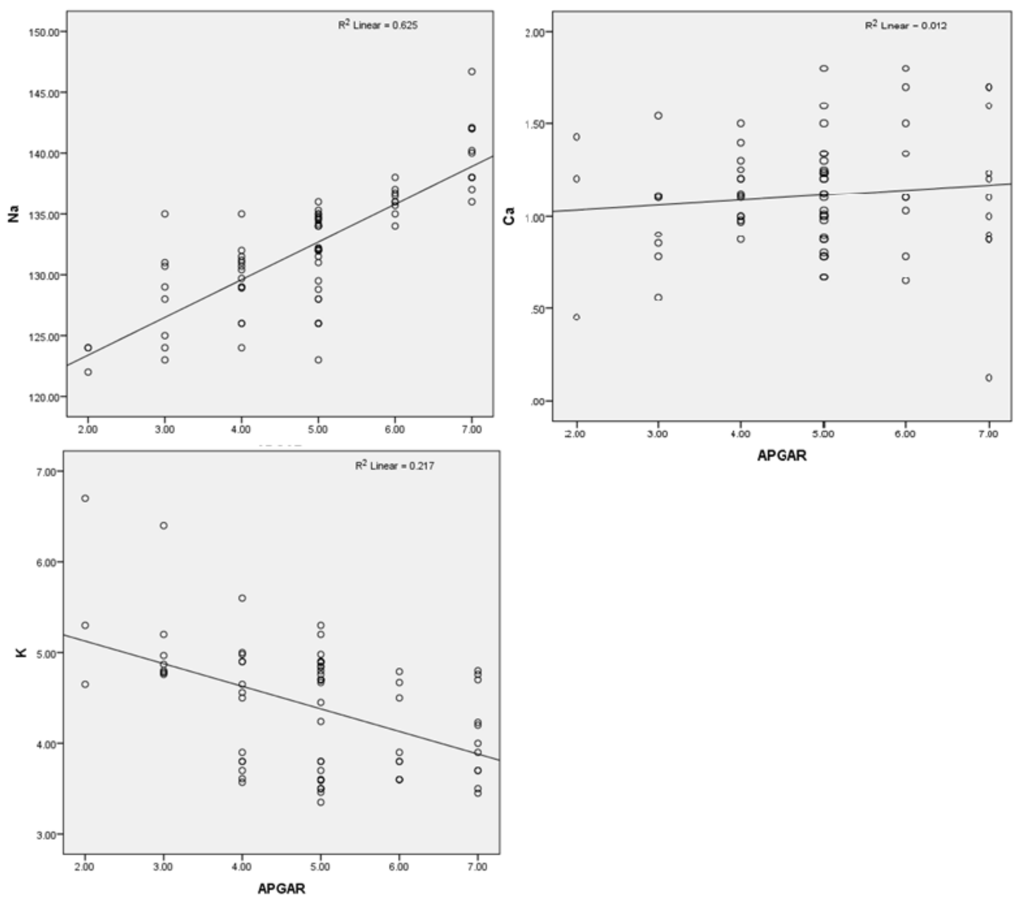


**Figure 1.** Scatter plot of the correlation of electrolytes with Apgar score

P-value of 0.02. Although ionized calcium was low, compared to the reference values in stages II and III (1.08 and 0.967), the comparison between various stages of HIE indicated no statistical significance as shown in Table 5.

Five-min Apgar score was shown to have a positive significant correlation with sodium with the correlation coefficient (r) of 0.7904 and P < 0.0001. Potassium showed significant (P < 0.001, r=-0.446) negative correlation with Apgar score. As a result, when Apgar score increased, potassium level declined. Calcium showed no correlation with Apgar score (r=0.1106, P=0.3449) (Table 6, Figure 1).

## Discussion

The current study revealed a 78.7% prevalence of electrolyte imbalance in HIE, which included either hyponatremia, hyperkalemia, hypocalcemia, or a mixture of these abnormalities.

The mean sodium, potassium, and ionized calcium in our study were 132.36 mEq/ml, 4.406 mEq/ml, and 1.1099 mmol/ml, respectively. Similar results were shown in the study performed by Thakur et al. (13). These authors reported the mean levels of sodium, potassium, and ionized calcium as 130.73±4.60 mEq/l, 5.98±1.03 mEq/l, and 1.05±0.14 mmol/l, respectively. Therefore, the mean potassium level in the study conducted by Thakur et al. (13) was higher than our study.

However, the study completed by Vandana et al. (14) showed the means of sodium and potassium among the cases as 136.5±8.7 and 4.48±0.36 mEq/l, respectively. It is concluded that the potassium level in the mentioned study is similar to our study. The difference in some electrolyte levels among these studies could be attributed to the timing of collecting the samples for electrolyte estimation. We collected the samples as soon as possible after the stabilization of the neonates (almost ≤ 30 min) in our study.

Our study revealed that with elevation in the severity of HIE, sodium levels diminished and potassium levels augmented. Thakur et al. (13) and Basu et al. (15) found similar results with the present investigation. Furthermore, calcium level decreased with the severity of HIE; However, the correlation was not significant. Such result was supported by the study performed by Thakur et al. (13), Schedewie et al. (17), and Jagoo et al. (16).

The correlation of sodium with Apgar score was shown to be positive and significant. On the other hand, potassium was negatively correlated with Apgar score. The results reported by Thakur et al. (13) and Basu et al. (15) are consistent with our findings in this regard.

According to the findings of this study, we recommend to take meticulous care of body sodium and potassium levels and start therapy when is needed according to the clinical signs because the imbalance of electrolytes can have remarkable effects on body. Calcium level was low in our study and had no correlation with the severity of hypoxia. Nonetheless, we suggest calcium therapy at normal recommended concentrations because other studies support this idea and the sample size of our study was very low.

## Conclusion

To summarize, significant hyponatremia, hyperkalemia, and hypocalcemia was observed in HIE. It was shown that as the severity of HIE increases, hyponatremia and hyperkalemia are exacerbated. Apgar score has a strong correlation with hyponatremia and hyperkalemia. Therefore, it can be used as a better indicator to start prophylactic electrolyte therapy in asphyxiated neonates.


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## Conflicts of interests

The authors declare no conflict of interest for the present study.

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