



## Original Article



## Comparison Between Serum Electrolyte Levels in Full-Term Healthy Neonates Versus Neonates with Hypoxic Ischemic Encephalopathy

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## ABSTRACT

Hypoxic ischemic encephalopathy (HIE) is a major cause of neonatal mortality and neurological disability. Hypoxia leads to multisystem involvement, causing electrolyte disturbances such as hyponatremia, hyperkalemia, and hypocalcemia, causing adverse clinical outcomes. Most studies assess these abnormalities after 24 hours of life. Detection within the first 12 hours may help reduce complications and long-term disability. **Objectives:** To compare serum sodium, potassium, and calcium levels in full-term healthy neonates versus those with HIE. **Methods:** This cross-sectional study was conducted at King Edward Medical University from June 2025 to November 2025 (IRB letter no. 512/RC/KEMU). Patients presenting to Mayo hospital over six months period were evaluated to determine the frequency of hypoxic-ischemic encephalopathy (HIE). After taking informed consent, 228 eligible subjects were identified, comprising 114 HIE and 114 non-HIE patients. Serum sodium, calcium, and potassium levels were measured within the first 12 hours of life and were compared between the two groups. Data were analyzed using SPSS version 27.0, and an independent t-test and Chi-square test were applied with a p-value <0.050. **Results:** The frequency of neonates diagnosed with HIE was 9.7%. Hyponatremia (32.3%), hyperkalemia (22.8%), and hypocalcemia (8.8%) were significantly more common in neonates with HIE. These differences were statistically significant (p<0.001). **Conclusions:** Compared to healthy neonates, neonates with HIE demonstrated significantly higher rates of electrolyte abnormalities. Identification of these electrolyte abnormalities is crucial, as timely detection and correction can play an important role in preventing further neurological damage, thereby enhancing clinical outcomes in affected neonates.

## INTRODUCTION

Hypoxic Ischemic Encephalopathy is a leading cause of neonatal mortality, morbidity, and neonatal brain injury despite advancements in neonatal medicine. Approximately 17% of infants with HIE die in the neonatal period, and 25% of survivors face permanent cerebral palsy, decreased IQ, cognitive impairment, and other developmental abnormalities. The frequency of HIE ranges from 0.5 to 2% of live births [1, 2]. A study conducted in Pakistan reported the neonatal mortality rate of 64% following perinatal asphyxia (roughly 80,000 deaths/year) [2]. Hypoxic ischemic encephalopathy is an antepartum or intrapartum fetal insult causing various adverse biochemical and functional changes in the body [3]. Birth asphyxia is the most common preventable cause of

neonatal central nervous system injury [4]. The American College of Obstetricians and the American Academy of Pediatrics recommend HIE diagnosis to include the occurrence of a sentinel event immediately before or during labor, low Apgar scores, and evidence of fetal acidosis, signs of multi-organ injury affecting the heart, liver, or kidneys, and MRI findings consistent with acute intrapartum or peripartum asphyxia [3, 5]. The serum electrolyte levels play a pivotal role in the outcome of neonates with hypoxia [6]. Deviation of electrolytes from the normal levels can lead to shock, convulsions, and other types of metabolic abnormalities [7]. HIE can cause dilutional hyponatremia by causing increased secretion of antidiuretic hormone. Hyponatremia in HIE could also be



the result of elevated sodium excretion via collecting tubules [8, 9]. Hyperkalemia may occur in HIE due to increased pH of the extracellular environment that brings more potassium out. Acute kidney injury, seen in HIE, also results in hyperkalemia [10, 11]. Hypocalcemia is also observed in HIE, probably due to decreased effect of parathyroid hormone under the influence of hypoxia [1]. Early detection and immediate correction of biochemical derangements in birth asphyxia can prevent the complications and lifelong disabilities associated with it [12-14]. Although several studies elaborate on the underlying physiological association between electrolyte imbalance and hypoxic tissue damage, most of the studies determine electrolyte levels at 24h of life or later. Hyponatremia was found to be significant in all stages of birth asphyxia, hyperkalemia was associated with increased severity of birth asphyxia, whereas hypocalcemia was not found to be related to birth hypoxia [8]. The frequency of hypoxic ischemic encephalopathy in the developing world is at an alarmingly high level of 10% [15]. Early detection and immediate correction of biochemical derangements in newborns with hypoxic ischemic encephalopathy can prevent lifelong disabilities related to birth asphyxia that may occur due to injury to vital organs, particularly the brain.

There is no multicenter data available on electrolyte disturbances in HIE in Pakistan, and most research is the experience of a single center. None of the longitudinal studies have evaluated the benefits of timely electrolyte correction within 12 hours of birth on the neurodevelopmental outcome in the long run. The Mayo Hospital, Lahore, has a single-center design, which limits the generalizability throughout Pakistan. The cross-sectional design does not allow a causal or temporal correlation of HIE and electrolyte disturbances. Therefore, this study is needed to find abnormalities of serum electrolytes in hypoxic neonates within the first 12 hours of life. This study aims to compare serum sodium, potassium, and calcium levels in healthy neonates and neonates with HIE.

## METHODS

This comparative cross-sectional study was carried out at Mayo Hospital, Lahore, with approval from the Institutional Review Board (IRB letter reference no. 512/RC/KEMU Dated: 28th June, 2025 and CPSP no: CPSP/REU/PED-2022-066-7108 Dated 13th April, 2025). During June 2025 to November 2025, all neonates were assessed to determine the frequency of hypoxic-ischemic encephalopathy (HIE), diagnosed based on history and examination. After completing the inclusion criteria and taking informed consent from parents, a total of 228 full-term neonates ( $\geq 37$  weeks of gestation) were enrolled using non-

probability consecutive sampling, including 114 with HIE and 114 healthy controls. The sample size was calculated using the single population proportion formula using 95% confidence interval, 5% margin of error, and an expected percentage of HIE as 10% [15]. Inclusion criteria comprised of full-term neonates admitted within 12 hours of birth and diagnosed with HIE based on history (e.g., delayed cry, meconium-stained liquor), APGAR score of less than 7 at 5 minutes, and Sarnat staging. Syndromic babies, infants of diabetic mothers, and infants born to mothers on antiepileptics or antihypertensives were excluded from the study. Serum sodium, serum potassium, and serum calcium levels were measured within the first 12 hours of life. 3 ml venous blood was collected under aseptic conditions for serum sodium, potassium, and calcium estimation using a standard autoanalyzer. The normal reference ranges were defined according to standard laboratory reference intervals (CLSI guidelines) and Nelson's textbook as follows: serum sodium 135-145 mEq/L, serum potassium 3.5-5.0 mEq/L, and total serum calcium 8.0-10.5 mg/dL.

SPSS version 27 was used. Quantitative variables were expressed as mean  $\pm$  standard deviation. Chi-square test and independent sample t-test were used with a p-value  $< 0.050$  as statistically significant.

## RESULTS

During the study period, the frequency of HIE among full-term neonates was 9.7%, with approximately 56% of cases being male and 44% female. The majority of neonates with HIE had evidence of fetal distress, as indicated by documented fetal distress during labor. In the HIE group, the mean age of gestation was  $39.1 \pm 1.0$  weeks, with a range of 37.0 to 41.2 weeks. In the non-HIE group, the mean age of gestation was  $39.0 \pm 1.0$  weeks, with a range of 37.0 to 41.0 weeks, indicating comparable gestational ages between the groups. Additionally, mean birth weight and mode of delivery were similar between the two groups. The comparison of mean serum electrolyte levels between patients with and without HIE is presented (Table 1).

**Table 1:** Comparison of Mean Serum Electrolytes Between HIE and Healthy Neonates (Group Statistics)

Electrolytes	HIE Status (Yes/No)	Number of Subjects (n)	Mean $\pm$ SD	SD Error Mean
Sodium (Na)	No	114	139.81 $\pm$ 3.772	0.353
	Yes	114	135.25 $\pm$ 5.347	0.501
Potassium (K)	No	114	4.042 $\pm$ 0.3703	0.0347
	Yes	114	4.511 $\pm$ 0.7596	0.0711
Calcium (Ca)	No	114	8.894 $\pm$ 0.5481	0.0513
	Yes	114	8.321 $\pm$ 0.9835	0.0921

An independent sample T test was performed to look for a statistically significant difference between the electrolyte levels of HIE and non-HIE groups (Table 2).

**Table 2:** Independent Samples t-Test Comparing Serum Electrolytes Between HIE and Non-HIE Groups

Parameters	t	df	p-value	Mean Difference	95% CI of Difference
Na	7.442	203.13	<0.001	4.561	3.353 to 5.770
K	-5.918	163.84	<0.001	-0.468	-0.624 to -0.312
Ca	5.432	177.01	<0.001	0.572	0.364 to 0.780

Among the 228 neonates studied, sodium levels showed a clear difference between those with and without hypoxic-ischemic encephalopathy (HIE). 92.1% of the healthy neonates had normal sodium levels, in comparison, only 64.9% of HIE neonates were within normal range. Hyponatremia was more frequent in HIE subjects, whereas hypernatremia was less frequent and similar in both groups (~3%)(Table 3).

**Table 3:** Distribution of Serum Sodium Levels in HIE and Non-HIE patients

HIE Status	Sodium within Normal Range (%)	Low (%)	High (%)	p-value
No	92.1	4.4	3.5	<0.001
Yes	64.9	32.3	1.8	
Total	78.5	18.9	2.6	

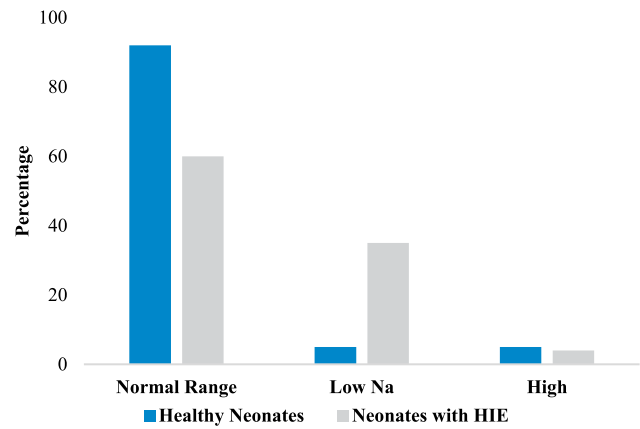
Among HIE neonates, 88.3% had normal serum calcium, while 8.8% showed hypocalcemia, and only 2.6% had hypercalcemia. In contrast, almost all healthy neonates had normal calcium levels, with only 0.9% showing low calcium. Calcium abnormalities were more frequent in the HIE group (p=0.001), indicating an association between HIE and calcium imbalance, particularly hypocalcemia. In addition, only 65.8% HIE neonates had normal potassium levels, while 11.4% had hypokalemia and 22.8% had hyperkalemia. In comparison, 95.6% of healthy neonates had potassium levels within the normal range, and only 1.8% having low and 2.6% having high Potassium levels. Overall, potassium abnormalities, especially hyperkalemia, were significantly more common in HIE neonates than in controls (p<0.001), indicating a strong association between HIE and potassium derangements (Table 4).

**Table 4:** Distribution of Serum Calcium Levels and Serum Potassium Levels in HIE and Non-HIE Patients

HIE Status	Within Normal Range (%)	Low (%)	High (%)	p-value
<b>Calcium</b>				
No	99.1%	0.9%	0.0%	0.001
Yes	88.6%	8.8%	2.6%	
Total	93.9%	4.8%	1.3%	
<b>Potassium</b>				
No	95.6%	1.8%	2.6%	<0.001
Yes	65.8%	11.4%	22.8%	
Total	80.7%	6.6%	12.7%	

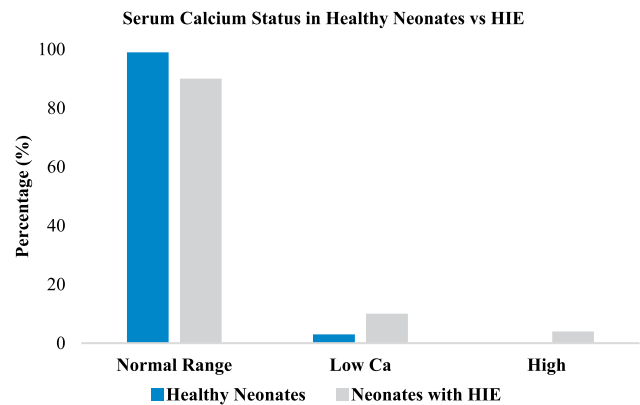
Electrolyte disturbances were significantly more common in HIE neonates: hyponatremia (33.1% vs 3.8%),

hyperkalemia (20.8% vs 2.3%), and hypocalcemia (8.5% vs 0.8%), all p<0.001. The study compares the distribution of serum sodium levels between healthy neonates and those with hypoxic-ischemic encephalopathy (HIE)(Figure 1).



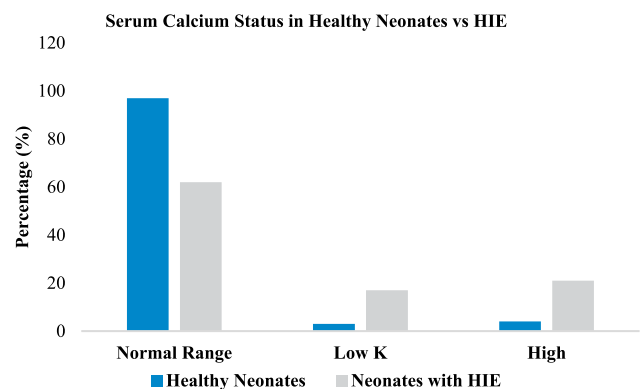
**Figure 1:** Comparison of Serum Sodium Levels Between Healthy and HIE Neonates

The results compare the distribution of serum calcium levels between healthy neonates and those with hypoxic-ischemic encephalopathy (HIE)(Figure 2).



**Figure 2:** Comparison of Serum Calcium Levels Between Healthy and HIE Neonates

The results compare the distribution of serum potassium levels between healthy neonates and those with hypoxic-ischemic encephalopathy (HIE)(Figure 3).



**Figure 3:** Comparison of Serum Potassium Levels Between Healthy and HIE Neonates

## DISCUSSION

Hypoxic Ischemic Encephalopathy remains a major cause of neonatal morbidity and mortality, especially in developing countries where the prevalence may reach up to 10% of live births [16]. This study aimed to find the frequency of neonates presenting at Mayo Hospital who are affected with HIE and to compare serum electrolyte levels, specifically sodium, potassium, and calcium, between full-term healthy neonates and those diagnosed with HIE. The findings highlight that 9.7% of the neonates had HIE, with significant electrolyte disturbances observed among the asphyxiated neonates. Study shows that the degree of hyponatremia, hyperkalemia, and hypocalcemia progressively worsened with increasing severity of HIE at baseline and subsequently [17]. In moderate to severe HIE, the most commonly mildly affected organ systems were the respiratory system, acid-base and electrolyte balance on the first day, and the cardiovascular system on the second day [18]. Neonates with HIE showed a significantly higher frequency of electrolyte disturbances, especially hyponatremia, hyperkalemia, and hypocalcemia. Hyponatremia was more frequently observed in neonates with HIE compared to healthy controls. This disturbance is likely multifactorial and may be a result of increased secretion of antidiuretic hormone in response to hypoxia, causing water retention and dilutional hyponatremia [6, 9]. Additionally, hypoxic damage causes renal tubular dysfunction that impairs sodium reabsorption, which results in increased urinary sodium loss despite low serum levels. These findings are similar to the study by Bhat *et al.* and Segar *et al.* which report hyponatremia to be a significant biochemical derangement in all stages of HIE, and it is closely linked to the severity of hypoxia and risk of seizures [8, 9]. Hyperkalemia was noted in neonates with moderate to severe HIE. The pathophysiology involves impaired renal excretion due to acute kidney injury and hypoxia-induced acidosis, leading to extracellular shifts of potassium [10, 11]. Jha *et al.* reported a strong association between hyperkalemia and asphyxia severity, suggesting its potential use as a severity marker [11]. These findings were further supported by Rajesh *et al.* who found that perinatal asphyxia significantly contributes to potassium elevation by renal compromise [10]. The correlation between hyperkalemia and the severity of asphyxia governs cardiac monitoring and timely intervention. Hypocalcemia was observed in the HIE group, which was less significantly correlated with severity compared to other electrolyte disturbances. This may be due to low parathyroid hormone responsiveness under hypoxic stress [1, 12]. Studies by Injeti *et al.* and Pyati *et al.* support this hypothesis, though the clinical significance of early hypocalcemia remains controversial [1, 12]. While some

studies show associations with poor feeding and hypotonia, other studies, such as Bhat *et al.* found no statistically significant association between hypocalcemia and birth asphyxia severity [8]. The electrolyte imbalances, such as hyponatremia, hyperkalemia, and hypocalcemia, reflect the systemic effects of perinatal hypoxia. These abnormalities demonstrate underlying pathophysiological processes affecting neurologic, endocrine, and renal systems. Acharya *et al.* emphasize that early identification and correction of these imbalances can enhance short-term clinical outcomes and lower the risk of long-term neurological complications, including cerebral palsy and developmental delay [7]. In a study conducted in 2019, 59 out of 75 newborns having HIE (78.7%) exhibited electrolyte abnormalities, including hyponatremia, hyperkalemia, hypocalcemia, or combinations of these disorders. The findings showed that electrolyte disturbances worsened with increasing severity of HIE [8]. A recent study by Nasrin *et al.* demonstrated similar electrolyte derangements [19]. Another study demonstrated similar electrolyte disturbances, which were independently associated with low Apgar scores, severe hypoxic-ischemic encephalopathy, convulsions, dehydration, need for resuscitation at birth, low birth weight, and prolonged intravenous fluid therapy [20]. Furthermore, this study highlights the importance of assessing electrolytes within the first 12 hours of life. Unlike many previous studies that assessed electrolyte levels after 24 hours, early biochemical testing allows for timely medical intervention, potentially avoiding many complications. The clinical importance of such early testing supports existing literature supporting early evaluation and stabilization in birth asphyxia management protocols [13, 14].

A limitation of this study is that the potential confounders, such as duration of birth asphyxia and early fluid or electrolyte management, were not controlled, which may have influenced the observed electrolyte abnormalities, although HIE severity was limited to moderate and severe cases. Prospective cohort studies based on multicenter studies across tertiary hospitals in Pakistan are required in order to determine the national HIE prevalence and electrolyte patterns. The need to evaluate whether early electrolyte correction positively affects neurodevelopmental outcomes should be done through longitudinal follow-up (12-24 months).

## CONCLUSIONS

Neonates with HIE exhibited significantly more frequent electrolyte disturbances, particularly hyponatremia (32.3%), hyperkalemia (22.8%), and hypocalcemia (8.8%), compared with healthy neonates ( $p < 0.001$ ). These findings highlight the strong association between HIE and electrolyte imbalance. Early detection and correction of

these disturbances is essential to minimize complications and improve outcomes. Timely electrolyte screening in neonatal resuscitation and early postnatal care in resource-limited settings with a high burden of HIE can have substantial public health benefits.

### Authors' Contribution

Conceptualization: SFI

Methodology: KI

Formal analysis: MH

Writing and Drafting: KI, SFI, MH

Review and Editing: KI, SFI, MH

All authors approved the final manuscript and take responsibility for the integrity of the work

### Conflicts of Interest

All the authors declare no conflict of interest.

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