

Characteristics and Frequency of Hyponatremia in Newborns

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ABSTRACT

Background: Hyponatremia, defined as a serum sodium level below 135 meq/L, is a significant and often overlooked problem in neonatal intensive care unit. Local data on the severity and chronicity of hyponatremia in neonates is lacking. This study aimed to investigate the features, risk factors, and frequency of hyponatremia in infants admitted to our NICU.

Objective: To determine the incidence, identifying potential risk factors, assessing its severity, as well as understanding the recovery period and the duration of hospital stay associated with hyponatremia in neonates. **Study Design:** Cross-sectional study. **Settings:** Study was conducted in Neonatal ICUs of Fatima Memorial Hospital, Lahore Pakistan. **Duration:** January to December 2022 (1 Year). **Methods:** Sample size was 300, calculated with 95% confidence interval, 10% margin of error and 5% level of significance. It was done by using formula; $n = Z_s (p)(1-p)/d^2$ by using consecutive, non-probability sampling technique. After IRB approval all neonates meeting the inclusion criteria were included in the study after seeking informed consent from parents and relevant data was collected on the predesigned proforma. **Results:** Among 300 neonates included in final study 42% had mild hyponatremia and 58% had moderate-severe hyponatremia. Risk of severe hyponatremia were GA 28-32⁺⁶ weeks, IUGR and APGAR-5<7. PIH increased the risk of chronic hyponatremia. **Conclusion:** In our study population 58% neonates had moderate to severe hyponatremia. Among 73.1% neonates born at GA 28-32⁺⁶ had moderate to severe hyponatremia. APGAR-5 of <7 and IUGR increases the risk of moderate-severe hyponatremia by 42374 and 200 times respectively. Whereas maternal PIH is associated with increased risk of chronic hyponatremia.

Keywords: Hyponatremia, IUGR, APGAR-5<7, PIH, Moderate, Severe, Acute, Chronic.

INTRODUCTION

Sodium is a vital electrolyte of extracellular fluid in human body. Hyponatremia, characterized by serum sodium levels below 135 meq/L, is a common and clinically significant concern, especially in neonates. Roughly 33% of very low birth weight infants and 65% of seriously ill neonates experience this condition. It is categorized into mild (130-134 meq/L), moderate (125-129 meq/L), and severe (<125 meq/L) depending upon severity.^{1,2}

Hyponatremia can also be classified based on its duration. If it lasts less than 48 hours, it is called "acute,"

while if it persists for more than 48 hours, it is termed "chronic." Late-onset hyponatremia, occurring after the first week of life, is three times more common than early-onset hyponatremia, which presents within the first week of life.^{3,4}

In the human body, maintaining the delicate equilibrium of water and sodium is vital for normal homeostasis.⁵ When serum sodium levels dip, it signifies an imbalance in this equilibrium, often due to either insufficient sodium or water intake or excessive sodium or water excretion. These imbalances are frequently linked to underdeveloped renal, cutaneous, or intestinal functions. Numerous risk factors contribute to the development of

hyponatremia in neonates, including factors such as prematurity, renal issues, medical conditions like necrotizing enterocolitis, vomiting or nasogastric drainage, birth-related asphyxia, infections like meningitis, and clinical sepsis.^{6,7}

Hyponatremia in neonates presents with a broad spectrum of symptoms, ranging from being asymptomatic to neonates displaying signs of irritability, seizures, poor feeding, lethargy, dehydration, and edema.^{8,9} Diagnosis is typically confirmed through blood tests that measure sodium levels and other electrolytes. Treatment commonly involves addressing fluid and electrolyte imbalances and resolving the underlying cause.^{10,11}

Neglected neonatal hyponatremia can result in severe complications, underscoring the critical importance of early identification and swift intervention in managing this condition. In the Asian population, there is a dearth of knowledge regarding its causes and prevalence, and notably, no data from Pakistan is available. To address this gap, comprehensive studies should be conducted.

Our study is designed to fill this void by aiming to discern the profile of neonates affected by hyponatremia, which includes determining its incidence, identifying potential risk factors, assessing its severity, as well as understanding the recovery period and the duration of hospital stay associated with this condition. This research endeavor is geared toward gaining a comprehensive understanding of the scope of the issue and to inform decisions on whether to incorporate routine screening for neonatal serum sodium levels in standard medical investigations.

METHODS

After receiving approval from the Institutional Review Board (IRB), a descriptive cross-sectional study was carried out. The study spanned 12 months, commencing in January 2022 and concluding in December 2022. The sample size was calculated to be 300, and calculation was performed based on a 95% confidence level, a 10% margin of error, and a 5% significance level, taking into account the average percentage of hyponatremia, which stands at 33%. This calculation was executed using the formula $n = z^2(p)(1-p)/d^2$.

In order to recruit participants, non-probability consecutive sampling was employed. Neonates who met the inclusion criteria, which involved having a serum sodium level of less than 135 meq/L, were enrolled in the study. Exclusion criteria encompassed neonates with malformations or life-incompatible anomalies, those who were discharged or passed away before a serum sodium test could be conducted, those who declined to participate, and those with missing data.

The serum sodium levels of all neonates were assessed in accordance with the unit protocol. Neonates with documented hyponatremia during their hospital stay were included in the study as a baseline for subsequent analysis. Following this baseline assessment, additional serum sodium measurements were conducted at intervals of every 12 hours until the correction of hyponatremia was achieved.

Data on the mothers was gathered, including information on their diabetes mellitus (GDM), hypertension (PIH), chorioamnionitis, oxytocin, and hypotonic fluids 24 hours before delivery.

Neonatal data, including demographics [gestation age, weight, gender, APGAR score at 1 and 5 minutes], clinical characteristics [HIE 2/3, weight for gestation age (appropriate for gestational age (AGA), large for gestational age (LGA) and intrauterine growth restriction (IUGR), pneumonia, DSD, symptoms (lethargy, reluctance to feed, feed intolerance)], and medication use (caffeine), total parenteral nutrition, intravenous fluids restriction (IVF), and Na requirement extra to maintenance(0, 3-4, >4 meq/kg/day)] and comorbid conditions [sepsis (leukocytosis or leukopenia or ANC<150 along with raised CRP and platelets <100 and or positive blood culture), presence of hemodynamically significant patent ductus arteriosus (hsPDA), intraventricular hemorrhage (IVH), intracranial hemorrhage (ICH), disseminated intravascular coagulopathy (DIC), acute kidney injury(AKI), necrotizing enterocolitis (NEC) (modified Bell's stage II or III), dyskalemia (<3.5 or >5.5 meq/L), hypothyroidism, hypoalbuminemia (serum albumin<2.5 mg/dl), hypoglycemia (<55mg/dl)]. APGAR-5 minutes < 7, was labeled as peripartam stress in our study.

All neonates were monitored for their outcome in form of the duration of hospital stay and need for home sodium supplementation.

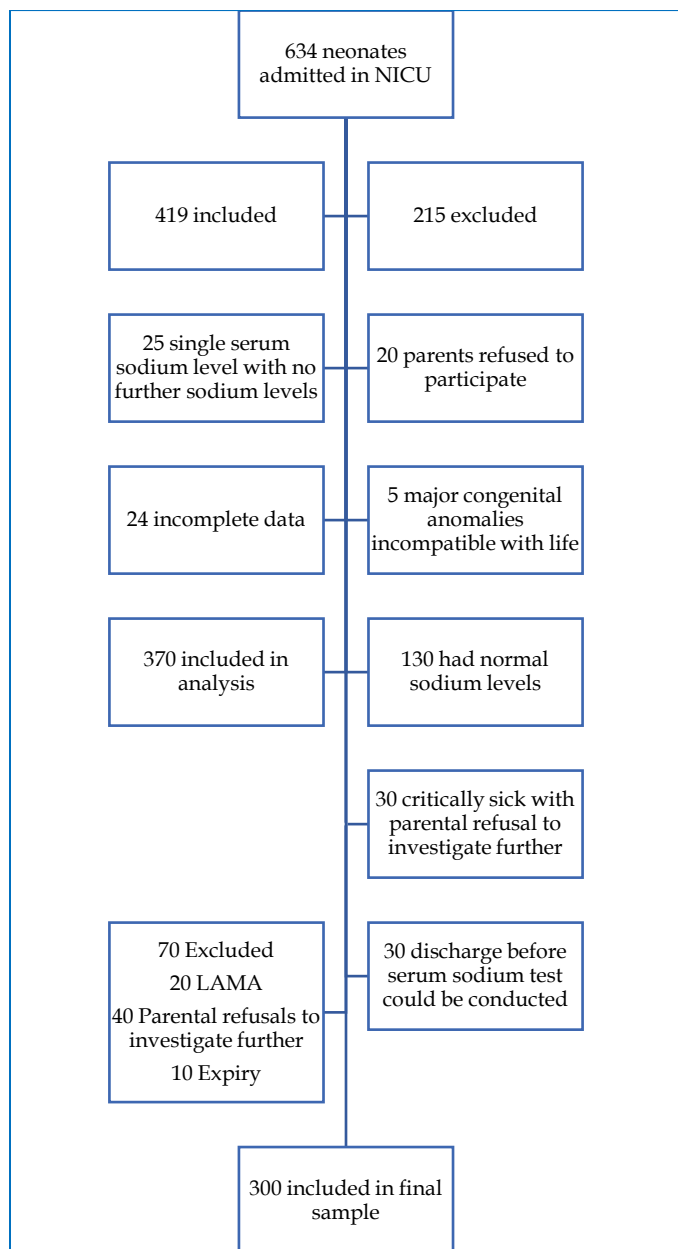
The data were analyzed with SPSS 25. The normality of data was analyzed with the Shapiro-Wilk test. Frequencies and percentages were used for qualitative while mean \pm SD were used for normal quantitative variables respectively. All categorical variables were analyzed by proportional differences with either the Pearson chi-square test or Fisher's exact tests. The z-test was applied to compare column proportions, and p-values were adjusted using the Bonferroni method. Maternal and neonatal characteristics of all neonates with mild hyponatremia were compared with those moderate-severe hyponatremias. All factors in the univariate model with a p-value < 0.05 were subsequently entered in a logistic regression model. Only the associations with a p-value < 0.05 were considered statistically significant, and their odds ratio (OR) with 95%CI was calculated.

Similarly, comparative descriptive statistics and multiple logistic regression were applied to identify all risk factor for acute and chronic hyponatremia in neonates while taking $p < 0.05$ as significant.

RESULTS

During the study period, 634 neonates were admitted to our neonatal intensive care units, out of which 419 met inclusion criteria, and finally 300 had complete data for final analysis (figure 1).

Figure 1: Flow chart of selected patients



Of these 300 neonates 127 (42%) had mild hyponatremia while 173 (58%) had hyponatremia of $< 130\text{mEq/L}$ hence labeled as moderate to severe hyponatremia.

The relationship between the severity of hyponatremia with birth weight and gestation age has been tabulated in table 1. The gestational age-based stratification of the cohort shows that neonate of gestation age 28-32⁺⁶ are more vulnerable to severe hyponatremia as compared to rest of study population. Every 4th neonate of gestation age 28-32⁺⁶ had mild hyponatremia as compared to every second neonate of gestation age ≥ 33 weeks (Table 1). The univariate analysis shows that statistically significant ($p < 0.05$) neonatal demographic risk factors for moderate-severe hyponatremia were birth weight, gestation age, age < 7 days at diagnosis, AGA, IUGR, low birth weight, and APGAR-5 of < 7 (table 1).

Table 1: Demographic data

Parameters	Mild-124 (42.3%)	Moderate to severe 173 (57.7%)	p value	
Maternal				
GDM	1 (3.6%)	27 (96.4%)	< 0.001	
PIH	12 (25.0%)	36 (75.0%)	0.006	
Chorioamnionitis	3 (30.0%)	7 (70.0%)	0.322	
Maternal oxytocin	9 (39.1%)	14 (60.9%)	0.463	
Hypotonic fluids(24 hours before delivery)	1 (3.6%)	27 (96.4%)	< 0.001	
Neonatal				
Gender	MALE	47 (43.9%)	60(56.1%)	0.384
	FEMALE	80 (41.5%)	113(58.5%)	
Birth Weight	Mean \pm SD	2.4 \pm 0.68	2.08 \pm 0.82	< 0.001
	$< 1.5\text{KG}$	22(28.2%)	56(71.8%)	
	1.5-2.5 KG	35(38.9%)	55(61.1%)	
	$> 2.5\text{ KG}$	70(53%)	62(47.0%)	
Preterm	YES	91(42.1%)	125(57.9%)	0.505
AGE < 7 days	Mean \pm SD	2.51 \pm 1.14	3.25 \pm 2.49	0.001
	YES	127(44.1%)	161(55.9%)	
Gestational age group (weeks)	Mean \pm SD	34.99 \pm 2.94	34.07 \pm 3.28	0.003
	28-32 ⁺⁶	21(26.9%)	57(73.1%)	
	33-36 ⁺⁶	70(50.7%)	68(49.3%)	
	≥ 37	36(42.9%)	48(57.1%)	
AS-1	Mean \pm SD	7.33 \pm 0.84	7.20 \pm 0.93	0.522
	< 7	59(42.1%)	81(57.9%)	
	> 7	68(42.5%)	92(57.5%)	
APGAR-5	Mean \pm SD	8.58 \pm 0.72	8.31 \pm 0.83	0.000
	< 7	13(24.1%)	41(75.9%)	
	> 7	114(46.3%)	132(53.7%)	
IUGR	YES	13(26.5%)	36(73.5%)	0.010
AGA	YES	111(45.9%)	131(54.1%)	0.008
LGA	YES	4(36.4%)	7(63.6%)	0.468

Similarly, neonates with peripartam stress, IVH, AKI, DSD, hs PDA, symptomatic hyponatremia along with use

of caffeine, Na extra to maintenance, home Na supplementation were significantly associated with moderate to severe hyponatremia (table 2).

Table 2: Parameters affecting the severity of hyponatremia

Parameters		Mild	Moderate - Severe	p-value
HIE 2/3	YES	122 (41.5%)	172 (58.5%)	0.051
Perinatal stress	YES	34 (29.8%)	80 (70.2%)	0.000
Sepsis	YES	115 (41.7%)	161 (58.3%)	0.280
NEC	YES	17 (47.2%)	19 (52.8%)	0.323
Pneumonia	YES	58 (43.9%)	74 (56.1%)	0.351
Hs PDA	YES	0 (0.0%)	6 (100.0%)	0.035
DSD	YES	6 (100.0%)	0 (0.0%)	0.005
AKI	YES	0 (0.0%)	18 (100.0%)	0.000
Symptoms	YES	18 (60.0%)	12 (40.0%)	0.031
Dyskalemia	YES	23 (43.4%)	30 (56.6%)	0.490
Hypothyroidism	YES	27 (46.6%)	31 (53.4%)	0.281
Hypoalbuminemia	YES	5 (35.7%)	9 (64.3%)	0.412
Caffeine	YES	21 (26.9%)	57 (73.1%)	0.001
TPN	YES	4 (22.2%)	14 (77.8%)	0.59
Hypoglycemia	YES	27 (48.2%)	29 (51.8%)	0.201
IVH	YES	12 (66.7%)	6 (33.3%)	0.029
Seizures	YES	29 (48.3%)	31 (51.7%)	0.182
Oliguria	YES	27 (40.9%)	39 (59.1%)	0.452
IVF restriction	YES	122 (41.5%)	172 (58.5%)	0.051
Na extra to maintenance	0	115 (92.7%)	9 (7.3%)	0.000
	4	10 (7.8%)	119 (92.2%)	
	>4	2 (4.3%)	45 (95.7%)	
Duration of stay	Mean ±SD	9.77± 6.18	12± 6.84	0.05
Home Na supplementation	YES	0 (0.0%)	7 (100.0%)	0.20

Similarly, maternal risk factors identified for neonatal moderate to severe hyponatremia were diabetes mellitus, hypertension, and use of hypotonic fluids 24 hours prior to delivery (table 1).

All independent statistically significant risk factors of moderate-severe neonatal hyponatremia were further analyzed by using multivariable logistic regression

model. Among these, APGAR-5 of <7 was the most significant risk factor as it increases the risk of moderate-severe hyponatremia by 42374 times. It is followed by IUGR that increases the risk by 200 times.

Similarly, comparative descriptive statistics were applied to identify all risk factor for acute and chronic hyponatremia in neonates that showed PIH, APGAR-5 <7, birth weight, pneumonia, NEC, and IVF restriction statistically significant. However, multiple logistic regression showed PIH increases risk of chronic hyponatremia by odds of 3.9 (table 3).

Table 3: Risk factors for chronic hyponatremia

Risk factors	P-value	OR	95% Confidence Interval
Birth weight <1.5kg	0.071	2.797	0.916 - 8.540
Birth weight 1.5-2.5kg	0.601	1.302	0.484 - 3.508
Birth weight >2.5kg	Ref	Ref	Ref - Ref
PIH	0.002	3.918	1.643 - 9.340
AS5 <7	0.665	1.239	0.469 - 3.275
Pneumonia	0.082	2.293	0.900 - 5.841
NEC	0.197	0.249	0.030 - 2.058
IVF-restriction	0.222	0.325	.053 - 1.977

DISCUSSION

Hyponatremia, defined as a serum sodium level below 135 meq/L, poses a significant and often overlooked challenge in neonatal intensive care unit (NICU) settings. There is a lack of comprehensive data on the severity and chronicity of hyponatremia in neonates. This study aimed to investigate the features, risk factors, and frequency of hyponatremia in infants admitted to our NICU.

Masood et al have demonstrated in their study that neonates with Apgar scores at 5 minutes less than 7 exhibited a higher incidence of hyponatremia when compared to the control group (p<0.01).¹³ Studies conducted by Rahman MK and Shah G S have revealed that 18% and 23.3% of asphyxiated newborns, respectively, developed hyponatremia.^{14,15} Our study revealed a pattern mirroring these findings, indicating that every fourth neonate with Apgar scores less than 7 at 5 minutes had hyponatremia. The neonates experiencing peripartum stress-related events in the context of syndrome of inappropriate antidiuretic hormone secretion (SIADH) exhibited dilutional hyponatremia due to heightened water retention. Additionally, these neonates faced acute renal injury, causing damage to collecting tubules and resulting in impaired sodium reabsorption. Another factor contributing to

hyponatremia in these neonates was partial resistance to aldosterone.^{16,17}

The placenta serves as the primary organ facilitating maternal-fetal interaction throughout pregnancy. In addition to its functions in supplying nutrients to the fetus and eliminating waste products, the placenta, with its endocrine capabilities, regulates the transfer of micronutrients, trace elements, and electrolytes between the mother and fetus. This orchestration ensures a harmonious homeostatic balance between the circulations of the two. Maintaining well-balanced maternal nutrition before and during pregnancy is a crucial factor for sustaining the in-utero environment, influencing fetal well-being and growth through its impact on fetal epigenetics.¹⁸

The IUGR neonates are prone to impaired nephrogenesis along with hypo functioning nephrons with tubular injury in utero as well as ex utero.¹⁹ In utero chronic stress, maternal malnutrition, eating disorders, pregnancy-induced hypertension (PIH), placental insufficiency, diabetes mellitus, anemia, substance use (including drugs and smoking), are directly associated with metabolic and electrolyte imbalances. Additionally, they pose a higher risk for neonatal complications, including intrauterine growth restriction (IUGR).²⁰ The nephrogenesis in neonates who are intrauterine growth restriction (IUGR) is further impacted after birth by various factors, including total parenteral nutrition (TPN), formula milk, challenges in establishing feeding, necrotizing enterocolitis (NEC), antibiotic use, nephrotoxic drugs, mechanical ventilation, central lines, sepsis.²¹

The regulation of sodium homeostasis in the body is primarily governed by the kidneys. In intrauterine growth restriction (IUGR) neonates, where nephron function is compromised, particularly in the context of prematurity and an immature renin-angiotensin-aldosterone axis, maintaining normal sodium levels becomes challenging, potentially leading to predisposition to hyponatremia. To the best of the author's knowledge, there is a lack of literature on the association between IUGR and hyponatremia. However, our study demonstrates a significant correlation between IUGR and hyponatremia.

In a cohort study conducted by Remer C et al., it was observed that hyponatremia was present in approximately one out of every seven pregnant females diagnosed with preeclampsia.²² Likewise, Xodo and Razavi reported that within the group of mothers with preeclampsia, 34% and 9.7% exhibited low sodium levels, defined as below 135, respectively.^{23,24} Maternal pregnancy-induced hypertension (PIH) and preeclampsia increase the susceptibility of mothers to

hyponatremia. This condition is influenced by factors such as psychogenic polydipsia, a reduced intake of dietary solutes, the use of sodium-active drugs like diuretics, and advanced renal failure.²⁵ Our study revealed a parallel pattern of results, indicating that neonates born to mothers with pregnancy-induced hypertension (PIH) and preeclampsia not only exhibited hyponatremia but also sustained this imbalance for more than 48 hours.

CONCLUSION

Hyponatremia is not uncommon in neonates admitted in NICU as 58% of our study population had moderate to severe hyponatremia. Our study showed that gestational age and severity of hyponatremia has directly proportional relationship as 73.1% neonates born at GA 28-32⁺⁶ had moderate to severe hyponatremia. APGAR-5 of <7 was the most significant risk factor as it increases the risk of moderate-severe hyponatremia by 42374 times. It is followed by IUGR that increases the risk by 200 times. Whereas maternal PIH is associated with increased risk of chronic hyponatremia. it is highly recommended to screen all newborns, preferably the high-risk babies to prevent deleterious effects of hyponatremia. Further studies are needed to consolidate our findings regarding hyponatremia in IUGR babies.

LIMITATIONS

Gestation age impact couldn't be determined it could have been done with a relatively large sample size over a longer duration.

SUGGESTIONS / RECOMMENDATIONS

A relatively large sample size study with multicenter design is recommended to further explore the causes of early versus late onset hyponatremia.

CONFLICT OF INTEREST / DISCLOSURE

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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