The Association of Serum Sodium Levels with Intraventricular Hemorrhage in Preterm Infants: A Prospective Longitudinal Study from Pakistan

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ABSTRACT

Objective: To evaluate the association of hypernatremia with intraventricular haemorrhage in preterm infants in a local setting.

Study Design: Prospective longitudinal study.

Place and Duration of Study: Neonatal Intensive Care Units (NICU), Pir Abdul Qadir Shah Jeelani Institute of Medical Sciences, Gambat Khaipur Mirs from Sep 2018 to Mar 2020.

Methodology: All the infants with the gestational age of <32 weeks of pregnancy were included, while infants who died <12 hours of life were excluded from the study. All relevant maternal and neonatal data were extracted from patient files and recorded in electronic form. The infants were further stratified into three groups: i) infants without intraventricular haemorrhage, ii) mild intraventricular haemorrhage, and iii) severe intraventricular haemorrhage.

Results: The intraventricular haemorrhage was 40%. 84 (29.2%) infants had a mild intraventricular haemorrhage, and 32 (11.1%) had a severe intraventricular haemorrhage. The highest sodium level was 145.91 ± 6.98 mEq/L and 143.51 ± 5.93 mEq/L in the mild IVH and severe intraventricular haemorrhage groups, respectively. The fluctuations in serum sodium levels from week 1 to week 2 were significantly more prominent in infants without intraventricular haemorrhage compared to intraventricular haemorrhage groups (12.31 ± 6.67 mEq/L, 10.11 ± 9.32 mEq/L, and 6.54 ± 7.53 mEq/L, respectively; *p*:0.001).

Conclusion: The fluctuation of serum sodium in infants with severe Intraventricular haemorrhage was significantly greater than in infants with mild intraventricular haemorrhage or without intraventricular haemorrhage.

Keywords: Hypernatremia, Intraventricular haemorrhage, Infant mortality, Serum sodium.

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INTRODUCTION

Intraventricular haemorrhage is a major reason for mortality and illness in neonates and is closely linked with negative neurological outcomes. The intensity and severity of intraventricular haemorrhage determine the prevalence of definite neurologic repercussions.[1] On ultrasound, IVH is also the most frequently acknowledged cerebral lesion in premature infants.[2] Different studies have suggested the perinatal risk factors of Intraventricular Hemorrhage like extremely low birth weight, preterm babies, gender, lack of steroid injections, low oxygen and high carbondioxide levels and metabolic syndrome, among others.[3-5] In extremely low birth weight infants, hypernatremia can contribute to an abnormal increase in the osmolarity of the body fluids. These osmotic shifts may be the basis of diminished brain volume, rupture of blood vessels, permanent brain damage, or even death.[6] In the brain cells, rapid input of solutes following diminished brain volume is a counter-mechanism that recovers the lost water and permits slow standardization of brain volume. As brain cells re-intake the fresh water and flush out the stored solutes, this rapid correction hypernatremia may result in cerebral oedema.[7-8] In infants, there is extensive evidence of the connection between hypernatremia and neurological incidences, including intraventricular haemorrhage.[9-10]

The objective of the present study was to determine the association between the intraventricular haemorrhage and fluctuations of sodium levels in the serum of infants. For this purpose, we first investigated the prevalence of Intraventricular Hemorrhage and divided it into three groups, namely, No IVH, mild IVH and Severe IVH, based on their grades. Second, we evaluated the Sodium levels in the serum of the infants participating in the study. Finally, we compared Sodium levels with the Intra ventricular haemorrhage grades. The primary aim of the present study was conducted to assess the serum levels of Sodium among different grades of IVH in Pakistani infants. The secondary objective was to analyze the

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demographic and clinical factors according to the severity of the intraventricular haemorrhage.

METHODOLOGY

This prospective longitudinal study was conducted between September 2018 to March 2020 for 18 months at the Neonatal Intensive Care Units (NICU), Pir Abdul Qadir Shah Jeelani Institute of Medical Sciences, Gambat, Khaipur Mirs. After ethical clearance from the Institutional Review Board (Reference number PAQSJIMS/IRB/0215), patients were enrolled in the study using non-probability consecutive sampling techniques. The sample size was obtained via select statistics sample size calculator. The incidence rate of IVH among infants was kept at 22.1 per 1000 live births10, with a confidence interval of 95% and margin of error of 4.05%, and a sample size of 287 was obtained. Informed consent was obtained from the infant's guardian prior to his or her enrollment in the study.

Inclusion Criteria: All the infants with gestational age (GA) less than 32 weeks of pregnancy were included in the study.

Exclusion Criteria: Infants who died less than twelve hours of life had missing data, or babies whose parents did not consent to participate were excluded from the study.

All relevant maternal and neonatal data were extracted from patient files and recorded in electronic form. In addition, data including the pregnancy outcomes and mode of delivery were also included. The infants were further stratified into three groups: i) infants without IVH (NO IVH), ii) Mild IVH, and iii) Severe IVH. Post-data collection stratification for gestational age, as well as serum sodium levels, were also performed.

The diagnosis of IVH was made by experienced neonatologists using reports from the serial cranial ultrasonography scans (CUSS), which was performed with standard protocols of the NICU on day 1, 3, and 7. IVH was defined as "Bleeding into one of the ventricles in an infant born less than 32 weeks of pregnancy". The IVH was graded using the Papile grading system for IVH.[11-12] Grade 1 was defined as "Blood in the periventricular germinal matrix region", and Grade 2 was when blood reached the lateral ventricular system. However, there was no dilatation. Grade 3 was declared when blood caused distention of the lateral ventricles, and grade 4 was when the blood invaded the ventricular system and the parenchyma. Grade 1 and 2 were grouped as "Mild IVH", while grade 3 and grade 4 were grouped as "Severe IVH".

Hypernatremia was defined as an electrolyte irregularity manifested as a rise in serum sodium concentration to a value greater than 145 mmol/L.[13]

All data were analyzed using Microsoft Excel 2010, and further statistical analysis was performed using IBM SPSS Statistics (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 24.0). As appropriate, data were presented as a minimum, maximum, mean, median and standard deviation. In addition, a comparison of variables between the groups of presence and absence of associated factors was performed using contingency tables. Finally, the Chi-square test and one-way ANOVA were used to explore the association between variables and observe the variance between groups. The *p*-value of ≤0.05 was considered statistically significant.

RESULTS

A total of 287 infants were included in the study, with 148/287 (51.5%) male infants and 139/287, 48.4 percent female infants. The birth weight ranged from 945 grams to 1500 grams. The mean body weight for babies without IVH was 1389.44 ± 353.4 g, for the mild IVH group, 1332.31 ± 244.1 g, and for the severe IVH group, it was 1256.11 ± 362.13 g.

The occurrence of IVH was 115/287 (40.0%), out of which 84/287 (29.2%) had mild IVH (Grade 1 and Grade 2) while 32/287 (11.1%) had severe IVH (Grade 3 and 4). All neonates had a birth body weight (BBW) of less than 1500 grams and gestational age of fewer than 32 weeks of pregnancy. The mean gestational age in mild IVH and severe IVH was significantly lower compared to the group without IVH, i.e. 28.91 ± 1.33 and 28.39 ± 2.01 versus 29.93 ± 1.63, respectively (p<0.001) (Table-I).

The highest sodium level was 145.91 ± 6.98 mEq/L and 143.51 ± 5.93 mEq/L in the mild IVH and severe IVH groups, respectively, compared with 144.21 ± 7.11 mEq/L in the No IVH group.

However, the fluctuations in serum sodium levels from week 1 to week 2 were significantly more prominent in infants without IVH compared to IVH groups (12.31 ± 6.67 mEq/L, 10.11 ± 9.32 mEq/L, and 6.54 ± 7.53 mEq/L, respectively; p<0.001) (Table-II).

One-way ANOVA and Tukey HSD ("Honestly Significant Difference") posthoc test indicate which groups differed significantly from which others. Serum

Table-I: Demographic and clinical factors according to the severity of the Intraventricular hemorrhage.

Factors	No Intraventricular Hemorrhage	Mild Intraventricular Hemorrhage	Severe Intraventricular Hemorrhage	*p*-value
Gender				
Male	81 (47.09%)	51 (60.71%)	16 (51.61%)	0.123
Female	91 (52.91%)	33 (39.29%)	15 (48.39%)	
Mean Gestational Age in years	29.93 ± 1.63	28.91 ± 1.33	28.39 ± 2.01	<0.001
Mean Birth Body Weight in grams	1389.44 ± 353.4	1332.31 ± 244.1	1256.11 ± 362.13	0.078
Steroid Administration				
Yes	58 (33.72%)	29 (34.52%)	7 (22.58%)	0.438
No	114 (66.28%)	55 (65.48%)	24 (77.42%)	
MgSO4 Administration				
Yes	28 (16.28%)	10 (11.90%)	3 (9.68%)	0.476
No	144 (83.72%)	74 (88.10%)	28 (90.32%)	

Table-II: Serum Sodium levels according to the severity of the Intraventricular hemorrhage.

Serum Sodium (mEq/L)	No Intraventricular hemorrhage	Mild Intraventricular hemorrhage	Severe Intraventricular hemorrhage	*p*-value
Na (Highest)	143.51 ± 5.93	145.91 ± 6.98	144.21 ± 7.11	0.0001
Na (Lowest)	136.42 ± 5.01	135.95 ± 2.97	136.44 ± 2.89	
Na (Difference)	6.54 ± 7.53	10.11 ± 9.32	12.31 ± 6.67	

sodium levels were significantly different between the three groups (p=0.0001).

The post hoc test showed that the change in serum sodium levels between the groups (Group 1 vs Group 2, Group 1 vs Group 3 and Group 2 vs Group 3) was significant, with a p-value of 0.0026 and 0.0008, respectively (Table-III).

Table-III: Tukey Honestly Significant Difference (HSD) post-hoc test for changes in the Serum Sodium levels as per severity of the disease

Comparison groups	Difference	95% CI	*p*-value
Group 1 vs Group 2	3.5700	1.0571 to 6.0829	0.0026
Group 1 vs Group 3	5.7700	2.0865 to 9.4535	0.0008
Group 2 vs Group 3	2.2000	-1.7672 to 6.1672	0.3928

Serum sodium levels were stratified into four categories: i) <130 mEq/L, ii) 130-145 mEq/L, iii) 145-160 mEq/L, and iv) >160 mEq/L. We observed that only a minority of 2 (6.45%) infants had <130 mEq/L serum sodium levels, and both of these patients were diagnosed with severe IVH. 102 (59.30%) infants without IVH had a normal range of serum sodium levels. About 50 out of 115 infants with both IVH (mild and severe), i.e., 43.5%, had serum sodium levels greater than 145 mEq/L or hypernatremia (Table-IV).

DISCUSSION

IVH is common neonatal morbidity among premature infants and is diagnosed by cranial ultrasound. Despite significant child and mother health improvements, Pakistan still faces high childhood mortality. IVH in preterm infants can lead to significant neurologic disability and even death.[14]

Table-IV: Distribution of study participants according to the serum sodium level categories (n=287).

Sodium Concentration	No Intraventricular Hemorrhage	Mild Intraventricular Hemorrhage	Severe Intraventricular Hemorrhage
<130 mEq/L	-	-	2 (6.45%)
130-145 mEq/L	102 (59.30%)	44 (52.38%)	19 (61.29%)
146-160 mEq/L	69 (40.12%)	37 (44.05%)	9 (29.03%)
>160 mEq/L	1 (0.58%)	3 (3.57%)	1 (3.23%)

This study focused on exploring the rela-tionship between the incidence of intraventricular haemorrhage in preterm infants and hypernatremia. To the best of our knowledge, this is one of the few prospective studies focused on highlighting the risk factors associated with IVH in infants born less than 32 weeks of pregnancy or with a birth body weight of fewer than 1500 grams, with special attention to the frequency of hypernatremia in infants with severe IVH.

We reported an occurrence rate of IVH of 40 percent, i.e. 115 out of 287 preterm infants. Out of the 115 infants with IVH, we found that 32/287 (11.1%) had severe IVH (Grade 3 and 4). In a previous study from Pakistan, the incidence of IVH in the preterm population was 22.1 per 1000 live births.[15] They further evaluated that babies with respiratory distress syndrome (RDS) (p<0.004) and those who needed mecha-

nical ventilation (p<0.001) were independent risk factors of IVH.

In contrast to the international study findings reported by Lim *et al,* where a seven and a half year retrospective data was used to evaluate the relationship between hypernatremia and severe IVH (Grade 3 and 4) among extremely low birth weight infants.[16] The authors reported that high sodium serum levels and greater change in serum sodium were both strongly associated with an increased risk of severe IVH of grade 3 or 4. The disparity could be explained by the minor difference in the current study's sample population, which included all preterm infants born with a birth body weight of <1500 grams and not just extremely preterm infants.

Takaku *et al,* indicated that hypernatremia is strongly related to the increased risk of infant mortality in patients with intraventricular haemorrhage. IVH damages the hypothalamic nuclei leading to a reduction of antidiuretic hormones which subsequently causes hypernatremia.[17] Geheb *et al,* believed that hypernatremia occurs first, leading to brain shrinkage and rupture of vasculature with subsequent cerebral bleeding and IVH.[18] Although the findings from the current study highlight the significant difference in gestational age and the greater fluctuation in serum sodium levels in the infants born with mild and severe IVH compared to the study controls without IVH, the question of which variable influences which remains unsolved. Further studies with a larger sample size can help better understand the role of hypernatremia in developing IVH or vice versa.

CONCLUSION

IVH is a very common finding in our setting. However, we do not know the exact role of hypernatremia in developing severe IVH in preterm infants. The fluctuation of serum sodium in infants with severe IVH was significantly greater than in infants with mild IVH or without IVH. Further studies with a larger sample size can help better understand the role of hypernatremia in developing IVH or vice versa.

Conflict of Interest: None.

Authors' Contribution

BAB: Design, concept, MAB: Acquisition, drafting, KASB: Critical approval, KA: Proofing of paper.

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