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Research Article

Hypernatremia in Exclusively Breastfed Hospitalized Neonates in Harare, Zimbabwe

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Keywords

- Neonatal hypernatremic dehydration
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Abstract

Background: Newborns are at increased risk of hypernatremia due to their inability to control their fluid intake and their large body surface area to weight/ height ratio. The main cause of hypernatremia in neonates is dehydration from lactation failure, primarily due to low volume intake of breast milk.

The aim of this study was to determine factors associated with hypernatremia and outcomes of neonates admitted with hypernatremic dehydration at two tertiary institutions in Harare, Zimbabwe.

Methods: A hospital based cross sectional study was conducted between June and December 2017 on neonates admitted with hypernatremia at two institutions in Harare.

Results: A total of 160 exclusively breastfed neonates were recruited into the study with 15 deaths giving a case fatality rate of 9.4% (95%CI: 5.8-14.8). The mean age at admission was 6.6 days (SD ± 5.6), and more than half (58.1%), of the mothers were first-time-mothers. Eighty percent of the infants had been discharged within 24hours of delivery. Fever, poor feeding and jaundice were the most common symptoms at presentation. Weight loss was noted in 92.5% of neonates on admission, with 71.4% having lost ≥ 10% of their birth weight. More than 70% of the infants presented with dehydration. The mean sodium concentration was 163.8 (SD 14.4), mmol/l at admission. Acute kidney injury was the most common complication observed.

Conclusion: Neonatal hypernatremia is common in exclusively breastfed neonates particularly in infants of primiparous mothers. Common presentation was fever, loss of weight, jaundice and dehydration with a significant risk for mortality.

ABBREVIATIONS

AKI: Acute Kidney Injury; A' Level: Advanced Level; ANC: Antenatal Clinic; AOR: Adjusted Odd Ratio; BFHI: Baby Friendly Hospital Initiative; BUN: Blood Urea Nitrogen; CI: Confidence Interval; CSF: Cerebrospinal Fluid; EBFN: Exclusively Breastfed Neonate; FBC: Full Blood Count ;HAART: Highly Active Antiretroviral Treatment; HB: Haemoglobin; HCT: Haematocrit; HIV: Human Immunodeficiency Virus; IQR: Interquartile Range; JREC: Joint Research Ethical Committee; LMIC: Low to Medium Income Countries; LSCS: Lower Segment Caesarean Section; MCV: Mean Corpuscular Haemoglobin; MOHCC: Ministry of Health and Child Care; MRCZ: Medical Research Council of Zimbabwe; NVD: Normal Vaginal Delivery; O' Level: Ordinary Level; SD: Standard Deviation; TSB: Total Serum Bilirubin; UNICEF: United Nations Children's Fund; U&E: Urea and Electrolytes; WCC: White Cell Count; WHO: World Health Organisation; ZDHS: Zimbabwe Demographic and Health Survey.

INTRODUCTION

Hypernatremia in neonates is defined as a total serum sodium concentration of ≥ 150mmol/l [1]. Newborns are at increased risk of hypernatremia due to inability to control their fluid intake and their large body surface area to weight or height ratio which results in high insensible water losses [2,3]. Lactation failure [4-7], and inadequate milk in the first weeks of life are commonly recognized causes of hypernatremia in breastfeed infants [8,9].

Studies on breast milk sodium concentration within the first few weeks of life show values that range from 22 (SD 12), mmol/L in colostrum within the first 5 days, to 7 (SD 2), mmol/L beyond day 15 of normal lactation [10]. In a series of individually reported cases, the breast milk sodium concentration analysed from 60 mothers of hypernatremic dehydrated infants, breast milk sodium concentration was found to be significantly increased compared to mothers of neonates without hypernatremia [9,11,12]. The clinical significance of high breast milk sodium

concentration in the etiology and pathogenesis of breastfeeding associated hypernatremic dehydration is unclear, though high sodium levels in breast milk are closely linked to lactation failure [9]. Other causes of neonatal hypernatremia like diarrhoea, central or nephrogenic diabetes insipidus, salt poisoning and iatrogenic administration of hypertonic sodium solutions are less common [2,4].

The incidence of neonatal hypernatremia varies widely depending on countries, regions, geographic settings or socioeconomic status, and has been increasing over the past three decades [6,8,13-15]. Resource rich countries report less than 2% incidence whilst in developing countries it ranges between 1.5% and 10%, though these studies differed significantly in study designs, geographic distribution and the newborn care medical practices [6,7,12,16-18].

Weight is the only reliable attribute to detect early dehydration [7], with weight loss exceeding 10% within the first week of life in a term infant suggestive of inadequate breastfeeding in those exclusively breastfed [7,15,19].

Hypernatremic dehydration is associated with intracranial haemorrhage, cerebral oedema, hydrocephalus and peripheral gangrene [20], which are all potentially lethal conditions. Other complications may include renal and liver failure, disseminated intravascular coagulation, venous thrombosis, seizures, and death. Intracranial hemorrhage, the most serious complication of untreated hypernatremic dehydration, can be subdural, subarachnoid or parenchymal hemorrhage [21].

This study aimed to determine factors associated with and outcomes of neonates admitted with hypernatremic dehydration at two tertiary institutions in Harare, Zimbabwe.

MATERIALS AND METHODS

A hospital based cross sectional study of neonates admitted to two tertiary referral hospitals, Parirenyatwa and Harare Central Hospitals was conducted between 11th June and 31st December 2017.

All neonates ≥ 35weeks at birth admitted with hypernatremia within their first 28days of life were eligible. Enrollment was within 24 hours of admission using convenient sampling.

Data Collection

At enrollment, a clinical evaluation was performed including detailed maternal and neonatal history; intrapartum history, birth weight and Apgar scores**.** Clinical examination findings including the hydration status using the WHO classification of dehydration [22], were performed. All participants were weighed on admission to the nearest 10g using a standardised Tanita baby scale (1380 series). Baseline investigations performed included urea and electrolytes, creatinine full blood count (FBC), C-reactive protein (CRP) and an infection screen (blood culture and/or lumbar puncture) as indicated. Outcomes recorded included survival, duration of stay in the hospital and weight on discharge.

Statistical Analysis

Data was entered into REDCap, then exported to STATA version 13.0 (StataCorp, College Station, TX, USA) for analysis. Categorical variables were summarized using frequencies. Initially continuous data was assessed for normality using the Shapiro Wilk test. Continuous variables that satisfied the assumptions of normality were summarized using means and standard deviations. The Chi-square test was used as measure of association for categorical variables and Fisher's exact test was used where cell frequencies were less than 5. Pearson's Correlation was used to assess the associations between continuous variables. The independent t-test was used to compare differences between means.

Ethical considerations

The study was approved by the Joint Research Ethics Committee for the University of Zimbabwe College of Health Sciences and Parirenyatwa Group of Hospitals (JREC/155/17), Harare Central Hospital Ethics Committee (HCHEC 300517/36), and the Medical Research Council of Zimbabwe (MRCZ/B/1313).

RESULTS

A total of 160 neonates with hypernatremia were enrolled into the study between June and December 2017. The majority of the study participants [125 (78.1%)], were from Harare Central Hospital. There were 82 males (51.3%), and the mean age at admission was 6.6 days (SD ± 5.6)

Maternal and Perinatal Factors

The mean maternal age was 25.9 years (SD 6.0; range 16-41), with the majority of mothers being married and literacy level equivalent to General Certificate of Education (Ordinary level) [23]. Majority of mothers, 93/160 (58.1%), were primiparous with 27 (16.9%), being second-time mothers. Only 10% of the neonates were delivered by caesarian section. The infants were mostly term (95.0%), and 79.9 % discharged within the first 24 hours of delivery with only 14 (8.75 %), being discharged more than 72 hours after delivery post caesarian section (Table 1). Half of the infants [81(50.6%)] had been started on breastfeeding within the first hour of delivery and all were reported to be on exclusive breastfeeding. The reported median time to perceived adequate milk production was 4 days (IQR: 3-5).

Clinical characteristics of neonates admitted with hypernatremia

The mean birth weight was 3107g (SD 542.1g) with a mean weight of 2654g (SD 495.70g), at admission. A total of 147 (92.5%) infants were noted to have lost weight with 105 (71.4%), infants having lost more than 10% of their birth weight. Overall, the infants had mean weight loss of 16.3% (SD 8.9; range 0-37%), at a mean age of 6.6 (SD 5.6), days. Fever was the most common presenting symptom followed by poor feeding and jaundice **(**Table 2**).**

Clinical examination findings in neonates admitted with hypernatremia

The mean admission temperature was 38.5°C (SD 1.0). Dehydration was present in 112 infants (70%); 66 (41.3 %), were classified as some dehydration, 46 (28.8 %), as severe dehydration and 48 (30 %) as no dehydration. The commonest

Table 1: Maternal and perinatal factors associated with neonatal hypernatremia.

Variable	Frequency (%)
Marital status	
Single	12 (7.5)
Married	148 (92.5)
Mother's level of education	
Primary	6 (3.8)
Secondary	23 (14.4)
Secondary with "O" Level	102 (63.8)
Secondary with "A" Level	12 (7.5)
Parity	
0	93 (58.1)
1	27 (16.9)
2	23 (14.4)
3	13 (8.1)
4	4 (2.5)
Estimated gestational age	
Late pre-term	4 (2.5)
Term	152 (95.0)
Post-term	4 (2.5)
Mode of delivery	
NVD	144 (90.0)
LSCS	16 (10.0)
Place of delivery	
Hospital	81 (50.6)
Local clinic	77 (48.1)
Home	2 (1.3)
Maternal risk of sepsis	
Yes	12 (7.5)
No	148 (92.5)
Post-natal discharge time	
Within 6 hours	18 (11.2)
6-24 hours	109 (68.1)
25-48 hours	11 (6.9)
49-72 hours	8 (5.0)
>72hours	14(8.8)

Table 2: Clinical characteristics of neonates admitted with hypernatremia.

Clinical presentation	Frequency (%)
Fever	127 (79.4)
Poor feeding	103 (64.4)
Yellow eyes	65 (40.6)
Irritability	27 (16.8)
Grunting	14 (8.8)
Loss of weight	12 (7.5)
Decreased urine output	11 (6.9)
Fast breathing	11 (6.9)
Coughing	6 (3.8)
Seizures	6 (3.8)
Vomiting	3 (1.9)
General body weakness	2 (1.3)
Salt rubbing*	1 (0.6)
*Cultural norm of rubbing salt on newborn fontanelle, palate, axilla	

Table 3: Clinical examination findings at admission in neonates with hypernatremia in Harare, Zimbabwe.

Examination finding	Frequency	(%)
Hydration status		
Sunken eyes	53	(33.1)
Skin turgor slow	92	(57.5)
Skin turgor very slow	31	(19.4)
Drinking poorly	42	(26.3)
Drinking eagerly	56	(35.0)
Irritability/restless	12	(7.50)
Lethargy/unconscious	42	(26.3)
Hydration classification		
No dehydration	48	(30.0)
Some dehydration	66	(41.3)
Severe dehydration	46	(28.8)
Other findings		
Jaundice	75	(46.9)
Hypereflexia	35	(21.9)
Hypertonia	36	(22.5)
Hypotonia	10	(6.3)
Peripheral gangrene	1	(0.6)

presenting sign of dehydration was reduced skin turgor (Table 3). Clinical jaundice was detected in nearly half of the neonates [75(46.9%)]. Hypertonia [36 (22%)], and hyper-reflexia [35 (21.9%)], were more common than hypotonia 10(6.3%).

Fifteen of the 160 enrolled neonates died, giving a case fatality rate of 9.4% (95% CI: 5.8-14.8%). Fourteen of the 15 deaths were lethargic on admission, 6 were hypotonic and 6 were hypertonia **(**Table 4**).**

Laboratory investigations

Mean sodium concentration on admission was 163.8 (SD 14.4), mmol/l, mean blood urea nitrogen was 23.8 (SD 2.25), mmol/l and mean creatinine was 196.5 (SD 27.38), mmol/l, all of which were above the upper limit of normal (ULN), for neonates (24,25) **(**Table 5**).** Five infants had peritoneal dialysis and only one survived. Level of total serum bilirubin (TSB), in 17 (25%), of the 68 neonates with clinical jaundice required phototherapy and none had levels within the recommended exchange transfusion range (26). Blood cultures were positive in 6 of the 21 infants who had the test done. The organisms cultured included *Klebsiella species* (2), *E-coli* (1), Group D *streptococci* (1) and *Staphylococcus epidermidis* (2). Cerebrospinal fluid (CSF), analysis was normal in all 50 neonates investigated for neonatal meningitis.

Outcome

Majority of infants were discharged [145(90.6%)], with an average of 6.9 days in hospital. The case fatality rate was 9.4% (15/160). Of the infants who died, the mean length of hospital stay (LOS) was 2.7 days (SD: 1.5). There was a positive correlation between the serum sodium concentration on admission and the percentage weight loss at admission ($r= 0.49$, $p<0.001$), and

Table 4: Association between clinical factors and mortality.

	Total	Deceased	Alive	OR (95% CI)	p-value
	160	15 (9.4)	145 (90.6)		
Hypotonic					
Yes	10	6 (60.0)	4 (40.0)	23.3 (5.6-97.9)	**<0.0001***
No	150	9 (6.0)	141 (94.0)	Reference	
Lethargic					
Yes	42	14 (33.3)	28 (66.7)	58.5 (8.0- 2493.1)	**<0.0001***
No	118	1 (0.8)	117 (99.2)	Reference	
Hypertonia					
Yes	36	6 (16.7)	30 (83.3)	2.56 (0.84-7.74)	0.09
No	124	9 (7.3)	115 (92.7)	Reference	
Fever					
Yes	127	13 (10.2)	114 (89.8)	1.69 (0.40-7.12)	0.46
No	33	2 (6.1)	31 (93.9)	Reference	
Mode of delivery					
Caesarian	16	2 (12.5)	14 (87.5)	1.44 (0.29-7.04)	0.65
NVD	144	13 (9.0)	131 (91.0)	Reference	

NVD: normal vaginal delivery; OR: odds ratio; CI: confidence interval

Table 5: Results of initial investigations performed on neonates admitted with hypernatremia.

Investigation (units)	Mean	SD	95% CI	Range
WCC ($x10^9$ /L)	12.6	5.0	11.8-13.4	5.1-42.0
HB (g/dL)	16.4	2.4	16.0-16.8	6.3-22.1
HCT (%)	49.1	6.9	48.0-50.2	31-66
MCV(fL)	99.4	9.4	97.9-100.8	75.9-144.0
Platelets ($x10^9$ /L)	249.0	113.7	231.2-266.7	14-775
Potassium (mmol/L)	5.4	1.3	5.2-5.6	3.3-9.6
Bicarbonate (mmol/L)	16.0	3.8	12.5-19.5	11.3-22.0
Urea (mmol/L)	**23.8**	**2.25**	**20.2-27.4**	**1.9-109**
Chloride (mmol/L)	124.9	13.7	122.7-127.2	102-173
Sodium (mmol/L)	**163.8**	**14.4**	**161.5-166.0**	**150-210**
Creatinine (µmol/L)	**196.5**	**27.38**	**152.3-240.6**	**10-1947**

SD: Standard deviation; CI: confidence interval; WCC: White cell count; HB: haemoglobin; HCT: haematocrit; MCV: mean corpuscular volume; CI: Confidence interval.

between the age of the neonates on admission and the percentage weight loss (r=0.43, p<0.001) (Figures 1 and 2 respectively). Mean serum sodium on admission was significantly higher [183.3 mmol/L (SD 17.1)] among the deceased infants compared to survivors [(161.8 mmol/ SD12.5); p<0.0001)].

Infants born through caesarian delivery had 19 times the odds of delayed initiation of breastfeeding (>1hr) compared to those who were delivered vaginally, OR=18.8 (95% CI: 2.4-146), p<0.0001. Mean sodium concentration at admission in infants delivered by caesarean section [170.9 mmol/L (SD: 18.2)] was significantly higher than in infants born through vaginal delivery [163.5 mmol/L (SD=13.2), p=0.04].

Infants who presented with hypotonia (10 of 160), had 23 times the likelihood of dying as compared to those without hypotonia. [OR=23.3(95% CI: 5.6-97.9), p<0.0001]. The odds of dying among lethargic infants was 59 times that of the non-lethargic infants on admission [OR=58.5(95% CI: 8.0-2493.1), p<0.0001]. Median urea plasma concentration among the deceased children [64.1 mmol/L (IQR: 33.0-77.0)], was significantly higher than among those who survived, [13.7 mmol/L (IQR: 9.2-22.3) p<0.0001]. Similarly, the median plasma creatinine concentration among the deceased children of 523.0 µmol/L (IQR: 443.0-702.0) was significantly higher than the median of 88.5 µmol/L (IQR: 60.5-137.0) among those who survived (p < 0,001).

DISCUSSION

Maternal and Perinatal Factors

Early initiation of breast-feeding is important for successful

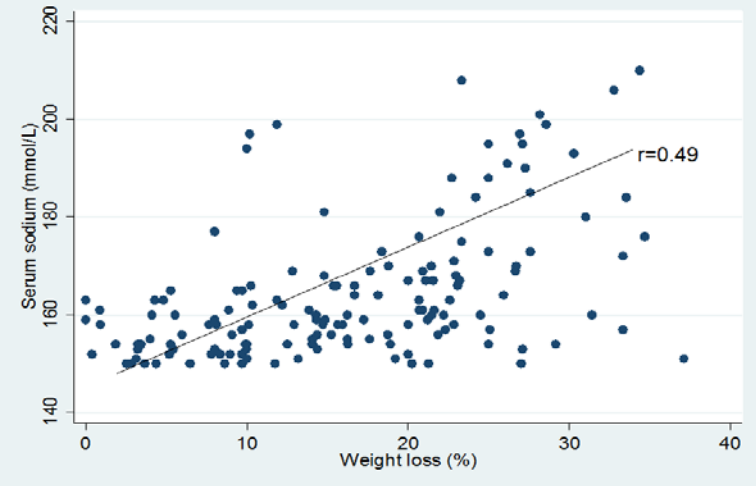

Figure 1 Correlation between serum sodium and percentage loss of weight.

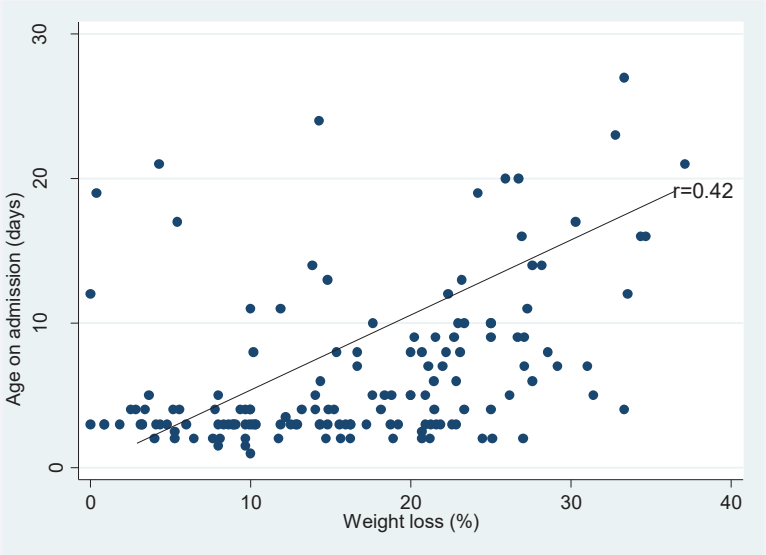

Figure 2 Correlation between age on admission and percentage weight loss.

lactation while delayed onset of lactation is a risk factor for suboptimal infant breastfeeding [27]. In this study, up to two thirds of neonates with hypernatremia had poor breastfeeding in the days preceding admission. This disadvantage of exclusive breastfeeding is far outweighed by advantages though [27,28]. Education of mothers on increased breastfeeding and breastfeeding support early neonatal life is important to reduce the incidence of hypernatremia in newborns [29,30].

Early lactation success is strongly influenced by parity [12,27,31], with primiparity as the strongest risk factor for delayed lactogenesis and early breastfeeding failure [27,31]. In this study, more than half (58.1%), of the mothers of hypernatremia infants were first-time mothers similar to earlier findings [32].

Caesarian section is a risk factor for excess weight loss and hypernatremia in exclusively breastfed infants [10,33]. Delay in initial feeding of these neonates is the main contributing factor to hypernatremia [10]. In this study, infants born through caesarian section had a higher mean serum sodium concentration and more likely to be initiated on breastfeeding later than the recommended (within first hour post-delivery) [30] compared to those delivered vaginally. Separation of mother and baby in theatre delays initiation of breastfeeding resulting in delayed lactogenesis and increased risk of hypernatremic dehydration [34].

In our study 80% of the hypernatremic infants were discharged less than 24 hours post-delivery. This was consistent with other studies and attributed to breast feeding failure associated hypernatremia [9]. Early discharge leaves mothers poorly prepared for breastfeeding thereby contributing to increased neonatal morbidity and mortality [35]. Reduced post-delivery length of hospital stay in newborns is a risk for readmission with dehydration, jaundice, feeding problems and

poor weight gain [36]. WHO recommends postnatal care within the health facility for the first 24-72 hours after delivery [37].

Neonatal Factors

Weight loss below 10% of birth weight during the first week of life, is acceptable physiologically (10), while ≥10% weight loss could be an early indicator of hypernatremic dehydration [7]. In this study, 92.5% of hypernatremic neonates presented with loss of weight with 71.4% of the study participants having lost ≥ 10% of birth weight. Several studies have reported an association between excessive weight loss and hypernatremic dehydration [12,32,38,39]. Iyer et al., found regular weight monitoring on day 3- 4 and then day7-10 of life, combined with a breastfeeding support strategy allows early detection of breastfeeding problems and intervention, thereby preventing hypernatremic dehydration and severe sequelae, compared to just weighing on the seventh to tenth day [40]. The WHO newborn health guidelines recommend early postnatal follow up of newborns on day 3 (48-72hrs) then between day 7-14 of life [37]. Zimbabwe adopted these guidelines a few years ago and recommended early postnatal reviews on day 3 and day 7. In this study the mean age at presentation was 6.6 days reflecting a possible delay in the first postnatal visit, thereby missing that early identification of neonates at risk of breastfeeding failure.

Clinical Presentation

Infants with hypernatremic dehydration have preserved extra cellular fluid volume and therefore have less pronounced clinical signs of dehydration [32,35,41]. Our study, however, had a high percentage the infants with clinical signs of dehydrated at presentation. These findings differ from what is commonly expected in infants with hypernatremic dehydration, this is probably because of clinical signs used to and classify dehydration in neonates are none specific and other lap with other common nonspecific presentation of newborn illnesses. Studies in India and Japan found acute kidney injury (AKI) as the most common complication in neonatal breastfeeding associated hypernatremia [18,42]. Decreased urine output was noted as an important clue in the history, leading to early identification of hypernatremic dehydration [42]. In this study however, a history of reduced urine output was noted by the mothers in only 6.9% of the infants. This finding will need further study.

Seizures were a less common presenting symptom in our study, occurring in only 3.8% of the infants much lower than reported incidence in other studies of 5.9% [18], 17.24% [42], and 22.6% [32]. The low incidence of seizures in the current study could possibly be due to under reporting.

Similar to previous reports, this study showed that fever and weight loss are often found in neonates with hypernatremia [9,18,35,43], The majority of patients in this study had no risk factors for sepsis and had negative septic screen results yet the commonest presenting symptom was fever, present in 80% of the infants, with a mean admission temperature of 38.5^{0}C. Fever was among the main reasons for admission, occurring in a third of all sepsis screen negative neonates admitted with hypernatremia in a study done in Turkey [35].

Fever as a presentation in hypernatremic dehydration poses a great challenge in differentiating from neonatal sepsis therefore further research is required on usefulness of other biomarkers of infection to differentiate the cause between these conditions [44].

A mean admission sodium concentration of 163.8 (SD14.4). mmol found in this study is comparable to other studies [32] . Similarly the serum sodium concentration correlated with percentage weight loss on admission as was found in other studies [12,18,32,43]. This underscores the importance of health worker education at primary care facilities on use of significant weight loss as a potential indicator of hypernatremic dehydration.

Exclusively breastfed healthy term infants in whom breastfeeding is not well established are also prone to hyperbilirubinaemia [45,46]. In this study, jaundice was the third most common presenting symptom and the second commonest clinical examination finding in infants with hypernatremia whose TSB was in phototherapy range. Similar studies on neonates with hypernatremia showed findings consistent with our study [18,35,47]. The high incidence of significant hyperbilirubinaemia may contribute to long-term neurologic sequelae in infants with hypernatremia [32,48]. Measurement of serum sodium concentrations should be recommended as part of guidelines for the management of hyperbilirubinaemia.

Mortality

Hypernatremic dehydration among infants has been associated with increased risk of mortality [20,29]. Serious vascular complications and death were reported in previous studies of breastfeeding-associated hypernatremia [15,38]. Studies on neonatal hypernatremia from Europe, North America and Asia record minimal to no mortality [5,7,17,18,35,49,50]. However, this study unlike previous studies which were mainly done in medium to high income countries, had a high case fatality rate of 9.38%. There is limited data from Africa and other resource limited settings on hypernatremic dehydration related mortality with only few case reports on preterm babies from Nigeria [51].

The differences in mortality may be due to differences in resources and timing of presentation. In a study of 149 neonates with hypernatremia in Turkey, there was no mortality recorded, the infants had presented early with mean age of admission of 4.5 days (SD 3.8) [47], compared to 6.6 days (SD 5.6), in our study. Furthermore, the median urea and creatinine concentrations on admissions were significantly higher among neonates who deceased ($p < 0,001$) compared to those who survived. Late presentation was more likely to be associated with severe dehydration and AKI, increasing the risk of mortality in our study. This is consistent with findings from a neonatal mortality case series by Shroff et al [52].

LIMITATIONS

The limitations of this study include lack of specific information on breastfeeding technique, important risk factor for poor lactogenesis and milk production. Further investigations for complications of hypernatremic dehydration which could have contributed to the morbidity and mortality including performing neuroimaging was limited by inadequate resources. There was a wide confidence interval on analysis of hypotonia and lethargy

association with mortality in this study due to the small number of the deaths, a larger sample size study would be required to ascertain the association. Lack of information on specific treatment modalities which could have contributed to mortality is also a limitation of this study.

CONCLUSION

Breastfeeding associated hypernatremic dehydration is a common condition in exclusively breastfed infants particularly in first time mothers who are discharged early from postnatal care. Percentage weight loss on admission correlates positively with the admission serum sodium concentration in neonates with hypernatremic dehydration. Neonatal hypernatremic dehydration is associated with renal impairment and significantly high mortality in our setting.

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