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Borderline hypernatraemia and mortality rates in South African infants: A single-centre observational study

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Background. In children, hypernatraemia occurs most commonly in infants (younger than 1 year). Although hypernatraemia is associated with high mortality and morbidity rates, it is variably defined in the paediatric literature as either serum sodium ≥150 mmol/L or serum sodium >145 mmol/L. In hospitalised adults, a serum sodium level >145 mmol/L but <150 mmol/L (called borderline hypernatraemia) has recently been identified as an independent risk factor for mortality. There are limited data about a potential association between borderline hypernatraemia and mortality in infants.
Objectives. To determine whether borderline hypernatraemia is associated with increased mortality in hospitalised infants.
Methods. We conducted a single-centre, retrospective observational study of 8 343 infants admitted to a tertiary-level academic hospital in Johannesburg, South Africa, of whom 254 had borderline hypernatraemia, 376 had hypernatraemia (serum sodium ≥150 mmol/L), and 7 713 did not have hypernatraemia. Mortality rates were reported as odds ratios (ORs) with 95% confidence intervals (CIs).
Results. In 254 infants with borderline hypernatraemia, 115 (45.3%) were neonates (≤28 days old) and 140 (55.1%) were male. In 139 infants >28 days old with borderline hypernatraemia, the mortality rate (*n*=9/139; 6.5%) was significantly higher than the mortality rate observed in infants without hypernatraemia (*n*=194/5 857; 3.3%) (OR 2.02; 95% CI 1.03 - 3.98).
Conclusion. Borderline hypernatraemia may be a risk factor associated with higher mortality in hospitalised infants. Prospective studies are required to determine whether borderline hypernatraemia contributes independently to mortality risk in hospitalised infants.

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Most paediatricians regard hypernatraemia as the most severe electrolyte abnormality that is associated with poor outcomes in hospitalised children. Although there are no clinical studies that assign a definitive contributory role for hypernatraemia in adverse childhood outcomes, high mortality (12 - 19%) and morbidity rates (50 - 55%) are reported in children with hypernatraemia.[5-7] In hospitalised children, hypernatraemia is most commonly detected in infants younger than 1 year of age.[1-8] However, hypernatraemia is generally uncommon; the best estimates suggest that it is present in 0.4% of hospitalised neonates and 0.04% in hospitalised infants.[9]

Hypernatraemia is further classified as community-acquired (i.e. present at the time of hospital admission) or hospital-acquired (i.e. hypernatraemia that develops during the infant's hospital stay). In hospitalised infants, community-acquired hypernatraemia is thought to develop as a result of reduced infant feeding in any of the following situations: an inability to establish breastfeeding; reduced appetite in infants with severe illness; diarrhoeal disease; and, uncommonly, secondary to the intake of hypertonic fluids.[1-8]

The current consensus view is that most adverse outcomes associated with hypernatraemia such as the development of cerebral oedema, intracerebral bleeds and death[5-13] develop as a consequence of overly rapid correction of serum sodium levels.[14] For paediatricians, the prompt recognition and appropriate treatment of hypernatraemia may therefore improve outcomes in infants with hypernatraemia. However, hypernatraemia is variably defined as either serum sodium >145 mmol/L,[14] or ≥150 mmol/L.[1-10] Furthermore, some investigators use the term borderline hypernatraemia (or mild hypernatraemia) to describe serum sodium levels >145 mmol/L but <150 mmol/L.[15] In hospitalised adults, several recent studies have shown that borderline hypernatraemia is an independent risk factor for mortality.[15-17] However, it is not known whether an association exists between borderline hypernatraemia and increased mortality in hospitalised infants, and we therefore

undertook an observational study to test this hypothesis.

Ethics

Ethics approval for the study was obtained from the University of the Witwatersrand Human Research Ethics Committee (ref.no. M170672).

Methods

Study design and definitions

A retrospective study was undertaken to identify borderline community-acquired hypernatraemia in infants admitted to the Chris Hani Baragwanath Academic Hospital (CHBAH), Johannesburg, South Africa from 1 January 2015 to 31 December 2016. 'Borderline hypernatraemia' was defined as a serum sodium level >145 mmol/L but <150 mmol/L.[15] 'Definite hypernatraemia' was defined as serum sodium ≥150 mmol/L and 'community-acquired hypernatraemia' referred to the development of hypernatraemia prior to hospital admission.[18] Infants in the first 28 days of life were regarded as neonates, and infants beyond the neonatal period were older than 28 and younger than 365 days old.

Blood collection

At CHBAH, if indicated, clinicians obtain blood for testing immediately after clinical evaluation and prior to intravenous fluid or medical therapy. Serum sodium levels are measured by indirect ion-selective electrodes at the CHBAH National Health Laboratory Service (NHLS); the NHLS complies with the International Organization for Standardization requirements (ISO/IEC 17043:2010) for serum electrolyte measurement and the normal serum sodium level reference range is 136 - 145 mmol/L.

Patient selection: Inclusion and exclusion criteria

Demographic, clinical and laboratory data were obtained by reconciling data from two electronic databases: (*i*) the NHLS Track-Care database, which records sodium results; and (*ii*) the Respiratory and Meningeal Pathogens Research Unit (RMPRU) administrative database which records all paediatric hospital admissions and outcomes.[19] After identifying infants with admission serum sodium values >145 mmol/L from the NHLS database, the following corresponding variables were extracted from the RMPRU database: age; gender; anthropometric parameters; HIV status; main or primary discharge diagnosis (as defined by an ICD-10 code); and outcome (death or discharge). In neonates, hypernatraemic cases were exclusively categorised according to one of the following most-coded primary diagnoses: (*i*) neonatal infection (representing either neonatal sepsis or possible serious bacterial infection); and (*ii*) neonatal jaundice (NNJ). All remaining neonatal cases without the aforementioned primary diagnoses were categorised as 'other neonatal diagnoses'. In infants beyond the neonatal period, hypernatraemic cases were exclusively categorised according to one of the following most-coded primary diagnoses: (*i*) acute gastroenteritis; (*ii*) lower respiratory tract infection; and (*iii*) other infant infections. All remaining cases without the aforementioned primary diagnoses were categorised as 'other infant diagnoses'. The following cases were excluded from the present study: (*i*) children with hospital-acquired hypernatraemia; (*ii*) those with underlying medical conditions predisposing to hypernatraemia, i.e. abnormalities of the central nervous system, meningitis, diabetes mellitus or diabetes insipidus, accidental ingestion of poisons or medication, and renal disease; and (*iii*) neonates who were admitted directly to the neonatal unit after birth, i.e. predominantly premature neonates and term neonates requiring immediate hospitalisation after birth. We used the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) criteria to account for missing data.[21]

Statistical analysis

The prevalence of community-acquired hypernatraemia in hospitalised infants was determined as a proportion of the total number of infant admissions. Anthropometric *z*-scores, based on the World Health Organization (WHO) growth references, were calculated using WHO AnthroPlus software V.1.0.4. Comparisons of mortality between infants with borderline hypernatraemia, no hypernatraemia, and definite hypernatraemia were undertaken using contingency tables. Analyses were performed using either the Chi-square or Fischer's exact test – *p*-values, odds ratios (ORs) and 95% confidence intervals (CIs) were reported. Data were analysed using STATA software (version 13.0; Stata Corp., USA).

Results

For the study period, 15 943 discharge summary records were retrieved from the RMPRU database and 2 985 results of children with serum sodium levels >145 mmol/L were provided by the NHLS laboratory . These databases were reconciled, and 8 343 infants were analysed (Fig. 1). Of 8 343 hospitalised infants, 254

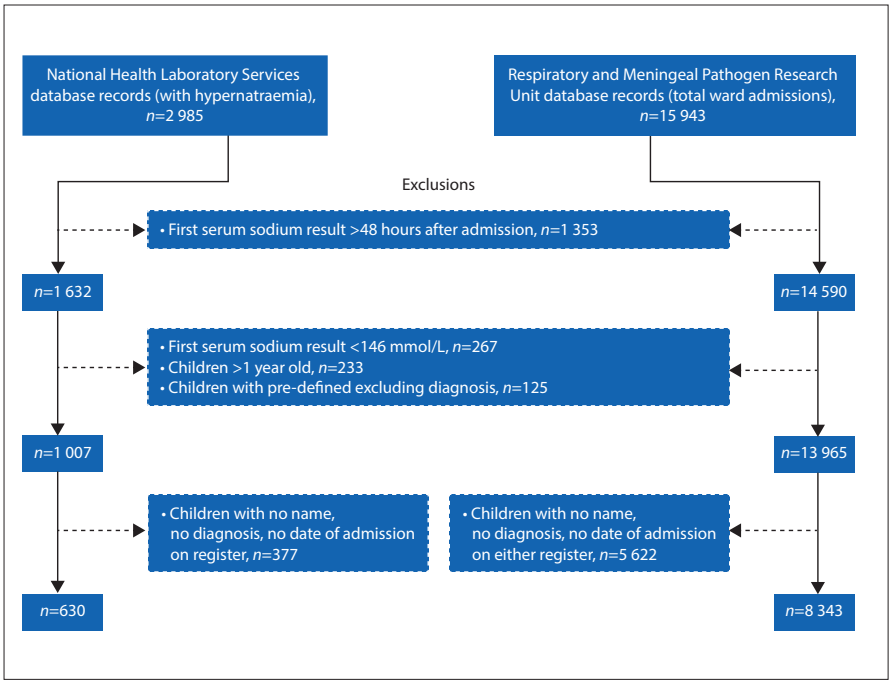


Fig. 1. Participant recruitment flow chart. During the study period (1 January 2015 - 31 December 2016), 2 985 children with serum sodium levels >145 mmol/L were provided by the NHLS laboratory and 15 943 discharge summary records were retrieved from the RMPRU database. The final analysis was performed on 8 343 infants, of whom 630 had admission serum sodium levels ≥146 mmol/L. (NHLS = National Health Laboratory Services; RMPRU = Respiratory and Meningeal Pathogen Research Unit).

Table 1. Demographic and clinical characteristics of 630 hospitalised infants with community-acquired hypernatraemia, stratified by serum sodium levels

Variable	Sodium levels (mmol/L), *n* (%)*					
	Non-hypernatraemia, *N*=7 713	**146 - 149, *n*=254**	**150 - 159, *n*=254**	**160 - 169, *n*=65**	**170 - 179, *n*=32**	**≥180, *n*=25**
Age						
≤28 days	1 856 (24.1)	115 (45.3)	99 (39.0)	21 (32.3)	12 (37.5)	12 (48.0)
>28 days - 12 months	5 857 (75.9)	139 (54.7)	155 (61.0)	44 (67.7)	20 (62.5)	13 (52.0)
Male gender	4 409 (57.2)	140 (55.1)	132 (52.0)	35 (53.9)	20 (62.5)	14 (56.0)
Anthropometry						
WAZ	*n*=7 045	*n*=229	*n*=229	*n*=61	*n*=27	*n*=24
Median (IQR)	−1.04 (−2.38 - −0.33)	−1.42 (−2.58 - −0.33)	−1.65 (−2.78 - −0.52)	−1.58 (−2.88 - −0.84)	−2.41 (−3.52 - −1.06)	−2.13 (−4.06 - −1.38)
LAZ	*n*=5 444	*n*=183	*n*=181	*n*=48	*n*=19	*n*=19
Median (IQR)	−1.32 (−2.79 - 0.33)	−1.00 (−2.75 - 0.46)	−0.97 (−2.42 - 0.44)	−1.36 (−2.88 - −0.22)	−0.53 (−1.88 - 0.46)	−1.15 (−2.22 - 1.53)
WLZ	*n*=5 434	*n*=183	*n*=181	*n*=48	*n*=19	*n*=19
Median (IQR)	−0.64 (−2.00 - 0.55)	−1.12 (−2.66 - 0.06)	−1.63 (−3.04 - −0.15)	−1.46 (−2.34 - −0.81)	−2.73 (−4.44 - −1.21)	−2.37 (−5.51 - −0.44)
Primary diagnosis						
Neonate (1 - 28 days)						
Neonatal infection	1 091 (14.1)	54 (21.3)	49 (19.3)	11 (16.9)	5 (15.6)	10 (40.0)
Neonatal jaundice	608 (7.9)	50 (19.7)	44 (17.3)	8 (12.3)	3 (9.4)	0
Other neonatal diagnoses	157 (2.0)	11 (4.3)	6 (2.4)	2 (3.1)	4 (12.5)	2 (8.0)
Infant (29 - 365 days)						
Acute gastroenteritis	817 (10.6)	48 (18.9)	82 (32.3)	35 (53.8)	14 (43.8)	7 (28.0)
LRTI	3 160 (41.0)	56 (22.1)	38 (15.0)	4 (6.2)	2 (6.3)	2 (8.0)
Other infant infections	945 (12.3)	15 (5.9)	21 (8.3)	2 (3.1)	2 (6.3)	3 (12.0)
Other infant diagnoses	935 (12.1)	20 (7.9)	14 (5.5)	3 (4.6)	2 (6.3)	1 (4.0)
Days of hospitalisation, median (IQR)	3 (1 - 7)	5 (3 - 8)	5 (4 - 8)	6 (4 - 7)	7 (4.5 - 11.5)	5 (4 - 10)
Death rate	238 (3.1)	12 (4.7)	10 (3.9)	6 (9.2)	5 (15.6)	7 (28.0)

WAZ = weight-for-age Z-score; IQR = interquartile range; LAZ = length-for-age Z-score, WLZ = weight-for-length Z-score; LRTI = lower respiratory tract infection.
*Unless otherwise specified.

Table 2a. Mortality rates in hospitalised infants with no hypernatraemia, borderline hypernatraemia, and definite hypernatraemia

	No hypernatraemia (≤145 mmol/L)1	Borderline hypernatraemia (146 - 149 mmol/L)	Definite Hypernatraemia (≥150 mmol/L)
Number of admitted neonates (≤28 days)	1 856	115	144
Deaths, *n* (%)	44 (2.4)	3 (2.6)	12 (8.3)
Infants admitted beyond the neonatal period, *N*	5 857	139	232
Deaths, *n* (%)	194 (3.3)	9 (6.5)	16 (6.9)
All admitted infants (<365 days), *N*	7 713	254	376
Deaths, *n* (%)	238 (3.1)	12 (4.7)	28 (7.4)

Table 2b. Statistical comparisons* of mortality rates of hospitalised infants with borderline hypernatraemia and (*i*) no hypernatraemia and (*ii*) definite hypernatraemia

	Borderline v. no hypernatraemia	Borderline v. definite hypernatraemia
Neonates† (≤28 days)	*p*=0.75; OR 1.1 (95% CI 0.4 - 3.4)	*p*=0.06; OR 0.30 (95% CI 0.1 - 1.0)
Infants beyond the neonatal period	*p*=0.04; OR 2.0 (95% CI 1.0 - 4.0)	*p*=0.88; OR 0.94 (95% CI 0.4 - 2.1)
All infants (<365 days)	*p*=0.14; OR 1.6 (95% CI 0.9 - 2.8)	*p*=0.17; OR 0.62 (95% CI 0.3 - 1.2)

OR = odds ratio; CI = confidence interval.
*All comparisons were made using a one-sided Chi-square test, except for neonates
† in whom comparisons were made using a two-sided Fischer's exact test.

(3.0%) had borderline hypernatraemia (Table 1). In infants with borderline hypernatraemia, 115 (45.3%) were neonates (≤28 days of age) and 140 (55.1%) were male. In neonates with borderline hypernatraemia, the most common diagnoses were neonatal infections (*n*=54; 47.0%) and jaundice (*n*=50; 43.5%). In infants beyond the neonatal period (*n*=139), the most common diagnoses were lower respiratory tract infection (*n*=56; 40.3%) and acute gastroenteritis (*n*=48; 34.5%).

In neonates with borderline hypernatraemia, the mortality rate was 2.6% (*n*=3/115 cases). This mortality rate was comparable with neonates without hypernatraemia (2.4%; *n*=44/1 856; OR 1.10; 95% CI 0.36 - 3.41) but lower than the mortality rate in neonates with definite hypernatraemia (8.3%; *n*=12/144; OR 0.3; 95% CI 0.1 - 1.0) albeit not statistically significant (Tables 2a and 2b). In infants beyond the neonatal period, the odds of mortality were twice as high in infants with borderline hypernatraemia compared with infants without hypernatraemia (OR 2.0; 95% CI 1.0 - 4.0); mortality rates were similar in infants with borderline hypernatraemia (6.5%; *n*=9/139) and definite hypernatraemia (6.9%, *n*=16/232; OR 0.9; 95% CI 0.4 - 2.1).

Discussion

Our study shows that borderline hypernatraemia (serum sodium >145 mmol/L but <150 mmol/L) in hospitalised infants beyond the neonatal period is associated with higher mortality; this is in keeping with results showing an association between borderline hypernatraemia and mortality in adults.[14-16] Borderline hypernatraemia (serum sodium >145 mmol/L) was present in a significant proportion (40.3%) of all hypernatraemic cases. In our study, mortality rates were higher in infants with severe hypernatraemia – a trend described in other studies.[4-6,10] In our resource-limited setting, the overall mortality rate in hypernatraemic infants was high; we speculate that this could be due to: (*i*) lack of close monitoring of the rate at which intravenous fluids are administered; (*ii*) liberal prescription of fluid boluses and high infusate volumes to children presenting with sepsis or a 'sepsis-like' illness;[22] and (*iii*) difficulty in obtaining results timeously from our medical laboratory.

Study limitations

We cannot attribute a direct causal role implicating borderline hypernatraemia and mortality; the relatively low numbers (in comparison to adult studies) did not allow us to adjust for confounding variables that contribute independently to mortality, e.g. underlying diagnosis, duration of illness, nutritional status, as well as the rate and volume of intravenous fluid therapy. Compared with non-hypernatraemic infants, proportionately more children with hypernatraemia were underweight or had wasting; however, because admission weights are not a true reflection of the actual weight in dehydrated children, we cannot reliably infer potential associations with hypernatraemia. HIV-infected children may be at risk of hypernatraemia but we could not verify this association because of the small number of HIV-infected children in our study. In the present study, HIV-exposure is more reliably determined in under-6-month-olds, and in this group we did not find an association between HIV-exposure and case fatality rates (data not shown). We did not show a significantly higher mortality rate in neonates with borderline hypernatraemia but other investigators have reported lower fine motor scores (during later developmental assessments) in preterm infants whose serum sodium levels exceeded 145 mmol/L in the first week of life.[23]

Conclusion

Despite the limitations of an observational study, we analysed outcomes in a very large number of infants, and in keeping with adult findings, we found a significant association between borderline hypernatraemia and increased mortality in hospitalised infants. Borderline hypernatraemia may be a risk factor for increased mortality in hospitalised infants and we suggest that hypernatraemia in children be defined as serum sodium levels of >145 mmol/L rather than ≥150 mmol/L. Until evidence-based treatment guidelines are available, we recommend that clinicians avoid overly rapid correction of the serum sodium levels using intravascular fluids in infants with borderline hypernatraemia.

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Author contributions. ZD and SGL: conceptualised and designed study; designed data collection instruments; analysed data, reviewed and revised manuscript (equal contributions). NN: designed data collection instruments, collected data and carried out initial analysis, drafted initial manuscript, reviewed and revised manuscript. FS, AI and SAM: maintained database employed in the study, critically reviewed the manuscript for important intellectual content. JMP: assisted with the study design and analysis, critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Conflicts of interest. None.

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