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ARTICLE

Dysnatremia in extremely low birth weight infants is associated with multiple adverse outcomes

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Abstract

Objective The objective of this study is to discern patterns of serum sodium in a broad cohort of extremely low birth weight (ELBW) infants and associate those patterns with hospital outcomes.

Study Design Retrospective cohort study of ELBW infants from 323 neonatal intensive care units (NICUs) discharged from 2004 to 2014. We included patients who survived at least 7 days and had daily sodium levels available, and categorized infants by their minimum and maximum sodium levels.

Results We identified 26,871 infants of whom 12,428 met inclusion criteria. Only 1964 (15.8%) maintained eunatremia for the first week. We found most dysnatremias to be associated with increased overall mortality compared with eunatremic patients including moderate hyponatremia (12.9% vs. 8.6%, $p < 0.05$) and severe hypernatremia (34.8% vs. 8.6%, $p < 0.001$). Most of these associations were maintained after regression modeling for mortality.

Conclusion Sodium fluctuations occurring within the first week of life are associated with increased mortality.

Introduction

The role of sodium administration in the fluid management of preterm infants remains unclear. Relative fluid restriction in the first week of life in larger birth weight preterm infants is associated with decreased incidence of bronchopulmonary dysplasia (BPD), symptomatic patent ductus arteriosus (PDA), and necrotizing enterocolitis (NEC) [1–6]. Extremely low birth weight (ELBW) infants have increased and more variable insensible fluid losses [7, 8]. Recent literature suggests that hypernatremia during the first week of life has an association with greater severity of intraventricular hemorrhage (IVH) and adverse neurodevelopmental outcomes [9, 10].

We sought to discern patterns of serum sodium over the first week after birth and to associate these patterns with mortality in a broad cohort of ELBW infants. Limited data are available regarding the abnormalities in sodium levels, or dysnatremias, experienced by ELBW infants early in life. To examine these patterns, we evaluated the minimum and maximum sodium levels over the first week and hypothesized that the greater severity of dysnatremias would be associated with increased mortality and other adverse outcomes.

Patients and methods

We performed a retrospective cohort study of infants from the Pediatrix Clinical Data Warehouse (CDW), a large, multicenter, de-identified dataset. The data in the CDW are sourced from Babysteps, a standardized documentation and billing software tool used by participating neonatal intensive care units (NICUs) managed by Pediatrix Medical Group. The CDW captures data prospectively until death or discharge. Laboratory data may be either hand entered or automatically

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imported into the CDW, depending on local site setup. Local data are consolidated within the CDW, de-identified, and made compliant with the Health Insurance Portability and Accountability Act of 1996 regulations. For this analysis we queried the following specific CDW tables: demographics, laboratory results, diagnoses, and procedures.

Our cohort included infants from 323 Pediatrix-managed NICUs from 1 January 2004 to 31 December 2014 within the United States. We included inborn infants ≤1000 g birth weight with an estimated gestational age at birth of 23–29 weeks, who had daily sodium levels captured for the first 7 days after the day of birth. We excluded patients with significant congenital anomalies. From 2004 through 2014, we identified a total of 853,240 infants cared for in a Pediatrix-managed NICU. Of these, 26,871 (3.1%) infants met the stated weight and gestational age criteria. From this population, 14,443 infants were excluded due to death/transfer within 7 days of birth or missing daily sodium in the first 7 days of life leaving 12,428 infants whose records underwent further analyses (Fig. 1) Exclusions consisted of 3052 deaths, 67 transfers, as well as 4279, 1614, 928, 906, and 3597 missing one, two, three, four, or five sodium values, respectively.

From these 12,428 patients, the daily serum sodium level from day of life (DOL) 1 (defined as the first day after birth) through 7 was used to determine the range of serum sodium levels for each subject. For patients with multiple sodium values on a single day, an average value was generated. The degree of dysnatremia was classified based on minimum and maximum sodium values as follows: severe hyponatremia (<125 mEq/L, class −2), moderate hyponatremia (125–34 mEq/L, class −1), eunatremia (135–144 mEq/L, class 0), moderate hypernatremia (145–154 mEq/L, class 1), and severe hypernatremia (>154 mEq/L, class 2). Using these five sodium classifications, we generated nine groups of distinct sodium range exposures in the first 7 days after birth (Fig. 1). We took as the control population those patients for whom the minimum and maximum sodium level fell within the "normal" range, class 0, so described as group "0 to 0," whereas a patient who experienced both severe hyponatremia (class − 2) and severe hypernatremia (class 2) is described as group "− 2 to 2".

Univariate analyses were performed using a one-way analysis of variance with a Tukey–Kramer correction for comparing the varying levels of dysnatremia to subjects with normal levels. The primary outcome was mortality after 7 days, which we defined as death before discharge but not during the first week of life, and secondary outcomes included grade 3 and 4 IVH (high-grade IVH), stage 4 and surgical retinopathy of prematurity (ROP), BPD defined as oxygen use at 36 weeks post menstrual age (PMA), medical/surgical NEC, and PDA diagnosis among surviving infants past 7 days.

In addition, multiple logistic regression analysis was performed for mortality after 7 days controlling for gestational age at birth, birth weight, gender, administration of antenatal steroids, and renal insufficiency as defined as creatinine (Cr) > 1.3 on DOL 3 [11]. These results are presented as odds ratios with their corresponding 95% Wald's confidence intervals.

Results

Only 15.8% of infants maintained eunatremia (135–144 mEq/L) throughout the first week after birth (Fig. 1). The most frequent dysnatremia we noted, isolated moderate hypernatremia (group 0 to 1), incorporated 43.7% of the cohort. Overall, 65.4% of the cohort experienced hypernatremia during the first week, 35.1% hyponatremia, and 16.4% both hyponatremia and hypernatremia. This led us to examine daily mean sodium levels among ELBW infants in the first 7 days of life. We found sodium levels followed a characteristic pattern increasing from baseline to peak

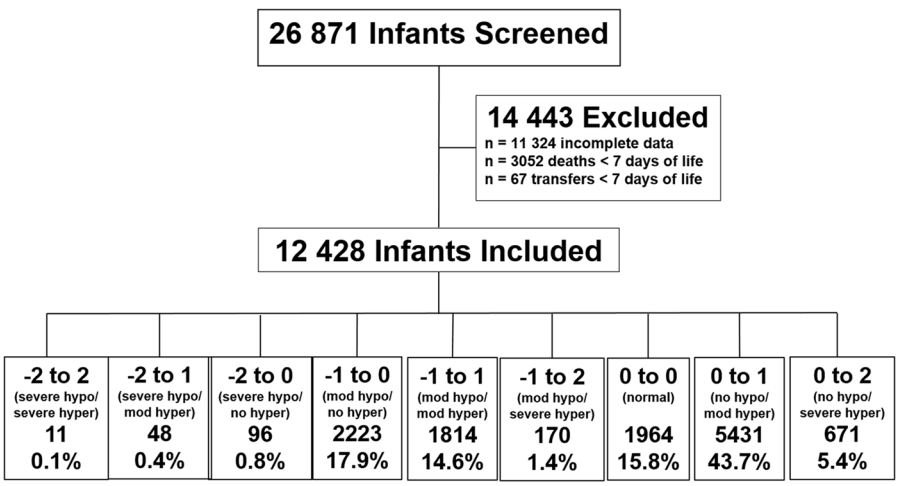

Fig. 1 Study population. Screening criteria included infants with birthweights <1000 g, as well as estimated gestational ages between 23 and 29 weeks. Exclusion criteria included incomplete data. Annotation of subgroups are as follows: negative values indicate hyponatremia and positive values indicate hypernatremia, and numerical values refer to degree of dysnatremia (0 = none, 1 = moderate, 2 = severe)

values around DOL 2 with subsequent return to baseline by DOL 4 (Fig. 2). On days 1–3 and 7, 23–24 weeks' infants had significantly higher mean sodium values compared with 25–26 weeks' infants. The 27–29 weeks' cohort had significantly lower sodium values every day within the 7-day period compared with both 23–24- and 25–26-week cohorts. Mean daily sodium values remained within the normal range during the first 7 days of life for all cohorts with the exception of the mean sodium of 146 mEq/L among 23–24 weeks' infants on the second day after birth.

Primary and secondary outcomes were evaluated by dysnatremia groups. We present data limited to comparisons of the most common dysnatremias (−2 to 0, −1 to 0, − 1 to 1, 0 to 1, and 0 to 2) for the two following reasons. We determined a priori the sodium ranges that clinicians presumably would accept outside of normal values, i.e., moderate hyponatremia (125–134 mEq/L, group −1 to 0), moderate hypernatremia (145–154 mEq/L, group 0 to 1), or both (group −1 to 1), and also reported outcomes from groups with severe range dysnatremia (<125mEq/L, >155 mEq/L) (−2 to 0, 0 to 2). This reduced the number of comparisons to five but did not significantly change the results as compared with the full dataset.

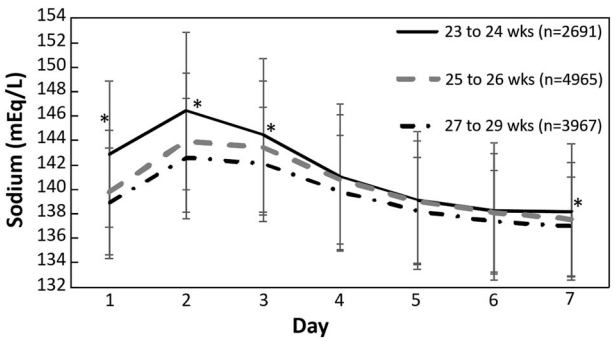

Fig. 2 Daily sodium levels (mean ± SEM) over first 7 days of life. Infants (11,623) shown in the figure (excludes 805 infants with renal insufficiency). Twenty-seven- to 29-week infants had significantly lower sodium values on all measured days compared with the two younger gestational age cohorts. Repeated-measures ANOVA with Tukey–Kramer correction where $*p < 0.0001$ between 23/24 weeks and 25/26 weeks

Table 1 contains neonatal demographics of these selected subgroups. Infants with moderate and severe hypernatremia were more premature, had lower birthweights, more male, and had lower Apgar scores. Patients with either severe hyponatremia or severe hypernatremia have significantly less frequent antenatal steroid exposure and significantly more frequent renal insufficiency.

Table 2 demonstrates univariate analysis of both primary and secondary outcomes among the most common ranges of dysnatremia in comparison with the eunatremia group. ELBW infants with normal daily sodium values throughout the first 7 days had the lowest mortality rate of 8.6%. However, infants with either severe hyponatremia (<125 mEq/L) or severe hypernatremia (>155 mEq/L) had the highest mortality after 7 days at 32.3% and 34.8%, respectively. Similarly, these groups had significantly higher rates of grades 3 and 4 IVH compared with the normal sodium level group. Compared with controls, increases in BPD was only found in patients experiencing hypernatremia, with the highest rate among the normal-to-severe hypernatremia sodium group (0 to 2) with a BPD rate of 63.9%. There were no differences among groups for NEC, but the presence of PDA was higher among those with moderate or severe hypernatremia and moderate hyponatremia. We further analyzed mortality outcome within the subset of infants with normal-to-moderate hypernatremia (0 to 1) and found no linear correlation between rising sodium values, e.g., 145–149 vs. 150–154, and mortality.

In order to assess whether dysnatremia was related to increased mortality after 7 days by virtue of its relationship

Table 1 Demographics by selected sodium range (mEq/L)

	Normal (0 to 0)	Severe hyponatremia to normal (−2 to 0)	Moderate hyponatremia to normal (−1 to 0)	Moderate hyponatremia to moderate hypernatremia (−1 to 1)	Normal to moderate hypernatremia (0 to 1)	Normal to severe hypernatremia (0 to 2)
Sample size	1964	96	2223	1814	5431	671
Gestational age, weeks (mean ± SD)	26.4 ± 1.6	25.9 ± 1.7*	26.3 ± 1.6	25.6 ± 1.6**	25.6 ± 1.5**	24.5 ± 1.3**
Birth weight, g (mean ± SD)	788 ± 140	754 ± 154	786 ± 140	759 ± 146**	755 ± 146**	662 ± 139**
Female gender (%)	1136 (58%)	51 (53%)	1235 (56%)	922 (51%)*	2703 (50%)*	286 (43%)**
APGAR 1 min (median, 10–90%)	5 (3, 7)	4 (2, 6)*	5 (3, 7)	4 (2, 6)**	5 (3, 6)**	4 (2, 6)**
APGAR 5 min (median, 10–90%)	8 (7, 8)	7 (5, 8)*	7 (6, 8)	6 (4, 7)**	7 (6, 8)**	7 (5, 8)**
Antenatal steroids (%)	1670 (85%)	75 (78%)*	1864 (84%)	1473 (81%)*	4550 (84%)	511 (76%)**
Renal insufficiency (%)	81 (5%)	18 (22%)**	97 (5%)	123 (8%)*	297 (7%)	138 (25%)**
Ethnicity (%)	876 (44%)	32 (33%)	871 (39%)	736 (41%)	2299 (42%)	268 (40%)
White	575 (29%)	28 (27%)	663 (30%)	605 (33%)	1993 (37%)	253 (38%)
Black	351 (18%)	26 (27%)	492 (22%)	348 (19%)	797 (15%)	97 (14%)
Hispanic	69 (4%)	4 (4%)	76 (3%)	56 (3%)	117 (2%)	20 (3%)
Asian/Pacific Islander	93 (5%)	6 (6%)	121 (5%)	69 (4%)	225 (4%)	33 (5%)
Other/not listed						

$*p < 0.05$, $**p < 0.001$ compared with normal (0 to 0)

Table 2 Outcomes among selected subgroups

Outcome *N* (%)	Normal (0 to 0)	Severe hyponatremia to normal (−2 to 0)	Moderate hyponatremia to normal (−1 to 0)	Moderate hyponatremia to moderate hypernatremia (−1 to 1)	Normal to moderate hypernatremia (0 to 1)	Normal to severe hypernatremia (0 to 2)
Sample size	1964	96	2223	1814	5431	671
Mortality	169 (8.6)	31 (32.3)*	287 (12.9)**	310 (17.1)**	771 (14.2)*	234 (34.8)*
ROP	185 (9.4)	9 (9.2)	289 (13.0)**	276 (15.2)**	728 (13.4)*	214 (31.9)*
IVH 3/4	157 (8.0)	28 (28.9)*	278 (12.5)*	321 (17.7)**	630 (11.6)**	184 (27.4)*
BPD	817 (41.6)	43 (44.8)	994 (44.7)	873 (48.1)**	2645 (48.7)*	429 (63.9)*
NEC	169 (8.6)	11 (11.5)	209 (9.4)	207 (11.4)	543 (10.0)	63 (9.4)
PDA	1318 (67.1)	75 (78.1)	1614 (72.6)*	1339 (73.8)*	3910 (72.0)**	517 (77.0)*
PDA ligation	410 (20.9)	17 (17.3)	485 (21.8)	432 (23.8)	1217 (22.4)	176 (26.3)

*$p < 0.001$, **$p < 0.05$ compared with normal (0 to 0)

Table 3 Multiple logistic regression analyses

OR (95% CI)	Mortality
Severe hyponatremia to severe hypernatremia (− 2 to 2)	6.61 (1.61, 27.23)*
Severe hyponatremia to moderate hypernatremia (− 2 to 1)	2.09 (0.99, 4.43)
Severe hyponatremia to normal (−2 to 0)	4.47 (2.63, 7.59)**
Moderate hyponatremia to normal (−1 to 0)	1.61 (1.29, 2.01)**
Moderate hyponatremia to moderate hypernatremia (−1 to 1)	1.44 (1.16, 1.81)*
Moderate hyponatremia to severe hypernatremia (−1 to 2)	2.93 (1.98, 4.34)**
Normal to moderate hypernatremia (0 to 1)	1.17 (0.97, 1.43)
Normal to severe hypernatremia (0 to 2)	2.12 (1.63, 2.75)**

Odds ratios for mortality adjusted by gestational age, birth weight, antenatal steroids, gender, and renal insufficiency diagnosis

*$p < 0.05$, **$p < 0.001$

with other confounding influences, we performed a multiple logistic regression analysis that accounted for factors including gestational age, birth weight, gender, exposure to antenatal steroids, and renal insufficiency. (Table 3). Mortality rates in the logistic regression showed a similar pattern to that found in the univariate analysis. The odds of death increased directly in proportion to the degree of dysnatremia with a compounding effect when both hypernatremia and hyponatremia are present. Compared with the normal group, mortality odds among isolated moderate hypernatremia group (0 to 1) trended higher at 1.17, but moderate hyponatremia (−1 to 0) had 1.61 increased odds for mortality. For severe isolated hypernatremia (0 to 2) and hyponatremia (−2 to 0), the odds were 2.12 and 4.47, respectively, higher. The odds of mortality were the highest in the combined severe hyper and hyponatremia group (−2 to 2) at 6.61 (Table 3).

Discussion

In this large cohort of ELBW infants, we found dysnatremia in 84% of ELBW infants who survived the first week after birth. All types and severities of dysnatremia had an association with increased mortality after 7 days on univariate analysis, most of which persisted even after controlling for multiple factors known to affect outcome. Dysnatremias also had associations with multiple common complications of prematurity including severe IVH, ROP, PDA, and BPD.

Our observation of the rise and subsequent return to baseline of serum sodium values in ELBW neonates aligns with a long-held acceptance that free water shifts occur in extremely preterm infants reflected by a natural rise in sodium values in the first few days following birth [12, 13]. These findings are similar to earlier reports in other cohorts, which reported this data incidentally but did not study dysnatremia in relation to outcomes [11, 14]. That only 16% of the total preterm infant cohort remained within the "normal" sodium range may indicate that traditionally agreed upon values, based on adult values [15, 16], may not be the norm for preterm infants in the first week after birth. Conversely, our data may suggest that the association of any dysnatremia with increased adverse outcomes may support clinicians targeting "normal" sodium values in this patient population.

Our study is the first to examine the association between dysnatremia, as reported by sodium fluctuations, and

mortality after 7 days of life. Infants with "normal" sodium values had the lowest mortality rate. Moderate hypernatremia comprises 44% of our dataset that we observed in the first week of life. When adjusted for additional factors, the mortality odds among this cohort of moderately hypernatremic infants did not reach statistical significance but did for more severely dysnatremic fluctuations. Although hyponatremia is more likely observed after the first week of life and attributed to inadequate sodium supplementation, early moderate and severe hyponatremia has previously been reported in a cohort of preterm infants within the first week [17]. Early hyponatremia also carries adverse consequences in the preterm population not just in terms of mortality and IVH but also growth and long-term neurodevelopment, to include cerebral palsy [18, 19]. The fact that we report an association between moderate and severe hyponatremia with increased mortality odds suggests that perhaps a more liberal fluid management strategy during the first week of life may not be optimal for extremely preterm infants in whom fluid redistribution are rapidly occurring.

Our unadjusted outcomes data suggest that dysnatremia are associated with increased rates of IVH, BPD, PDA, and ROP but not NEC. Prior studies have also reported associations between dysnatremia and IVH, BPD, PDA, and adverse neurodevelopmental outcomes [1–5, 9]. Costarino et al. [2] reported that sodium restriction strategy prevents hypernatremia, suggesting lower incidence of BPD among sodium-restricted infants ($n = 9$) compared with maintenance-supplemented infants ($n = 8$). All these infants' reported serum sodium values were eunatremic (135–144 mEq/L), whereas we report adverse associations among a substantially larger cohort of infants with dysnatremia. Whereas Oh et al. [4] primarily examined fluid intake and weight gain in a large cohort of ELBW infants and BPD incidence in contrast to our sodium-focused investigation, we concur regarding the importance of careful attention to a comprehensive fluid management strategy. Baraton et al. [10] reported that infants who exhibited the widest sodium fluctuations had lower gestational ages and birthweights, and had higher rates of RDS, BPD, PDA, and sepsis diagnoses. The significance between early dysnatremia and ROP remains unclear and more likely represents an association between more critically unstable infants and adverse outcomes. Although we report association in the first week of life, an earlier report noted an association between late-onset hyponatremia (<132 mEq/L after 2 weeks of life) and ROP in a small cohort of preterm infants <34 weeks' gestation [20]. Whether dysnatremia has a causative role regarding clinical outcomes remains unclear. Dysnatremia may represent a marker for physiologic immaturity or a reflection of the underlying illness/wellness state (e.g., sepsis, pulmonary hypertension, adrenal insufficiency, etc). Finally, dysnatremia may be the iatrogenic result of fluid management strategies, which we are unable to ascertain.

Several limitations to this work should be acknowledged. Our decision to include only those with at least one sodium value per day over the first 7 days of life limited the cohort to 46% of ELBWs in the database. About one-fourth of excluded infants were due to early death and three-fourth due to incomplete data. Although those with early death clearly had higher acuity than the final cohort, those without daily sodium levels for 7 days may have been clinically more stable or reflected variations in local practice. We cannot rule out differences between our final dataset and the larger cohort. However, our a priori goal to investigate associations between sodium levels over the first 7 days and clinical outcomes required either the exclusion of these patients or extrapolation from incomplete data. Nevertheless, our dataset includes 12,428 infants across the United States. In addition, we acknowledge that limitations within the dataset preclude our ability to comment on fluid or electrolyte management therapies that may affect the sodium levels and outcomes discussed in this report. Available data do not allow us to surmise practitioners' intent targeting specific sodium values/daily fluid goals, the incorporation of specific sodium/fluid restriction strategies, or the utilization of fluids in other conditions, i.e., hypotension, for which boluses could contribute to increased mortality/morbidity. We are also unable to assign additional illness severity measures to adjust as confounding factors. Lastly, given its retrospective design, we caution against our findings as a means to actively target normal serum sodium values or moderate hypernatremia in ELBW infants.

In conclusion, serum sodium levels in ELBW infants within the first week of life follow a natural rise and subsequent normalization. We find that sodium fluctuations occurring within the first week of life, particularly extreme changes in both directions, are associated with increased mortality. Further research is needed to prospectively target sodium levels as part of a comprehensive fluid management strategy and evaluate its association with important neonatal outcomes.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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