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ORIGINAL ARTICLE

Nutrition

Excessive sodium supplementation but not fluid load is correlated with overall morbidity in extremely low birth weight infants

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Abstract

Objectives: Sodium homeostasis in extremely low birth weight (ELBW) infants is critical. While a lack of sodium delays growth, excessive supplementation increases morbidity.

Methods: We performed a single-center retrospective study on sodium and fluid management during the first 2 weeks of live including all ELBW infants born between June 1, 2017 and May 31, 2019.

Results: Forty-seven patients (median GA 26 + 6 weeks, median BW 845 g) were included. Mean sodium intake was above the ESPGHAN recommendation, 4.58 mmol/kg/day during the first 2 days and 1.99 mmol/kg/day during the following period. Incidence of PDA, IVH, and ROP was directly associated with sodium intake (OR 1.6, 1.3, and 1.4, respectively), but not with fluid supplementation. No association to BPD was found. The most important source for inadvertent sodium intake were 0.9% saline given by arterial lines. Sodium supplementation did not correlate directly with serum sodium levels, but a linear regression model combining sodium intake and fluid supplementation was able to predict serum sodium changes 24–48 h in advance (correlation coefficient of 0.294, $p < 0.05$).

Conclusions: Sodium application substantially exceeded ESPGHAN recommendations in ELBW infants. An excess in sodium was associated with an overall increased morbidity, justifying increased efforts to identify inadvertent sodium sources in these patients with the aim to decrease sodium excess.

KEYWORDS

hypernatremia; infant, extremely low birth weight; retrospective studies; sodium, dietary/adverse effects

1 | INTRODUCTION

Transition from the intra- to the extrauterine environment is associated with major changes in water and electrolyte, particularly sodium homeostasis. In the early phase, this is mainly characterized by volume contraction of extracellular fluid and sodium loss. In premature infants, this adaptation is substantially complicated due to immature kidneys lacking full regulatory functionality and an increased transdermal water loss.[1–3] Thus, premature infants are prone to hypernatremia early in life. In contrast, beyond the immediate postnatal period with maturation of the skin preterm infants are prone to hyponatremia due to the inability of the premature kidney to retain salt.[4,5] This often necessitates high sodium substitution to ensure adequate growth and neurological development.[6–8] Currently, the European Society for Paediatric Gastroenterology Hepatology and

Nutrition (ESPGHAN) recommends a sodium supplementation up to 2(–3) mmol/kg/day for the first 2 days, followed by up to 5 mmol/kg/day on the following days (even up to 7 mmol/kg/day in cases of high urinary Na loss), to enable a proper contraction of ECF including a negative sodium balance in the first few days without risking hyponatremia.[9]

Recent data emphasize the importance of sodium homeostasis in premature infants. Whereas a delay in sodium supplementation has been associated with severe intraventricular hemorrhage (IVH), hypernatremia has been correlated with increased incidences of bronchopulmonary dysplasia (BPD), retinopathy of prematurity (RPM), and persisting ductus arteriosus botalli (PDA).[10–14] Similarly, high amounts of fluid supplementation have been associated with an increased incidence in PDA, necrotizing enterocolitis (NEC), and BPD.[13,15–18] Interestingly, a recent retrospective analysis on this topic, while associating an inadvertently high sodium load with an increased overall morbidity in extremely low birth weight (ELBW) infants, did not find any correlation of sodium intake and sodium serum levels.[19]

Three major obstacles in defining the importance of sodium homeostasis are the substantial differences in standard of care for ELBW infants between different tertiary neonatal intensive care units (NICU) as well as different time periods and the difficulty to perform prospective studies on this topic.

The aim of this study was therefore to analyze the importance of sodium homeostasis for neonatal mortality and morbidity in our unit. In addition to previous studies however, we did not only consider sodium supplementation but also fluid load aiming to investigate whether high sodium load might just be secondary reflecting a higher need for volume supplementation due to higher disease severity.

What is Known

- Water and electrolyte imbalance in extremely low birth weight (ELBW) infants during the first 2 weeks of life are common.
- Sodium intake in ELBW infants during the first 2 weeks of life is associated with an increased morbidity.

What is New

- Sodium intake often exceeds European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recommendations.
- Sodium intake does not simply reflect a more critical disease state, but is more related to unawareness of possible sodium sources.
- For accurate interpretation of serum sodium levels, both sodium and fluid intake need to be taken into consideration.

2 | METHODS

This single-center retrospective study was conducted between June 1, 2017 and May 31, 2019 at the NICU of the Children's Hospital Kassel, Germany. All inborn ELBW inborn during this period were included in the study. Infants with congenital malformations, underlying genetic or syndromic diseases as well as infants who died during the first 48 h of live were excluded from the study.

2.1 | Epidemiological data

Medical, nursing, and laboratory records of all newborns with a birth weight <1000 g admitted to the neonatal ward between June 1, 2017 and May 31, 2019, were reviewed. Anonymized data including date of birth, sex, gestational age, birth weight, mode of birth, morbidities, mortality, and applied medications including fluid therapy, administration of intravenous/central catheters or nasogastric tubes, enemas, parenteral and enteral nutrition were collected and analyzed. For enemas only 30% of the fluid and sodium were calculated as absorbed. The amount of fluid and sodium absorbed from saline Enemas has not been researched in our study population. Considering an intake of 5.5% of instilled Sodium in an adult population we estimated an average uptake of 30% in our population in light of higher incidence of hypernatremia and hyperphosphatemia after application of hypertonic sodium phosphate solutions.[20,21]

Daily intake of sodium (mmol/kg/day) and intravenous fluids (mL/kg/day) were calculated for the first 2 weeks of life. For these calculations, we included following data: parenterally administered fluids, arterial lines, parenteral nutrition, carrier solutions, drugs, enemas, and enteral nutrition as outlined in Table 1.

Serum sodium was measured at least daily in all infants using point-of-care diagnostics (GEM® Premier™ 5000). For multiple daily measurements, we calculated the mean average for these days. In all cases, double wall incubators were used exclusively with an initial humidity of 85%–90% on the first day of and a subsequent reduction by 5% per week.

A serum sodium level of >145 mmol/L was categorized as hypernatremia. IVH was diagnosed via echoencephalography according to Papile,[22] NEC according to the Bell criteria,[13] ROP according to the International classification of Retinopathy,[23] and BPD as oxygen supplementation >0.21 at a postmenstrual age of 36 + 0 weeks.[24] Hemodynamic relevant PDA was defined as requiring medical or surgical treatment.

Primary outcome was mean sodium intake in the first 14 postnatal days. Secondary outcomes were the

TABLE 1 Sodium content of applied medications.

Group	Sodium sources	Carrier solution	Sodium	
Crystalloids as bolus	Sodium chloride 0.9%		0.15	mmol/mL
	Electrolyte-Glucose-Solution		0.13	mmol/mL
Arterial infusion	Sodium chloride 0.9%		0.15	mmol/mL
	Sodium chloride 0.45%		0.08	mmol/mL
Antibiotics	Ampicillin	Aqua	0	mmol/mg
	Gentamicin	Aqua	0.13	mmol/dose
	Vancomycin	Aqua	0	mmol/mg
	Meropenem	Aqua	0	mmol/mg
	Cefotaxime	Aqua	0	mmol/mg
	Metronidazole		0.03	mmol/mg
	Fluconazole		0.08	mmol/mg
Blood products	Fresh frozen plasma		0.14	mmol/mL
	Thrombocyte concentrate		0.1	mmol/mL
	Human serum albumin 5%, 20%		0.15	mmol/mL
Drug perfusors	Catecholamines	NaCl 0.9%	0.13	mmol/mL
	Insulin	NaCl 0.9%	0.14	mmol/mL
	Fentanyl	NaCl 0.9%	0.14	mmol/mL
Diverse	Hydrocortisone	NaCl 0.9%	0.07	mmol/mg
	Tranexamic acid		0	mmol/mg
	Theophylline	NaCl 0.9%	0.03	mmol/mg
	Furosemide		0.02	mmol/mg
	Ibuprofen	NaCl 0.9%	Varied	mmol/mg
	Paracetamol		0	mmol/mg
	Sodiumbicarbonate	Aqua	0.5	mmol/mL
	Sodium glycerophosphate		2	mmol/mL
	Phenobarbital		0.01	mmol/mg
Enemas	Sodium chloride 0.9%		0.15	mmol/mL

Note: Sodium includes the amount applied from carrier solution.

incidence of IVH, BPD, NEC grade 2 and higher, ROP stage 2 and higher, and mortality, as well as serum sodium levels and hypernatremia over the first 2 weeks.

2.2 | Standards of fluid and sodium substitution

In the case of peripheral/central venous lines, a 10% Glucose solution was administered, with adjustments made based on daily requirements and enteral nutrition. Sodium was added to the infusion solution when hyponatremia was observed, and the adjustments were made in accordance with sodium intake and serum levels.

For arterial lines, a solution of NaCl 0.9% (typically at a rate of 1 mL/h) was administered.

In instances of hypotension, 1–2 boluses of balanced electrolyte solution (10 mL/kg) were administered. Prolonged hypotension that resulted from perceived intravascular depletion necessitated additional boluses of balanced electrolyte solution, accompanied by a 5% human albumin solution.

Target volume standards for daily fluid intake were applied, starting at 80 mL/kg on Day 1 and

incrementally increasing by about 20 mL/kg/day, reaching a maximum of 180 mL/kg on Day 6.

On Day 3, parenteral nutrition was introduced, and its composition was adjusted based on the clinical context of the patient.

2.3 | Statistical analysis

Data was collected in Excel (Microsoft, Version 2002, Build 12527.21594) and statistical analysis was performed via SPSS (IBM, Version 26.0.0.0). Pearson's test was used for determination of correlation for sodium serum level versus intake. Morbidity data was analyzed with Pearson's test and logistic regression. Odds ratios and 95% confidence intervals were calculated for all outcomes where applicable. A linear regression model was used for analyzing the effect of fluid and sodium on the sodium serum level.

2.4 | Ethics

The study was approved by the University of Southampton Faculty of Medicine Ethics Committee (FOMEC) on Ethics and Research Governance Online II (ERGO II) in July 2020 (ERGO number 55903.R2) and the Landesaerztekammer Hessen.

3 | RESULTS AND DISCUSSION

3.1 | Results

During the study period, 51 ELBW infants were born at the tertiary care center. After exclusion of two patients due to early demise and two patients due to other reasons. Forty-seven ELBW infants were included in the study. Patient characteristics are shown in Table 2.

TABLE 2 Epidemiological data.

Baseline characteristics	Median (mean) $n = 47$	Interquartile range
Gestational age (weeks) ($n = 51$)	26 + 6 (27 + 1)	[25 + 1;29 + 1]
Mothers age (years) ($n = 50$)	32 (31)	[23;38]
Birth weight (g) ($n = 51$)	845 (810)	[690;950]
Birth length (cm) ($n = 49$)	34 (33.4)	[32;35]
Time until discharge in days	88 (90.1)	[70;104]
APGAR score ($n = 49$)	7/8/9 (6/8/9)	
		%
Male (%)	18	38.3
Female (%)	29	61.7
Multiple birth (%)	10	21.3
Steroid therapy (%)	30	63.8
Congenital birth defects (%)	0	0
Cesarean section (%)	41	87.2
Bronchopulmonary dysplasia (%)	20[a]	43.5
Necrotizing enterocolitis (%)	1	2.1
Retinopathy of Prematurity (%)	30[a]	68.2
Intraventricular hemorrhage (%)	10	22.3
Persistent ductus arteriosus (%)	24	51.1
Hypernatremia (%)	34	72.3
Mortality (%)	3	6.4

[a]Three patients excluded due to death before 36 weeks of gestational age.

3.2 | Sodium intake

During the first 2 days, patients received an average of 6.93 mmol/kg/day of sodium (median 6.11 mmol/kg/day, IQR 4.51–8.36 mmol/kg/day), and afterward, an average of 6.58 mmol/kg/day (median 5.41 mmol/kg/day). This exceeded the upper limit recommended by ESPGHAN during the first 2 days by 4.58 mmol/kg/day and on the following days by 1.99 mmol/kg/day. Only 32% of patient days met the ESPGHAN recommendations at any time during the first 14 days of life, and no patient met the recommendations over the whole period.

When further defining the sources of sodium intake, we found that supplementation of sodium via enteral and parenteral feeding was within ESPGHAN recommendations (Figure 1A). The sodium excess during the first week was mainly driven by NaCl 0.9% infusion via arterial lines, intravenous fluid bolus during the first day, and intravenous drugs (Figure 1A). Moreover, the estimated sodium intake via rectal enemas for meconium mobilization was also quite substantial, with a mean intake of 0.6 mmol/kg/day during the first week (Figure 1A). In fact, factors identified as inadvertent sodium sources accounted for less than 10% of the total fluid supplementation (Figure 1B).

3.3 | Weight change

The median of weight change during the first 7 days of life was plotted in Figure 3. The Nadir of body weight was reached on Day 5 with a maximum weight loss of 2% compared with birth weight. After this, a steady increase in body weight was observed.

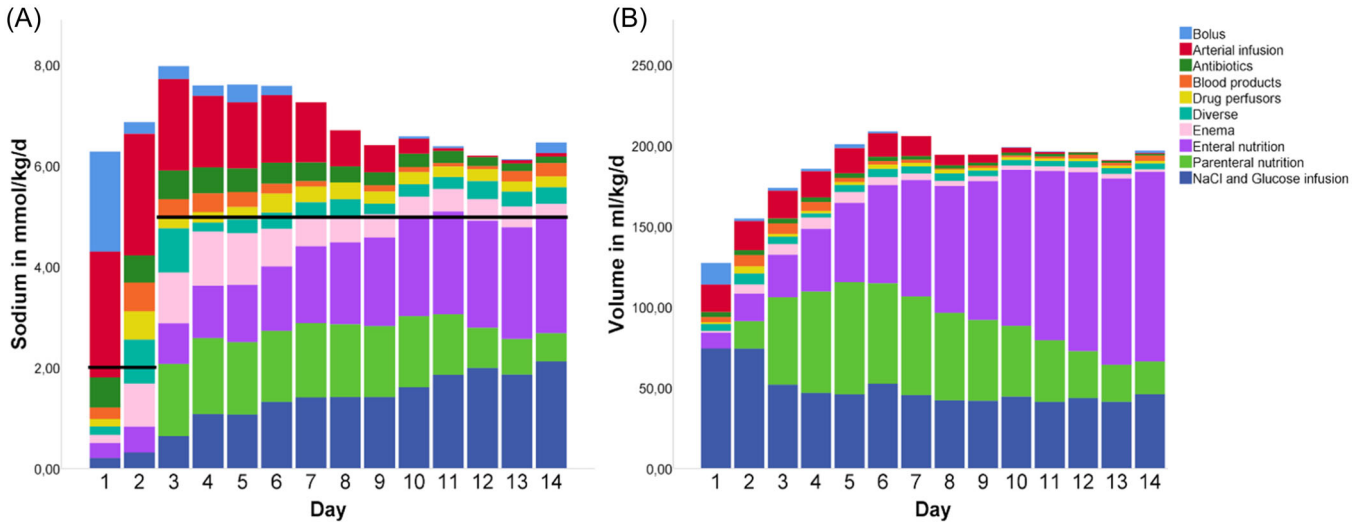

FIGURE 1 Sources of sodium and distribution of fluid supplementation. (A) Sodium supplementation by enteral and parenteral feeding (violet, green, and blue bar) were according to ESPGHAN recommendations. Excess sodium supplementation was mainly driven by arterial lines, intravenous medication, and enemas. ESPGHAN recommendations are displayed as black line. (B) Fluid load and sodium supplementation did not correlate demonstrating that sodium excess was mainly driven by solutions with high sodium content (i.e., NaCl 0.9% via arterial lines).

3.4 | Sodium serum levels

The average serum sodium levels were 140.6 mmol/L during the first 2 days, 143.9 mmol/L between Days 3 and 5, and 141.4 mmol/L (median 141.2 mmol/L, IQR: 139.7–143) over the entire timespan. Maximum sodium levels occurred between Days 2 and 5.

Hypernatremia (>145 mmol/L) occurred in 72% of all patients on at least 1 day during the first 2 weeks of life. Severe hypernatremia (>150 mmol/L) was found in 32% of the patients. Sixty-four percent of the patients had persistent hypernatremia, defined as sodium levels >145 mmol/L on 2 consecutive days. Whereas daily sodium intake did not correlate with the average serum level on a day-to-day basis (correlation coefficient of 0.047, $p = 0.25$), there was a significant correlation between sodium intake and the occurrence of hypernatremia (correlation coefficient of 0.294, $p < 0.05$).

Importantly, a linear regression model combining the intake of sodium as well as fluid per day was able to predict the change in serum sodium levels on the following day (standardized regression coefficients: sodium 0.287, $p < 0.01$, fluid −0.334, $p < 0.01$). For every 1 mmol/kg/day increase in sodium intake, sodium serum levels could be expected to rise by 0.187 mmol/L on the following day, whereas for every 10 mL/kg/day increase in fluid supplementation, there was a fall in sodium by 0.2 mmol/L on the following day.

3.5 | Association between sodium intake and morbidity

As shown in Figure 2A, increased sodium intake was significantly associated with the occurrence of IVH, PDH, and ROP ($p < 0.05$). No significant increase in BPD incidence was observed (Figure 2A). The odds ratios were 1.19 ($p > 0.05$) for BPD, 1.33 for IVH ($p < 0.05$), 1.6 for PDA ($p < 0.01$), and 1.43 for ROP ($p < 0.05$) (Figure 2A). There was no significant association between sodium intake and overall mortality. We performed a stepwise logistic regression analysis that included the overall intake of sodium, occurrence of hypernatremia, and occurrence of hyponatremia for BPD, ROP, IVH, and BPD, which reaffirmed the results of earlier regression analysis. An additional significant effect of hypernatremia was detectable only for ROP.

To further analyze the potential influence of fluid supplementation or fluid overload on morbidity and mortality, we separately analyzed the occurrence of BPD, IVH, PDA, and ROP in relation to fluid supplementation. We compared the two lower quartiles of patients with the two higher quartiles. Here, no association between volume supplementation and the incidence of PDA, BPD, and IVH was found, whereas higher fluid supplementation was associated with a slightly higher incidence of PDA (OR 1.063, $p < 0.01$) (Figure 2B).

3.6 | Discussion

In this retrospective single-center study, we analyzed the supplementation of sodium and fluid in ELBW infants during their first 2 weeks of life in relation to the ESPGHAN recommendations and the potential consequences of sodium and volume excess on hypernatremia, morbidity, and mortality. We could demonstrate that the effective mean sodium intake was significantly

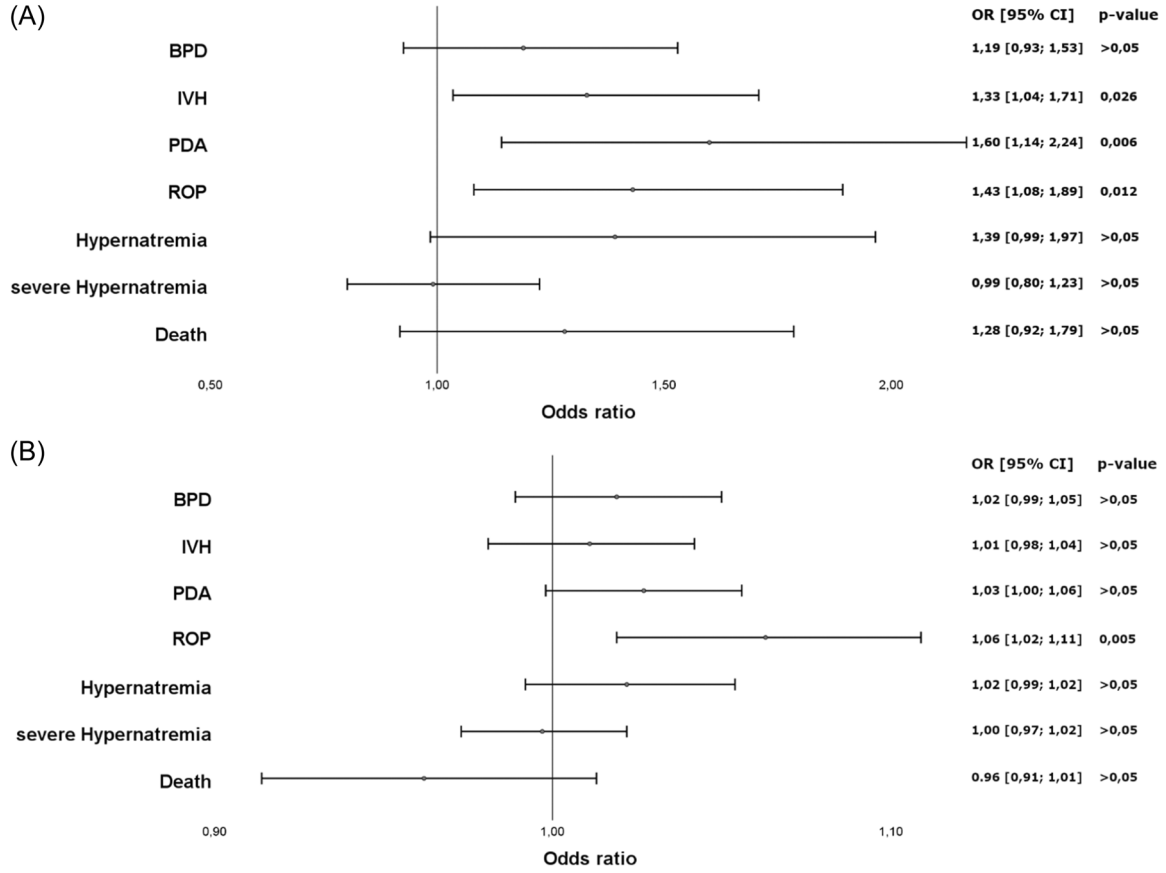

FIGURE 2 Forest Plot for sodium and fluid supplementation. (A) A significant increase in incidence of IVH (Intraventricular Hemorrhage), PDA (Persistent ductus arteriosus botalli), and ROP (Retinopathy of prematurity) for every mmol of sodium administered over the first 14 days. No significant effect on BPD (bronchopulmonary dysplasia) was observed. (B) An increase in ROP incidence for every mL of fluid intake in the first 2 weeks. In contrast to Sodium the effect on PDA and IVH was not significant.

higher than recommended by the ESPGHAN. This excess was quite substantial, above the upper limit of ESPGHAN recommendations by several folds. The highest excess was seen on Day 2 with 5.99 mmol/L. Importantly, none of the patients received sodium intake according to the official ESPGHAN recommendations. This finding confirms the data by Eibensteiner et al.[19]

We also found that higher sodium intake in our study was associated with an increased risk for BPD, IVH, and ROP. No association to NEC was found, but NEC incidence was very low in our unit. These results are largely in line with most of the previous studies.[10] Beyond the focus of the other studies, we also analyzed the effect of fluid supplementation, but did not find any association to BPD, IVH, ROP, or overall mortality. This suggests a direct role of sodium in the pathogenesis of IVH and ROP, possibly mediated by fluid shifts between the different intra- and extracellular compartments as suggested by Eibensteiner et al.[14,19]

Not surprisingly, the most important source of inadvertent sodium intake during the first 5 days was arterial lines continuously flushed with 0.9% saline. One might argue that patients requiring an arterial line are more critically ill. However, if this were the case, one would also expect higher fluid supplementation in these patients due to the application of balanced crystalloids to treat hypotension, and therefore, an association of fluid load similar to sodium supplementation with an impaired outcome. This was not the case in this study, suggesting that high sodium intake does not simply reflect a more critical status of the patients. In fact, a critical review of the medical charts revealed that in most cases, the placement of arterial lines was part of the routine management for blood pressure monitoring and blood gas analyses. Considering the fact that evidence for invasive blood pressure measurement and even more for treating low blood pressure in the absence of clinical signs of hypoperfusion, with normal superior vena cava flow, normal cardiac output, and normal cerebral Doppler flows is scarce, the value of invasive blood pressure measurement should be questioned in every individual case.[25] As consequence, routine management was changed in our unit. A more restrictive approach to arterial lines,

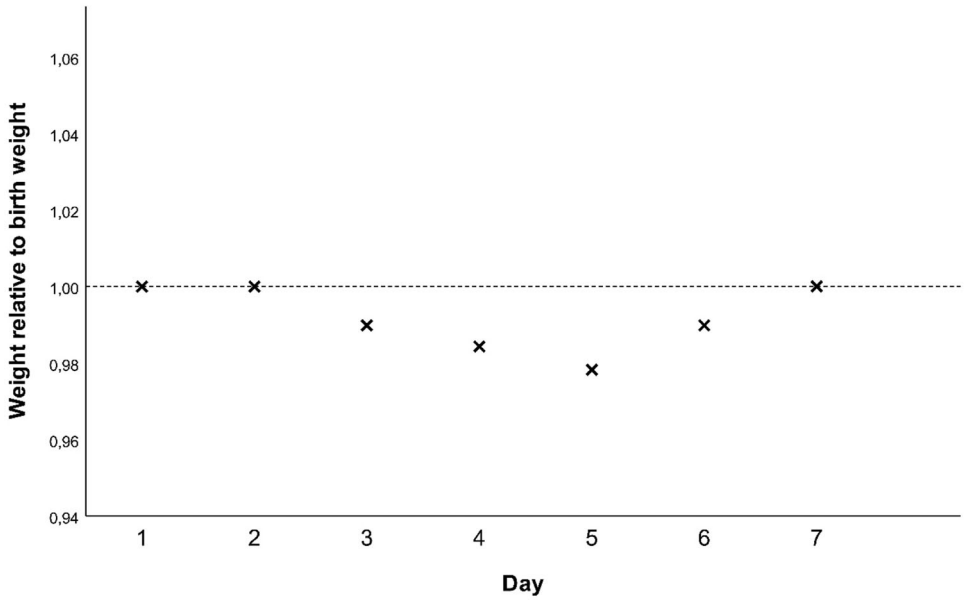

FIGURE 3 Development of median relative weight compared with birth weight over the first 7 days of life. The graphical representation provides insight into the median weight changes relative to birth weight. There is a decrease of 2%, which stands in contrast to the prevalent range of 7%–10% observed in ELBW infants. Furthermore, the data highlights a notable shift in the timing of the weight nadir to Day 5 while usually occuring on Days 2–3.

while simultaneously changing the standard infusion from NaCl 0,9% to NaCl 0,45%, was introduced.

Regarding other inadvertent sodium sources, we noticed substantial differences compared to Eibensteiner et al.[19] We do not use sodium bicarbonate on a daily basis but used rectal enemas more often—responsible for about 15% of sodium intake during the first week in our unit. This clearly demonstrates that inadvertent sodium sources might differ substantially between NICU. Thus, every NICU needs to critically review their own sodium regime.

Interestingly we observed a comparatively small weight loss of 2% at weight nadir (Figure 3) in comparison to commonly reported weight loss of 5%–15%. We believe this might stem from the high influx of sodium during the first 2 days of life.

In the last part of the study, we analyzed the correlation between sodium supplementation and sodium serum levels. Whereas a natural assumption is that these two parameters should correlate, previous data regarding the relationship between sodium intake and serum levels are inconclusive with some studies showing no correlation[6,23] while others report an increase in serum level according to higher intake.[26,27] Interestingly, we were not able to find a study analyzing sodium supplementation in relation to fluid load so far, even though the physiological connection between sodium and fluid is obvious, particularly since in ELBW infants, hypernatremia can be considered as a sign of dehydration.[28] We therefore performed a linear regression model analysis. Here, we could demonstrate an opposing effect of sodium intake and fluid supplementation on the serum sodium level. Taking both factors into account we were able to predict the direction of the change in serum sodium levels on the following day. Thus, higher fluid intake can mask sodium excess as reflected by serum sodium levels, and interpretation of serum sodium levels as marker of sodium excess needs to be interpreted against the background of fluid intake. For our study, the excess of daily fluid intake over the recommended daily amount of 180 mL/kg is connected to the process of determining the infusion flow rate, which did not take the amount of fluid applied by other sources than parenteral nutrition into account. This has been rectified since then.

4 | CONCLUSION

In this study, we were first able to confirm the data from previous studies, particularly by Eibensteiner et al. regarding inadvertent sodium excess and correlated increase in morbidity in ELBW infants—even though the sources of sodium intake differed substantially.[19] Second, we found evidence that sodium intake does not simply reflect a more critical disease state. Third, we could show that for accurate interpretation of serum sodium levels, both sodium and fluid intake need to be taken into consideration.

However, due to the observational and retrospective nature of this study, no conclusions about causal correlations between sodium load and morbidity in ELBW infants can be drawn.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to restrictions [e.g., their containing information that could compromise the privacy of research participants].

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