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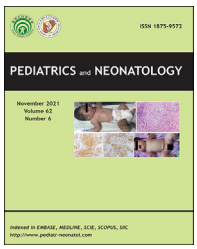

Original Article

Neurodevelopment of preterm infants with glucose and sodium abnormalities

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Key Words
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Background: Blood glucose and serum sodium abnormalities in very low birth weight infants may cause increased morbidity and mortality, but data regarding the long-term outcomes are limited. This study aimed to investigate the association between the peak and nadir blood glucose and serum sodium levels and neurodevelopmental outcomes in very low birth weight infants.

Methods: A single-center retrospective medical record of 284 infants with birth weight<1500 g born between February 1, 2011 and January 31, 2015 was reviewed. We analyzed the correlation between peak and nadir blood glucose and serum sodium levels during hospitalization and Bayley Scales of Infant and Toddler Development, third edition at 6, 12, and 24 months of corrected age.

Results: A total of 284 very low birth weight premature infants were eligible, and 223, 208, and 188 patients were assessed at 6, 12, and 24 months of corrected age, respectively. Multiple linear regression analysis with generalized estimating equations showed that the BSID-III cognitive scores were significantly lower in the peak serum sodium group when sodium was ≧150 mmol/L (95% confidence interval −11.681 to −0.822) than when sodium did not exceed 150 mmol/L.

Conclusion: A peak serum sodium of ≧150 mmol/L is associated with poor cognitive outcomes in very low birth weight infants. Further studies are necessary to determine if this association is causal or an expression of disease severity.

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1. Introduction

Abnormal blood glucose and serum sodium levels are common problems in both term and preterm infants.[1–3] Prolonged symptomatic hypoglycemia is associated with brain injury,[4,5] and early transient newborn hypoglycemia may result in lower achievement test scores at age 10.[6] However, some studies have shown conflicting results.[7,8] Hyperglycemia in preterm infants is associated with increased morbidity and mortality, including neurological and behavioral problems and retinopathy of prematurity (ROP).[9–11] Hyponatremia may be associated with developmental delays, bronchopulmonary dysplasia (BPD), and ROP.[12,13] Hypernatremia may be associated with intraventricular hemorrhage (IVH), cerebral edema, and thrombosis,[3,14] but data regarding the long-term outcomes are limited.

As studies describing the long-term outcomes of abnormal blood glucose and serum sodium levels are limited, which is especially true in cases where these abnormalities do not exhibit any signs or symptoms, we performed a retrospective study to investigate the impact of hyperglycemia, hypoglycemia, hypernatremia, and hyponatremia on very low birth weight (VLBW) infants. Our primary objective was to study the neurodevelopmental outcomes in infants with abnormal blood glucose or serum sodium levels. The secondary objective was to study the associated complications including IVH, periventricular leukomalacia (PVL), ROP, BPD, necrotizing enterocolitis (NEC), patent ductus arteriosus (PDA), neonatal seizures, cerebral palsy (CP), duration of invasive mechanical ventilation use, length of hospitalization (LOH), and mortality in such infants.

2. Methods

2.1. Patients

We retrospectively identified all premature infants having a birth weight $<$1500 g admitted to the neonatal intensive care unit (NICU) of a tertiary hospital between February 1, 2011 and January 31, 2015. The study design was approved by the appropriate ethics review board. Infants with congenital anomalies, brain injury, those who died before day 3 or were admitted after day 3 of life, and infants transferred to other hospitals were excluded.

2.2. Study design

The medical records of the infants were reviewed, and the prenatal and postnatal variables were recorded. The prenatal variables included single or multiple births, maternal preeclampsia, pregnancy-induced hypertension (PIH), and preterm premature rupture of membranes (PPROM). Intrapartum and labor-associated variables included sex, gestational age, birth body weight, birth body length, birth head girth, and the 1-min and 5-min Apgar scores. The postnatal factors included postnatal corticosteroid administration and sepsis. Clinical outcomes such as the rates of mortality, IVH, PDA, BPD, ROP, NEC, PVL, neonatal seizures, and CP, duration of invasive mechanical ventilation use, and LOH were also recorded.

According to our NICU protocol, blood glucose, which was measured in whole blood, was monitored every 8 h and repeated as required until the patients achieved full enteral feeding. The electrolyte levels of the patients were assessed at birth and once a week and repeated as required until the cessation of parenteral nutrition. According to the blood glucose and serum sodium levels recorded during hospitalization, the patients were divided into four groups. The nadir blood glucose group was further divided into neonates with the lowest blood glucose $<$2.5 mmol/L and those with levels $\geq$2.5 mmol/L; the peak blood glucose group was further divided into neonates with the highest blood glucose $<$10 mmol/L and those with levels $\geq$10 mmol/L; the nadir serum sodium group was further divided into neonates with the lowest serum sodium $<$135 mmol/L and those with levels $\geq$135 mmol/L; and the peak serum sodium group was further divided into neonates with the highest serum sodium $<$150 mmol/L and those with levels $\geq$150 mmol/L.

2.3. Assessment at 6, 12, and 24 months

VLBW premature infants were followed up at our outpatient clinic after discharge until 24 months of corrected age. At 6, 12, and 24 months of corrected age, the patients underwent a neurological examination and developmental function assessment using the Bayley Scales of Infant Development III (the BSID-III is a norm-referenced scale in which composite scores are assessed according to the scale mean [$\pm$SD] of 100 $\pm$ 15, and lower scores indicate a greater impairment).[15]

2.4. Statistical analysis

All statistical analyses were performed using SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY), and statistical significance was defined as $p < 0.05$. The initial univariate analysis for the four groups was performed using Student's t-test for continuous variables and the χ^2 or Fisher's exact test, as appropriate, for categorical variables. Standard deviations are shown for continuous variables. From this initial univariate analysis, multiple linear regression analysis with generalized estimating equations (GEE) was performed to determine the effects of extreme blood glucose and serum sodium levels on neurodevelopmental outcomes, adjusted for significant clinical risk factors.

3. Results

A total of 298 infants were born with a birth weight <1500 g between February 1, 2011 and January 31, 2015, of whom 284 were eligible. Of these, 223, 208, and 188 patients underwent neurodevelopmental evaluations at 6, 12, and 24 months of corrected age, respectively (Fig. 1).

In the nadir blood glucose group, there was no significant difference except in maternal PIH rates ($p = 0.002$). In the other groups there were several differences of baseline characteristics which are presented in Tables 1-1 and 1-2.

Tables 2-1 and 2-2 show the primary outcomes of the BSID-III scores at 6, 12, and 24 months of corrected age. In the nadir blood glucose group, there was no significant difference in the BSID-III cognitive, language, and motor scores at 6, 12, and 24 months of corrected age. In the peak blood glucose group, significant differences were noted in the BSID-III language scores at 12 months of corrected age ($p = 0.023$) and in the cognitive and language scores at 24 months of corrected age ($p = 0.034$ and $p = 0.016$, respectively). In the nadir serum sodium group, significant differences were noted in the BSID-III language scores at 12 months of corrected age ($p = 0.021$) and in the language and motor scores at 24 months of corrected age ($p = 0.019$ and 0.049, respectively). In the peak serum sodium group, there were significant differences in the BSID-III cognitive and motor scores at 12 months of corrected age ($p < 0.001$ and $p = 0.002$, respectively) and in the cognitive and language scores at 24 months of corrected age ($p = 0.006$ and 0.039, respectively).

The mortality rate significantly increased when nadir blood glucose was <2.5 mmol/L ($p = 0.011$), peak blood glucose was ≧10 mmol/L ($p = 0.018$), nadir serum sodium was <135 mmol/L ($p = 0.036$), and peak serum sodium was ≧150 mmol/L ($p < 0.001$). Other secondary outcomes are summarized in Tables 3-1 and 3-2.

From this univariate analysis, multiple linear regression analysis was performed to analyze the association of blood glucose and serum sodium with neonatal outcomes while adjusting for other significant risk factors such as the gestational age, birth body weight, Apgar score, postnatal steroid use, and sepsis. Multiple linear regression with GEE revealed that the BSID-III cognitive scores were significantly lower in the peak serum sodium group when sodium was ≧150 mmol/L (95% confidence interval −11.681 to −0.822) than when sodium did not exceed 150 mmol/L (Table 4).

4. Discussion

The findings of this study indicate that hypernatremia in VLBW premature infants may be associated with poor cognitive outcomes. A glucose concentration of 2.5–2.6 mmol/L (45–47 mg/dL) is now a well-accepted definition of

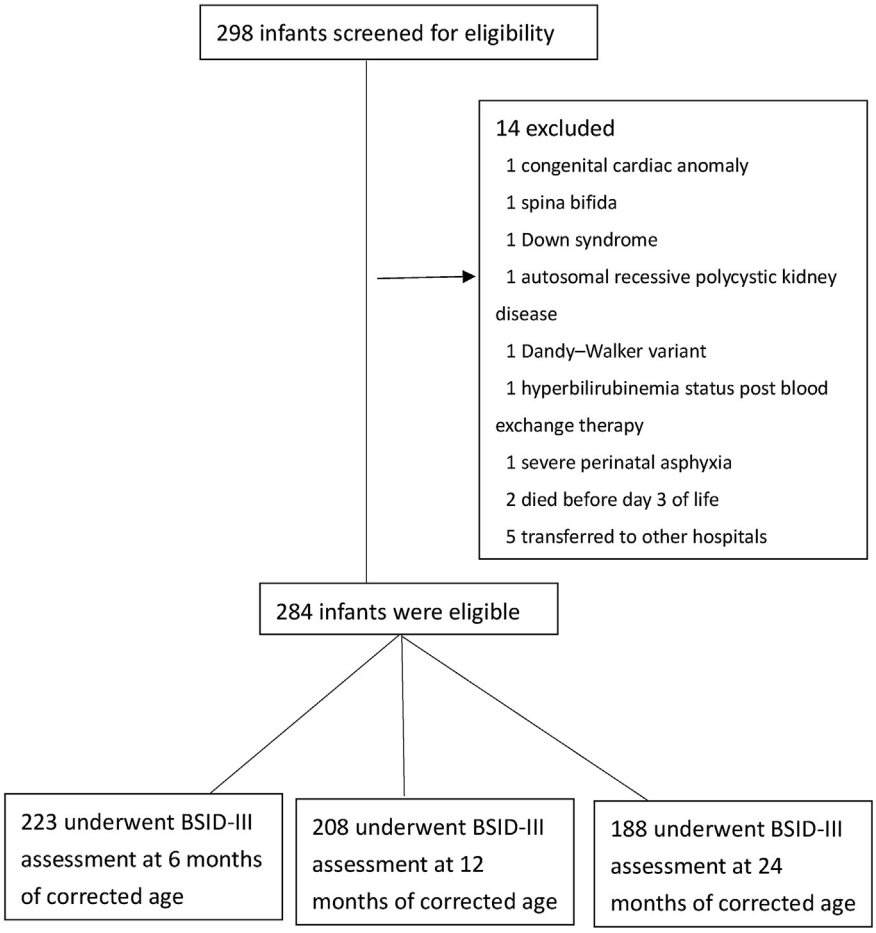

Figure 1 Patient enrollment flow chart.

Table 1-1 Baseline characteristics of the nadir and peak blood glucose group patients.

	Nadir blood glucose group			Peak blood glucose group		
	<2.5 mmol/L	≧2.5 mmol/L	p-value	<10 mmol/L	≧10 mmol/L	p-value
Number of patients	111	173		167	117	
GA, weeks; mean ± SD	30.0 ± 3.2	29.4 ± 3.0	0.112	30.8 ± 2.9	27.9 ± 2.6	<0.001*
BBW, gm; mean ± SD	1082.9 ± 303.9	1113.6 ± 248.3	0.375	1199.1 ± 229.0	962.4 ± 267.0	<0.001*
BBL, cm; mean ± SD	35.7 ± 5.0	36.7 ± 3.4	0.065	37.2 ± 4.2	35.0 ± 3.6	<0.001*
BHG, cm; mean ± SD	26.0 ± 2.6	26 ± 2.8	0.928	26.8 ± 2.5	24.8 ± 2.6	<0.001*
Apgar score 1'; mean ± SD	5.9 ± 2.0	6.1 ± 1.7	0.481	6.5 ± 1.5	5.3 ± 1.9	<0.001*
Apgar score 5'; mean ± SD	7.6 ± 1.7	7.8 ± 1.3	0.299	8.1 ± 1.1	7.2 ± 1.8	<0.001*
Male gender, n (%)	54 (48.6)	88 (50.9)	0.715	85 (50.9)	57 (48.7)	0.718
Twin or triplet pregnancy, n (%)	36 (32.4)	55 (31.8)	0.910	64 (38.3)	27 (23.1)	0.007*
Maternal preeclampsia, n (%)	14 (13.2)	13 (7.6)	0.126	16 (9.7)	11 (9.8)	0.973
Maternal PIH, n (%)	34 (32.1)	28 (16.4)	0.002*	42 (25.5)	20 (17.9)	0.137
PPROM, n (%)	34 (32.1)	56 (32.7)	0.907	41 (24.8)	49 (43.8)	0.001*
Postnatal steroids, n (%)	12 (11.3)	20 (11.7)	0.924	5 (3.0)	27 (24.1)	<0.001*
Sepsis, n (%)	15 (13.5)	18 (10.4)	0.425	11 (6.6)	22 (18.8)	0.002*

*$p < 0.05$.
BBL, birth body length; BBW, birth body weight; BHG, birth head girth; GA, gestational age; PIH, pregnancy-induced hypertension; PPROM, preterm premature rupture of membranes.

Table 1-2 Baseline characteristics of the nadir and peak serum sodium group patients.

	Nadir serum sodium group			Peak serum sodium group		
	<135 mmol/L	≧135 mmol/L	p-value	<150 mmol/L	≧150 mmol/L	p-value
Number of patients	243	41		262	22	
GA, weeks; mean ± SD	29.3 ± 3.0	31.8 ± 3.2	<0.001*	30.0 ± 2.9	25.1 ± 1.8	<0.001*
BBW, gm; mean ± SD	1077.0 ± 265.0	1247.1 ± 265.4	<0.001*	1132.9 ± 252.7	728.5 ± 199.5	<0.001*
BBL, cm; mean ± SD	36.0 ± 4.2	38.2 ± 2.9	<0.001*	36.7 ± 4.0	31.8 ± 3.4	<0.001*
BHG, cm; mean ± SD	25.8 ± 2.8	27.2 ± 2.1	0.003*	26.2 ± 2.6	22.6 ± 1.9	<0.001*
Apgar score 1'; mean ± SD	5.9 ± 1.8	6.5 ± 1.9	0.064	6.2 ± 1.7	4.1 ± 2.1	<0.001*
Apgar score 5'; mean ± SD	7.7 ± 1.5	8.1 ± 1.6	0.131	7.9 ± 1.4	6.0 ± 2.0	<0.001*
Male gender, n (%)	123 (50.6)	19 (46.3)	0.613	133 (50.8)	9 (40.9)	0.375
Twin or triplet pregnancy, n (%)	75 (30.9)	16 (39.0)	0.300	89 (34.0)	2 (9.1)	0.016*
Maternal preeclampsia, n (%)	18 (7.6)	9 (23.1)	0.006*	26 (10.1)	1 (5.0)	0.704
Maternal PIH, n (%)	50 (21.0)	12 (30.8)	0.175	60 (23.3)	2 (10.0)	0.264
PPROM, n (%)	86 (36.1)	4 (10.3)	0.001*	83 (32.3)	7 (35.0)	0.804
Postnatal steroids, n (%)	30 (12.6)	2 (5.1)	0.277	22 (8.6)	10 (50.0)	<0.001*
Sepsis, n (%)	33 (13.6)	0 (0)	0.007*	26 (9.9)	7 (31.8)	0.007*

*$p < 0.05$.
BBL, birth body length; BBW, birth body weight; BHG, birth head girth; GA, gestational age; PIH, pregnancy-induced hypertension; PPROM, preterm premature rupture of membranes.

hypoglycemia requiring treatment in the newborn.[7,16–18] The blood glucose concentration threshold levels for hyperglycemia are variable, including 7 mmol/L (125 mg/dL), 8.3 mmol/L (150 mg/dL), and 10 mmol/L (180 mg/dL).[9,10,19] Hyponatremia is usually defined as serum sodium <130–135 mmol/L,[20] and previous studies defined hypernatremia that could induce adverse outcomes as serum sodium >145 mmol/L or >150 mmol/L.[21,22] In this study, the cut-off points of lowest and highest values of blood glucose and serum sodium were according to the definitions of previous studies.

The purpose of this study was to investigate if blood glucose or serum sodium abnormalities (either very high or very low levels), occurring even once, could impact neurological outcomes. A systematic review and meta-analysis by Shah et al. in 2019 demonstrated that neonatal hypoglycemia may have important long-lasting adverse effects on neurodevelopment that may become apparent at later ages, but the overall quality of evidence was low to very low.[23] In 2006, Hays et al. reported that prolonged periods of hyperglycemia had a greater impact on the LOH

Table 2-1 BSID-III scores of the nadir and peak blood glucose group patients (univariate analysis).

	Nadir blood glucose group			Peak blood glucose group		
	<2.5 mmol/L	≧2.5 mmol/L	p-value	<10 mmol/L	≧10 mmol/L	p-value
6 mo-cognitive; mean ± SD	94.6 ± 11.9	95.8 ± 12.1	0.466	96.1 ± 11.0	94.2 ± 13.4	0.232
6 mo-language;mean ± SD	91.6 ± 9.3	92.0 ± 9.9	0.757	92.2 ± 9.6	91.4 ± 9.8	0.572
6 mo-motor; mean ± SD	89.6 ± 14.2	88.9 ± 15.3	0.700	90.1 ± 13.8	87.7 ± 16.2	0.239
12 mo-cognitive; mean ± SD	92.8 ± 9.5	92.2 ± 12.2	0.678	93.4 ± 10.4	90.9 ± 12.3	0.113
12 mo-language; mean ± SD	91.2 ± 11.8	88.7 ± 11.8	0.135	91.2 ± 11.8	87.4 ± 11.6	0.023*
12 mo-motor; mean ± SD	95.5 ± 13.0	92.4 ± 14.2	0.118	94.8 ± 12.9	91.9 ± 14.9	0.141
24 mo-cognitive; mean ± SD	91.1 ± 9.2	90.4 ± 11.3	0.639	92.0 ± 9.9	88.7 ± 11.2	0.034*
24 mo-language; mean ± SD	93.8 ± 11.0	92.8 ± 12.7	0.616	94.9 ± 12.1	90.6 ± 11.7	0.016*
24 mo-motor; mean ± SD	93.4 ± 9.5	92.8 ± 12.9	0.752	94.2 ± 10.7	91.3 ± 12.9	0.092

*$p < 0.05$.
6 mo, 6 months of corrected age; 12 mo, 12 months of corrected age; 24 mo, 24 months of corrected age.

Table 2-2 BSID-III scores of the nadir and peak serum sodium group patients (univariate analysis).

	Nadir serum sodium group			Peak serum sodium group		
	<135 mmol/L	≧135 mmol/L	p-value	<150 mmol/L	≧150 mmol/L	p-value
6 mo-cognitive; mean ± SD	95.6 ± 12.0	93.7 ± 12.4	0.452	95.6 ± 11.9	90.4 ± 13.9	0.145
6 mo-language; mean ± SD	92.0 ± 9.6	91.0 ± 10.3	0.600	91.8 ± 9.4	92.9 ± 14.3	0.703
6 mo-motor; mean ± SD	89.2 ± 14.9	89.1 ± 15.0	0.986	89.5 ± 14.6	82.6 ± 17.2	0.115
12 mo-cognitive; mean ± SD	92.1 ± 11.4	94.9 ± 9.5	0.268	93.2 ± 10.8	80.8 ± 12.2	<0.001*
12 mo-language; mean ± SD	89.0 ± 11.6	95.1 ± 12.6	0.021*	89.9 ± 11.8	85.1 ± 11.1	0.153
12 mo-motor; mean ± SD	93.2 ± 14	97.2 ± 11.8	0.199	94.4 ± 13.5	82.2 ± 14.4	0.002*
24 mo-cognitive; mean ± SD	90.3 ± 10.6	94.2 ± 9.6	0.122	91.2 ± 10.4	82.3 ± 10.3	0.006*
24 mo-language; mean ± SD	92.5 ± 12.1	99.3 ± 9.7	0.019*	93.6 ± 12.1	85.9 ± 10.3	0.039*
24 mo-motor; mean ± SD	92.4 ± 11.7	98.0 ± 11.0	0.049*	93.3 ± 11.6	88.4 ± 12.4	0.175

*$p < 0.05$.
6 mo, 6 months of corrected age; 12 mo, 12 months of corrected age; 24 mo, 24 months of corrected age.

and postmenstrual age at discharge than isolated very high blood glucose levels did.[9] In 2013, Mohamed et al. reported that the duration of hyperglycemia was associated with ROP.[11] In a previous study, late-onset hyponatremia in premature infants lasting at least 7 days was significantly associated with a longer LOH and the development of moderate to severe BPD, PVL, and extrauterine growth retardation compared to the effects of no late-onset hyponatremia or late-onset hyponatremia lasting less than 7 days.[13] A retrospective study involving 66 preterm infants born at <27 weeks of gestation showed no significant increase in BPD, IVH, PDA, NEC, and death rates in hypernatremic as compared to normonatremic babies.[21] Two case reports demonstrated severe hypernatremia (peak serum sodium levels: 204 mmol/L and 199 mmol/L, respectively) in preterm infants without any associated morbidity.[24,25] Unlike previous studies that described the impact of the duration of dysnatremia or dysglycemia, in this study, we investigated the impact of the highest and lowest blood glucose and serum sodium levels.

There were several significant differences between the baseline characteristics of these four groups, probably because a smaller gestational age and birth body weight are associated with a greater electrolyte and blood glucose imbalance. We adjusted for the gestational age, birth body weight, Apgar scores, postnatal steroid use, and sepsis to avoid their confounding effects, because they have been identified as possible risk factors for neurodevelopmental outcomes. Multiple linear regression with GEE revealed that in the peak serum sodium group, there was a significant difference in the BSID-III cognitive scores. This implies that, with time, patients whose highest serum sodium levels were ≧150 mmol/L may have worse cognitive abilities than those in whom the highest serum sodium levels never exceeded 150 mmol/L. Several studies have described the association between hypernatremia and IVH in preterm infants.[14,22,26] However, in our study, multiple linear regression analysis revealed no significant association between hypernatremia and IVH; thus, IVH was not found to impact cognitive outcomes. Previous studies have suggested that hypernatremia can cause extrapontine myelinolysis[27,28] and brain shrinkage,[29,30] and we hypothesized that these may consequently impair functional outcomes. In previous studies, rapid fluctuations in serum sodium were not associated with IVH[31] and rapid correction of serum

Table 3-1 Secondary outcomes in the nadir and peak blood glucose group patients (univariate analysis).

	Nadir blood glucose group			Peak blood glucose group		
	<2.5 mmol/L	≧2.5 mmol/L	p-value	<10 mmol/L	≧10 mmol/L	p-value
Mortality; n (%)	10 (9.0)	4 (2.3)	0.011*	4 (2.4)	10 (8.5)	0.018*
IVH; n (%)	31 (28.2)	36 (20.8)	0.065	36 (21.6)	31 (26.7)	0.096
PVL; n (%)	8 (7.5)	19 (11.1)	0.319	15 (9.1)	12 (10.6)	0.672
BPD; n (%)	45 (42.9)	77 (45.0)	0.724	50 (30.3)	72 (64.9)	0.096
ROP; n (%)	33 (31.4)	70 (40.9)	0.393	40 (24.2)	63 (56.8)	<0.001*
NEC; n (%)	4 (3.8)	3 (1.8)	0.433	3 (1.8)	4 (3.6)	0.444
PDA; n (%)	30 (28.6)	49 (28.7)	0.988	37 (22.4)	42 (37.8)	0.005*
Neonatal seizures; n (%)	22 (21.0)	40 (23.4)	0.637	20 (12.1)	42 (37.8)	<0.001*
CP; n (%)	7 (6.7)	16 (9.4)	0.433	9 (5.5)	14 (12.6)	0.035*
Duration of invasive mechanical ventilation use, d; mean ± SD	9.5 ± 17.3	10.9 ± 20.8	0.546	4.1 ± 9.8	19.2 ± 25.6	<0.001*
LOH, d; mean ± SD	55.8 ± 27.9	61.6 ± 29.4	0.101	50.1 ± 19.4	72.6 ± 34.7	<0.001*

*$p < 0.05$.
BPD, bronchopulmonary dysplasia; CP, cerebral palsy; IVH, intraventricular hemorrhage; LOH, length of hospitalization; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

Table 3-2 Secondary outcomes in the nadir and peak serum sodium group patients (univariate analysis).

	Nadir serum sodium group			Peak serum sodium group		
	<135 mmol/L	≧135 mmol/L	p-value	<150 mmol/L	≧150 mmol/L	p-value
Mortality; n (%)	9 (3.7)	5 (12.2)	0.036*	7 (2.7)	7 (31.8)	<0.001*
IVH; n (%)	59 (24.4)	8 (19.5)	0.114	58 (22.1)	9 (42.9)	0.056
PVL; n (%)	23 (9.7)	4 (10)	>0.99	24 (9.3)	3 (15.8)	0.410
BPD; n (%)	118 (49.8)	4 (10.3)	<0.001*	106 (41.2)	16 (84.2)	<0.001*
ROP; n (%)	99 (41.8)	4 (10.3)	0.002*	89 (34.6)	14 (73.7)	0.001*
NEC; n (%)	7 (3.0)	0 (0)	0.598	6 (2.3)	1 (5.3)	0.396
PDA; n (%)	78 (32.9)	1 (2.6)	<0.001*	69 (26.8)	10 (52.6)	0.016*
Neonatal seizures; n (%)	60 (25.3)	2 (5.1)	0.005*	49 (19.1)	13 (68.4)	<0.001*
CP; n (%)	21 (8.9)	2 (5.1)	0.753	21 (8.2)	2 (10.5)	0.664
Duration of invasive mechanical ventilation use, d; mean ± SD	11.7 ± 20.5	2.3 ± 7.1	<0.001*	8.2 ± 15.9	36.3 ± 34.8	0.001*
LOH, d; mean ± SD	63.4 ± 28.6	35.6 ± 17.0	<0.001*	57.4 ± 24.3	83.1 ± 57.5	0.049*

*$p < 0.05$.
BPD, bronchopulmonary dysplasia; CP, cerebral palsy; IVH, intraventricular hemorrhage; LOH, length of hospitalization; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

Table 4 Multiple linear regression analysis with generalized estimating equations of the BSD-III cognitive scores.

Peak serum sodium	Estimate	Standard error	95% CI	p-value
≧150 mmol/L	−6.252	2.770	−11.681 to −0.822	0.024*
<150 mmol/L	0.000			
Peak blood glucose	Estimate	Standard error	95% CI	p-value
≧10 mmol/L	−0.365	1.309	−2.932 to 2.201	0.780
<10 mmol/L	0.000			

*$p < 0.05$.
CI, confidence interval.
Adjusted for the gestational age, birth body weight, Apgar score, postnatal steroid use, and sepsis.

sodium did not influence neurological outcome at six months in hypernatremic infants.[32] However, we did not record the correction rate of sodium, so we could not determine the association between rapid fluctuations of serum sodium and neurological outcomes. Hypernatremia is most commonly the result of lack of fluid intake and/or excess loss of water rather than excess sodium intake in preterm infants,[33] so we should maintain fluid balance carefully to avoid complications of hypernatremia.

In this study, hyponatremia was not associated with increased mortality or adverse neurodevelopmental outcomes, which conflicted with the results of previous studies.[34,35] As we did not record the duration of hyponatremia, the differences in the results may be related to the duration and degree of hyponatremia.

In two retrospective case—control studies, Garg et al. and Mohamed et al. found that hyperglycemia was associated with ROP.[11,36] High blood glucose concentrations also increased the risk of early death, grade 3 or 4 IVH, and an extended LOH,[9] and prolonged hyperglycemia in the first 96 h of life was strongly associated with severe IVH in preterm infants.[19] In this study, univariate analysis demonstrated that hyperglycemia increased the rates of mortality, ROP, neonatal seizures, CP, the duration of invasive mechanical ventilation use, and LOH. However, multiple linear regression analysis showed no statistically significant increase in mortality and morbidity. Regarding long-term outcomes, van der Lugt et al. found a higher incidence of neurological and behavioral problems at 2 years of age in very preterm infants with hyperglycemia treated with insulin during the neonatal period.[10] Contrary to the findings of previous reports, in this study, multiple linear regression analysis demonstrated that hyperglycemia had no impact on neurodevelopmental outcomes at the corrected age of 2 years. This may be due to the frequent and regular blood glucose monitoring that we performed, even in asymptomatic patients, and the prompt and aggressive treatment of abnormalities. This indicates that if hyperglycemia is not prolonged, neurological outcomes may not be adversely affected. However, as we did not record the duration of hyperglycemia, we could not predict the duration of hyperglycemia that may impact neurodevelopmental outcomes.

In this study, hypoglycemia was not associated with adverse neurologic outcomes, which was consistent with the findings of previous studies.[7,18] However, a recent systematic review and meta-analysis demonstrated that neonatal hypoglycemia was associated with neurodevelopmental impairment and low literacy and numeracy in mid-childhood rather than in early childhood.[23] This implies that neonatal hypoglycemia may have important long-lasting adverse effects on neurodevelopment which may become apparent at later ages. Owing to a limited number of studies meeting the inclusion criteria and the lack of adjustment for potential confounding factors, the quality of evidence was low to very low. The differences in the results between our study and those of the meta-analysis may be due to different hypoglycemia thresholds (range: 1.1—2.6 mmol/L in the meta-analysis). Different treatment protocols can also produce different results, and recent studies have suggested that higher glucose concentrations after hypoglycemia may also contribute to brain injury.[7] Differences in the age at follow-up may influence neurodevelopmental outcomes because adverse effects may become apparent at later ages. Furthermore, the relationship between the frequency, severity, and duration of neonatal hypoglycemic episodes and cerebral energy supply and utilization remains unclear[37]; thus, the best measure of exposure for use in analyses remains uncertain.[38]

This study has several limitations. This was a retrospective, observational, and single-center study. As the inability to obtain complete records and follow-up data may affect the study findings, we used the GEE method to reduce bias. Furthermore, the limited study period may influence the results as adverse neurodevelopmental effects may become apparent at later ages. If the duration of follow-up is increased, the long-term outcomes may be different. Additionally, whether dysglycemia or dysnatremia itself causes poor neurodevelopmental outcomes or acts as a marker of disease severity that influences outcomes remains unclear. Even though we adjusted for several known risk factors that are significant markers of illness, the possibility of residual confounders remains. We did not record the duration of glucose and sodium abnormalities and rate of fluctuation of glucose and sodium levels after treatment, which may have affected the outcomes.

5. Conclusion

The present study identified that in VLBW premature babies, a peak serum sodium of ≧150 mmol/L was associated with poor cognitive outcomes, so careful fluid management is critical. The different approaches to screening, diagnosis, and management of glucose abnormalities make assessing their impact on neurological development even more challenging. The use of glucose assays as the gold standard should be recommended in future studies. Further well-constructed, prospective studies are needed to fully evaluate the impact of abnormal peak and nadir blood glucose and serum sodium levels on neurodevelopmental outcomes.

Declaration of competing interest

None.

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