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ORIGINAL ARTICLE

Sodium supply from administered blood products was associated with severe intraventricular haemorrhage in extremely preterm infants

Cornelia Späth[1] | Elisabeth Stoltz Sjöström[2] | Johan Ågren[3] | Fredrik Ahlsson[3] | Magnus Domellöf[1]

[1]Department of Clinical Sciences, Pediatrics, Umeå University, Umeå, Sweden

[2]Department of Food, Nutrition and Culinary Science, Umeå University, Umeå, Sweden

[3]Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

Correspondence
Cornelia Späth, Department of Clinical Sciences, Pediatrics, Umeå University, 901 85 Umeå, Sweden.
Email: cornelia.spath@umu.se

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Abstract

Aim: The aim of this study was to investigate the associations between sodium supply, fluid volume, sodium imbalances and severe intraventricular haemorrhage (IVH) in extremely preterm (EPT) infants.

Methods: We used data from the EXtremely PREterm infants in Sweden Study (EXPRESS) cohort consisting of all infants born at 22 to 26 gestational weeks from 2004 to 2007 and conducted a nested case–control study. For every infant with severe IVH (grade 3 or peri-ventricular haemorrhagic infarction), one IVH-free control infant with the birthday closest to the case infant and matched for hospital, sex, gestational age and birth weight was selected ($n = 70$ case–control pairs).

Results: Total sodium supply and fluid volume were higher in infants with severe IVH compared with controls [daily total sodium supply until postnatal Day 2: mean ± SD (mmol/kg/day): 5.49 ± 2.53 vs. 3.95 ± 1.91, $p = 0.009$]. These differences were accounted for by sodium and fluid from transfused blood products. High plasma sodium concentrations or large sodium fluctuations were not associated with severe IVH.

Conclusion: Our results suggest a relationship between sodium-rich transfusions of blood products and severe IVH in EPT infants. It is unclear whether this is an effect of sodium load, volume load or some other transfusion-related factor.

KEYWORDS
intraventricular haemorrhage, preterm infants, sodium imbalances, sodium supply, transfusions

1 | INTRODUCTION

Extremely preterm (EPT) infants frequently experience intraventricular haemorrhage (IVH) mainly occurring within the first 72 h after birth.[1,2] The incidence of IVH is inversely related to gestational age (GA) and birth weight (BW), and very immature preterm infants are more likely to experience the higher grades of IVH occurring earlier after birth.[2–4] While mild IVH (grades 1 and 2) has been shown to increase the risk of neurodevelopmental impairment to a lesser extent, severe IVH (grade 3 or peri-ventricular haemorrhagic infarction [PVHI]) is a major risk factor for subsequent neurodevelopmental disability.[5] Besides immaturity, several risk factors have been

Abbreviations: BW, birth weight; CRIB, clinical risk index for babies; EPT, extremely preterm; EXPRESS, Extremely Preterm Infants in Sweden Study; GA, gestational age; IVH, intraventricular haemorrhage; P-Na, plasma sodium.

associated with IVH such as male sex, birth at a lower-level hospital, birth asphyxia, severity of illness, acidosis, hypotension, early-onset sepsis, transfusions of blood products, absence of antenatal steroid treatment, delivery mode and chorioamnionitis.[6–11] Furthermore, EPT infants born from preeclampsia pregnancies have been shown to be protected against severe IVH.[12]

Sodium imbalances such as hypernatremia and large fluctuations in serum or plasma sodium have also been suggested to be risk factors for IVH.[6,13] These conditions are common in EPT infants and coincide with the timing of IVH.[14] We have previously shown that 21% of infants in the EXtremely PREterm infants in Sweden Study (EXPRESS) cohort [GA (weeks + days): 22 + 0 to 26 + 6] had a plasma sodium (P-Na) concentration >150 mmol/L during the first postnatal week, most frequently appearing at postnatal Days 2 to 4.[15] The supply of sodium and not fluid volume was the main determinant of P-Na concentrations and the risk of hypernatremia in that cohort. However, data on the relationships between sodium supply, sodium imbalances and IVH in EPT infants are scarce. The present study aimed to investigate the associations between severe IVH and sodium imbalances as well as sodium supply and fluid volume in EPT infants. We hypothesised that a higher early postnatal sodium supply contributes to sodium imbalances and thus contributes to the pathogenesis of IVH.

Key Notes

- Data on the relationships between sodium supply, fluid volume, sodium imbalances and intraventricular haemorrhage (IVH) in extremely preterm (EPT) infants are scarce.
- EPT infants who developed severe IVH showed higher early total sodium supply and fluid volume compared with IVH-free controls.
- Sodium and fluid from transfused blood products accounted for these differences.

2 | STUDY POPULATION AND METHODS

2.1 | Study population and design

We used data from the population-based EXPRESS cohort that consists of all live-born EPT infants with a GA of 22 weeks + 0 days to 26 weeks + 6 days born from 1 April 2004 to 31 March 2007 in Sweden (n = 707). Cohort characteristics, neonatal morbidity and infant mortality have previously been reported.[16,17] We included all infants who survived the first 24 h (n = 602) and excluded (a) infants with major congenital or chromosomal anomalies (n = 9), (b) infants with missing cranial ultrasound (n = 10) and (c) infants with missing P-Na concentrations at postnatal Days 2 and 3 (n = 50), leaving 533 infants with a mean ± SD GA of 25.3 ± 1.1 weeks and BW of 763 ± 169 g for inclusion (Figure 1). To minimise confounding, we performed a matched nested case–control study. For every case infant with severe IVH (grade 3 or PVHI), one IVH-free control infant (grade 0) with the birthday closest to the case, and matched for hospital, sex, GA (±1 week) and BW (±170 g) was selected. The matching criteria for GA and BW were selected to allow for a sufficient number of controls. Due to the limited cohort size, two cases could not be matched, leaving 70 matched case–control pairs for data analyses.

2.2 | Data collection

Data for sodium supply and fluid volume on the day of birth, Day 1 and Day 2, the first obtained plasma or serum sodium concentration each day, as well as the first obtained haemoglobin level each day between the day of birth and Day 3 were retrospectively retrieved from hospital records. Intakes on the day of birth were corrected for the time of birth. Total supply of sodium and fluid included parenteral and enteral fluids, flush solutions and transfused blood products. The sodium content of the different products, including transfused blood products, was calculated from manufacturer information and published values.[18,19] Since point-of-care blood gas analysers (most common system: ABL blood gas analyser [Radiometer]) were almost exclusively used to obtain plasma values, sodium concentrations are presented as P-Na. Antenatal, perinatal and morbidity data including delivery mode, chorioamnionitis, born from preeclampsia pregnancies, date of birth, GA, BW, sex, multiple pregnancy, Apgar score at 5 min, original clinical risk index for babies (CRIB) score, antenatal steroid treatment, duration of mechanical ventilation and the presence and severity of IVH were prospectively collected within the EXPRESS cohort.[16,17] Routine cranial ultrasound was used for IVH diagnosis and grading of IVH was made according to the Papile classification.[20] Severe IVH was defined as IVH grade 3 or PVHI.

2.3 | Data management

The exact time point for IVH diagnosis was not registered in the database. Since studies have shown that the vast majority of infants develop IVH during the first three postnatal days,[1,2] we limited the exposure period for sodium imbalances from the day of birth up to Day 3. All nutritional intakes, including sodium supply, fluid volume and transfusions of blood products, were calculated between 6 AM and 6 AM the following day, with the day of birth being defined as the period between birth and 6 AM. Therefore, nutritional intakes from the day of birth until the end of Day 2 were assumed to influence IVH development up to the morning of Day 3. Transfused blood products included erythrocytes, plasma, thrombocytes and albumin. Hypernatremia was defined in three levels: P-Na >145 mmol/L, P-Na >150 mmol/L and P-Na >155 mmol/L, and the fluctuation in P-Na calculated as the difference between the peak and nadir values from birth to Day 3.

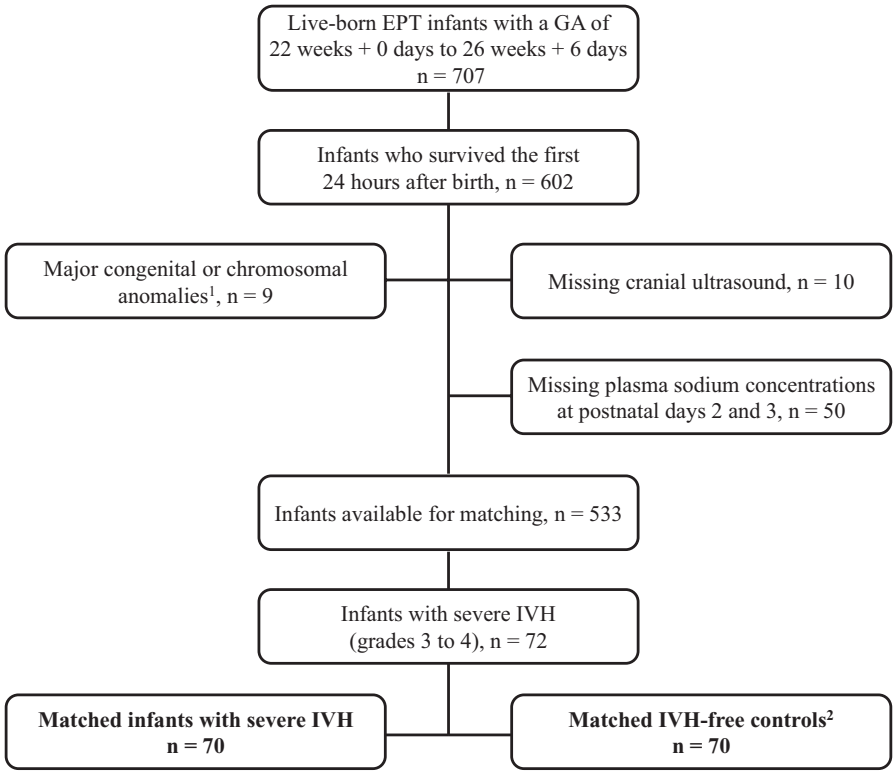

FIGURE 1 Included and excluded infants. [1]Multiple congenital anomalies, $n = 2$; Gastrointestinal malformation, $n = 2$; Limb reduction defects, $n = 2$; Chromosomal anomalies, $n = 3$. [2]Birthday closest to the case infant and matched for hospital, sex, GA (±1 week), and birth weight (±170 g). The matching criteria for GA and birth weight were selected to allow for a sufficient number of controls. EPT, extremely preterm; GA, gestational age; IVH, intraventricular haemorrhage

Mothers were considered to have received a complete course of antenatal steroids if they had received two doses of betamethasone with the first dose administrated more than 24 h before birth. Infants with a BW <2 SD below the mean were classified as small for GA as previously described.[21] The Apgar score at 5 min and the original CRIB score were used as a proxy for severity of illness.[22]

2.4 | Statistical analyses

Post hoc power analyses showed that with 70 cases and one matched control for each case, the power to detect a difference between cases and controls was 82% for continuous explanatory variables using a two-tailed test, an effect size of 0.35 and a significance level of 5%.[23] Statistical analyses were performed with IBM SPSS Statistics (Version 25.0 for Windows). Differences between matched case–control pairs were identified using the paired sample *t*-test and the McNemar's test for continuous and binary variables, respectively. Treatment with mechanical ventilation, antenatal steroid treatment, small for GA, multiple pregnancy, Apgar score at 5 min and the original CRIB score were considered as potential confounding factors with the latter two being continuous variables. To identify risk factors for being a case, multivariable conditional logistic regression models were performed for each potential explanatory variable, adjusting for the confounding factors original CRIB score and mechanical ventilation, which differed significantly between cases and controls (Table 2). Analysis regarding differences in transfusion volume and the incidence of severe IVH between hospitals were based on all included infants ($n = 533$). To adjust for the inter-hospital differences in infant BW, multivariable logistic regression models were used. Continuous variables are expressed as mean ± SD, and categorical variables as numbers (percentage), unless otherwise noted. In the case of unobtainable data, data were included in the analyses as far as possible. A $p < 0.05$ was considered statistically significant.

2.5 | Ethics

The study was approved by the Regional Ethical Review Board in Lund, Sweden (Dnr 138-2008). A waiver of consent was declared.

3 | RESULTS

Of 533 EPT infants, 72 infants (13.5%) developed severe IVH (Table 1). Compared with controls, infants with severe IVH had a higher CRIB score and were more likely to receive sustained mechanical ventilation (both $p < 0.001$; Table 2), while the other potential confounding and matching factors were similar. Accordingly, all results were adjusted for the original CRIB score and mechanical ventilation unless otherwise noted. Results from the unadjusted analyses are shown in Tables S1 and S2. The first obtained haemoglobin levels each day in cases and controls between the day of birth and Day 3 are shown in Table S3.

3.1 | Sodium supply and fluid volume

The risk of developing severe IVH was significantly increased with higher total sodium supply and with higher total fluid volume administrated to the infants until postnatal Day 2 (Table 3). When we excluded the amount of sodium the infants received from transfused blood products from the calculation of sodium supply and fluid volume, respectively, the results did not remain significant. Increasing amounts of sodium and fluid from transfused blood products as well as increasing transfusion volume per se were associated with an increased risk of severe IVH. Infants with severe IVH received 45% of their total sodium intake from transfusions. Erythrocyte and plasma transfusions accounted for the vast majority of sodium exposure (Figure 2).

TABLE 1 IVH grades 0 to 3 and PVHI in extremely preterm infants born at 22 to 26 gestational weeks

IVH grade/PVHI	*n* (%)
0 (IVH-free)	323 (60.6)
1	88 (16.5)
2	50 (9.4)
3	30 (5.6)
PVHI	42 (7.9)

3.2 | Sodium imbalances

The incidence of hypernatremia and the magnitude of fluctuations or peak concentrations of sodium did not differ significantly between cases and controls (Table 4).

One of the seven University hospitals included in the study had more strict transfusion guidelines, resulting in infants receiving less mean daily transfusion volume between birth and Day 2 [Mean ± SD (ml/day): 2.2 ± 3.1 vs. 10.1 ± 6.7, $p < 0.001$, adjusted for BW]. In the hospital with the more strict guidelines, nine of 106 (8%) infants developed severe IVH compared with 63 of 427 (15%) infants in the rest of the EXPRESS cohort ($p = 0.076$, adjusted for BW).

4 | DISCUSSION

The present study showed that early total sodium supply and early total fluid volume were significantly higher in EPT infants with severe IVH compared with IVH-free controls. Transfusions of blood products contributed to a large extent to the sodium intake and explained these differences. Neither high P-Na concentrations, hypernatremia nor large fluctuations in P-Na during the first postnatal days were associated with an increased risk of severe IVH.

In line with our results, Dalton et al. in infants with a BW < 1000 g and a GA < 29 weeks found no associations between hypernatremia

TABLE 2 Matching and potential confounding factors in extremely preterm infants (22 to 26 gestational weeks) with severe IVH and in matched IVH-free controls

Matching and confounding factors	Severe IVH ($n = 70$)[a] Mean ± SD	Matched controls ($n = 70$) Mean ± SD	p[b]
Matching factors[c]			
Birth weight, grams	741 ± 144	736 ± 140	0.667
GA, weeks	25.0 ± 1.0	25.0 ± 1.1	0.247
Days born after study start	508 ± 302	540 ± 307	0.172
Potential confounding factors			
Apgar score at 5 min	6.9 ± 2.1	7.1 ± 2.0	0.534
Original clinical risk index for babies score ($n = 68$)[d]	8.7 ± 4.0	6.8 ± 3.0	<0.001
	n (%)	*n* (%)	p[e]
MV, daily until postnatal Day 3 ($n = 63$)[d]	51 (81.0)	27 (42.9)	<0.001
Antenatal steroids (complete course)	39 (55.7)	48 (68.6)	0.163
Small for GA	7 (10)	9 (12.9)	0.754
Multiple pregnancy	15 (21.4)	15 (21.4)	1.000
Vaginal delivery	33 (47.1)	30 (42.9)	0.690
Chorioamnionitis	12 ($n = 63$) (19.0)	8 ($n = 63$) (12.7)	0.424
Born from preeclamptic pregnancy	4 ($n = 65$) (6.2)	6 ($n = 65$) (9.2)	0.727

Abbreviation: MV, mechanical ventilation.

[a]Two infants with severe IVH (grade 3 or peri-ventricular haemorrhagic infarction, $n = 72$) could not be matched.

[b]Paired sample *t*-test.

[c]Further matching factors were sex and hospital.

[d]Different numbers of case–control pairs were due to unobtainable data.

[e]McNemar's test.

TABLE 3 Sodium supply and fluid volume between birth and Day 2 in extremely preterm infants (22 to 26 gestational weeks) with severe IVH and in matched IVH-free controls

	Severe IVH ($n = 65$)[a]	Matched controls ($n = 65$)[a]	Adjusted analyses	
Sodium supply and fluid volume	**Mean ± SD**	**Mean ± SD**	**OR [95% CI] ($n = 122$)[b]**	**p[c]**
Sodium supply, mmol/kg/day				
Transfused blood products included (total sodium)	5.49 ± 2.53	3.95 ± 1.91	1.893 [1.175–3.048]	0.009
Transfused blood products excluded	3.02 ± 1.64	2.55 ± 1.32	1.459 [0.890–2.391]	0.134
From transfused blood products only	2.47 ± 1.26	1.40 ± 0.93	3.029 [1.445–6.345]	0.003
Fluid volume, ml/kg/day				
Transfused blood products included (total fluid)	119.4 ± 20.6	110.1 ± 17.4	1.037 [1.000–1.076]	0.048
Transfused blood products excluded	97.9 ± 15.3	98.1 ± 13.3	1.000 [0.956–1.046]	0.999
From transfused blood products only	21.5 ± 10.9	12.0 ± 7.9	1.142 [1.047–1.246]	0.003
Transfusion volume, ml/day	14.4 ± 8.6	7.9 ± 5.2	1.196 [1.058–1.352]	0.004

[a]Two infants with severe IVH (grade 3 or peri-ventricular haemorrhagic infarction, $n = 72$) could not be matched, and five case–control pairs were excluded due to unobtainable data.

[b]Different infant numbers were due to unobtainable confounding factor data.

[c]Multivariable conditional logistic regression adjusted for the original clinical risk index for babies score and mechanical ventilation.

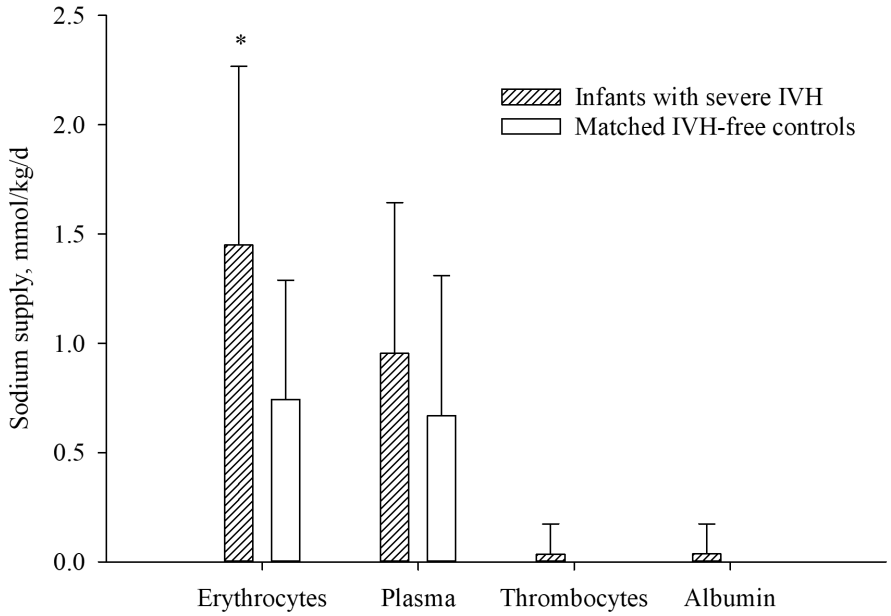

FIGURE 2 Mean daily sodium supply from erythrocytes, plasma, thrombocytes and albumin between birth and Day 2 in extremely preterm infants (22 to 26 gestational weeks) with severe IVH (grade 3 or PVHI, $n = 61$) and in matched IVH-free controls ($n = 61$). Two infants with severe IVH (n total = 72) could not be matched and nine case–control pairs were excluded due to unobtainable data. Values are expressed as mean ± SD. Multivariable conditional logistic regression adjusted for original clinical risk index for babies score and mechanical ventilation. *$p < 0.01$. IVH, intraventricular haemorrhage

(serum sodium ≥150 mmol/L) or rapid changes in serum sodium concentrations (≥10 and ≥15 mmol/day) in hypernatremic infants and severe IVH.[13] However, the authors found an association between hypernatremia and any IVH.

Furthermore, Lim et al. included 36 case–control pairs with a BW ≤1000 g and a GA ≤26 weeks and found no association between peak P-Na concentrations during the first three postnatal days and severe IVH.[6] On the other hand, contrary to our findings, the authors found that fluctuations in serum sodium >13 mmol/L within the first three postnatal days were associated with severe IVH. A limitation of that study, however, was that the authors used statistical methods appropriate for independent data and thus not considered the case–control design of their study.

Although comparable in GA and BW to our study, the cohorts of Dalton et al. and Lim et al. showed much more prominent sodium imbalances with a serum sodium concentration ≥150 mmol/L occurring in 58% of all infants[13] and a mean sodium fluctuation of 17.3 ± 10.4 mmol/L in infants who developed severe IVH.[6] For comparison, in our total cohort ($n = 533$), 20% of infants had a P-Na concentration >150 mmol/L, and the mean sodium fluctuation was 10.8 ± 5.2 mmol/L. This indicates that the risk of severe IVH might increase only with very pronounced sodium imbalances, of a magnitude that we did not observe in our cohort even though we included EPT infants from 22 gestational weeks of age.

Similar to our results, Barnette et al. reported no association between mean serum sodium concentrations of 138 to 142 mmol/L

TABLE 4 Sodium imbalances between birth and Day 3 in extremely preterm infants (22 to 26 gestational weeks) with severe IVH and in matched IVH-free controls

	Severe IVH ($n = 70$)[a]	Matched controls ($n = 70$)	Adjusted analyses	
Sodium imbalances	**Mean ± SD**	**Mean ± SD**	**OR [95% CI] ($n = 124$)[b]**	**p[c]**
P-Na concentration				
First, mmol/L	135.2 ± 3.4	135.7 ± 2.7	0.972 (0.832–1.137)	0.726
Highest, mmol/L	144.9 ± 5.8	146.6 ± 5.25	1.001 (0.911–1.099)	0.990
P-Na fluctuations				
Continuous, mmol/L	11.0 ± 5.6	11.6 ± 5.4	1.022 (0.929–1.124)	0.649
	***n* (%)**	***n* (%)**		
>10 mmol/L	37 (52.9)	31 (44.3)	1.397 (0.475–4.112)	0.544
>13 mmol/L	23 (32.9)	23 (32.9)	2.276 (0.628–8.247)	0.211
>15 mmol/L	12 (17.1)	16 (22.9)	0.864 (0.239–3.116)	0.823
Hypernatremia				
P-Na >145 mmol/L	28 (40.0)	41 (58.6)	1.028 (0.363–2.908)	0.958
P-Na >150 mmol/L	12 (17.1)	17 (24.3)	0.945 (0.294–3.040)	0.924
P-Na >155 mmol/L	5 (7.1)	3 (4.3)	5.374 (0.284–101.831)	0.263

Abbreviation: P-Na, plasma sodium.

[a]Two infants with severe IVH (grade 3 or peri-ventricular haemorrhagic infarction, $n = 72$) could not be matched.

[b]Different infant numbers were due to unobtainable confounding factor data.

[c]Multivariable conditional logistic regression analyses adjusted for the original clinical risk index for babies score and mechanical ventilation.

during the first three postnatal days and IVH in infants with a BW ≤1500 g.[24] A daily total sodium supply of >4.5 mmol/kg/day during the first postnatal week, on the contrary, was associated with an increased risk of IVH grades 2 to 4 and grades 3 to 4. These authors also found that if excluding infants who had received both transfusions of blood products and sodium bicarbonate, the association between sodium supply and IVH grades 3 to 4 was lost while the association with IVH grades 2 to 4 remained.

Another previous study by Lee et al. compared infants with a BW <1000 grams who developed severe IVH with infants who showed no or mild IVH and found severe IVH to be associated with sodium supply, even after excluding sodium from transfusions.[25] However, in that study, the analyses were adjusted for GA only, leaving other identified confounders unaccounted for. In accordance with our results, increasing amounts of sodium from transfused blood products and increasing transfusion volume per se were associated with severe IVH.

Interestingly, there was a non-significant trend towards lower haemoglobin levels in infants with severe IVH already on the day of birth. This difference became significant on postnatal Days 1 and 2 and was then not significant on postnatal Day 3 (Table S3). It has previously been shown that EPT infants with lower initial haemoglobin levels have an increased risk of IVH.[26] The mechanism has been suggested to be associated with early cord clamping, lower intravascular volume status and cerebral hypoperfusion. Thus, the slightly lower initial haemoglobin level in our cases was expected.

We cannot completely exclude reverse causation in our study, that is infants with severe IVH were given higher transfusion volumes contributing to increased sodium and fluid load due to a decrease in haemoglobin and blood pressure at the time of the intraventricular bleeding. To explore this further, we determined the proportion of infants with haemoglobin <140 g/L each day (Table S3), and indeed, there was a higher proportion of low haemoglobin levels in the severe IVH group during postnatal Days 1 and 2, which at least partly could explain the higher volume of blood transfusions in this group. Assuming that all those infants with haemoglobin <140 g/L received a blood transfusion of 10 ml/kg, this would explain slightly less than half of the difference in volume of transfused blood products.

To ensure the validity of our results we made efforts by (a) applying a nested case–control design, and (b) adjusting for relevant morbidity-related confounding factors. The association between total sodium supply and severe IVH was present after all adjustments, and to our best knowledge, this is the largest case–control study assessing associations between sodium supply, sodium imbalances and severe IVH so far.

Nevertheless, the present study has several limitations due to its retrospective approach. The data set does not hold information about different possible contributing factors, such as hypotension, mean arterial blood pressure or fluctuations in blood pressure, cerebral blood flow and/or vasopressor or inotrope use.[27–32] Another limitation is that we lack information on the exact time points at which the blood samples for haemoglobin were drawn in relation to the transfusions administrated. We further do not have data on the exact time point for IVH onset, and the ultrasound images were not reviewed by independent reviewers.

It has been shown that in very immature preterm infants, approximately half of IVHs are present already on the first day after birth and that only about 10% of haemorrhages have an onset later than postnatal Day 3.[1,2,33,34] This might indicate that postnatal sodium imbalances are less likely to be an important factor in the aetiology of IVH. However, it has been demonstrated that IVH progresses in severity in 20% to 40% of infants over a period of 3–5 days.[34] Severe sodium imbalances might therefore more likely be a contributing factor for IVH progression rather than for its onset.

Our understanding that a transfusion-related factor might explain the increased risk of severe IVH in our cohort of EPT infants is supported by the fact that the hospital with the stricter transfusion guidelines had a borderline lower incidence of severe IVH compared with the other hospitals. Arguably, there might exist other differences in care provision between the hospitals that were not accounted for in our analysis and the data set available.

To conclude, sodium from transfused blood products explained the association between higher total sodium supply and severe IVH. Whether this effect is mediated via sodium load, haemodynamic changes or other factors related to the transfusions remains unclear. Our interpretation of the findings in the present study is that early treatment with volume expansion to EPT infants using sodium-rich transfusions of blood products should be used with caution.

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CONFLICT OF INTEREST

None of the authors has a conflict of interest to disclose.

ORCID

Cornelia Späth https://orcid.org/0000-0003-2939-2020
Elisabeth Stoltz Sjöström https://orcid.org/0000-0002-4649-0653
Johan Ågren https://orcid.org/0000-0002-9510-048X
Fredrik Ahlsson https://orcid.org/0000-0002-8413-9274

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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