Received: 27 May 2019 | Revised: 4 September 2019 | Accepted: 5 September 2019

DOI: 10.1111/apa.15003

REGULAR ARTICLE

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

Neonatal clinical blood sampling led to major blood loss and was associated with bronchopulmonary dysplasia

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Funding information
This study was supported by the Swedish Medical Research Council #2016-01131, the Gothenburg Medical Society and Government grants, under the ALF agreement ALFGBG-717971.

Abstract

Aim: Studies indicate that reduced foetal haemoglobin levels are related to increased neonatal morbidity rates. This study investigated the relationships between sampling-related blood loss and adult blood transfusions administered during postnatal days 1-14 and the development of severe neonatal morbidities in extremely preterm infants born before 28 weeks of gestation.

Methods: The medical files of 149 extremely preterm infants born at two university hospitals in Sweden from 2013 to 2018 were investigated.

Results: Blood sampling resulted in a 58% depletion of the endogenous blood volume postnatal days 1-14 (median 40.4 mL/kg, interquartile range 23.9-53.3 mL/kg) and correlated with the adult erythrocyte transfusion volume (r_S = 0.870, P < .001). Sampling-related blood loss on postnatal days 1-7, adjusted for gestational age at birth and birth weight standard deviation score, was associated with the development of bronchopulmonary dysplasia (BPD) (odds ratio by a 10-unit increase 2.4, 95% confidence interval 1.1-5.4) (P = .03). No associations were found between blood sampling and intraventricular haemorrhage or necrotising enterocolitis in the full statistical model. The largest proportion of sampling-related blood was used for blood gas analyses (48.7%).

Conclusion: Diagnostic blood sampling led to major endogenous blood loss replaced with adult blood components and was associated with the development of BPD.

KEYWORDS

anaemia, blood sampling, bronchopulmonary dysplasia, extremely preterm, transfusion

1 | INTRODUCTION

Improved neonatal care has resulted in increased survival of extremely preterm infants. However, the rate of severe morbidities remains high and it is inversely related to gestational age (GA) at birth.[1] In the first week of life, extremely preterm infants are subjected to frequent diagnostic blood sampling and in critically ill infants, blood loss due to blood sampling is considered the primary cause of anaemia.[2-4] Extremely preterm infants with a relatively low bodyweight are particularly at risk. In critically ill adult patients, anaemia results in reduced oxygen transport capacity and leads to increased rates of cardiac morbidity and mortality.[5] Findings have shown that a reduction in the foetal haemoglobin in the first week of life was strongly correlated with increased morbidity.[6] Reductions in foetal haemoglobin were

Abbreviations: BPD, bronchopulmonary dysplasia; BW, birth weight; BW-SDS, birth weight standard deviation score; CI, confidence interval; GA, gestational age; IQR, interquartile range; IVH, intraventricular haemorrhage; NA, not applicable; NEC, necrotising enterocolitis; OR, odds ratio.

thought to be caused by transfusions with adult blood components. The functional and structural differences between foetal haemoglobin and adult haemoglobin have been well described.[7] Foetal and adult blood are composed of different types of blood components, including stem cells, sex steroids and growth factors[8-11] and likely there are other unidentified factors important for foetal development.

Extremely preterm infants often require blood transfusions during treatment in neonatal intensive care units and receive more transfusions than any other patient population.[12] A relationship between sampling-related blood volume loss and transfused blood volumes has been demonstrated in preterm infants.[13,14] However, to what extent this associates with gestational age and the impact of early blood sampling on morbidity in extremely preterm infants is not clear. Further, the contribution of different types of diagnostic clinical testing to early sampling-related blood loss in the extremely preterm has not been extensively studied. Thus, the present study aimed to in detail investigate the amounts of blood sampled due to clinical testing and adult blood transfused in extremely preterm infants during the first week of life and to investigate how the amount of early sampling-related blood volume loss is related to neonatal morbidity outcome.

Key notes

- Little is known about early postnatal sampling-related blood loss and the association to severe morbidities in extremely preterm infants.
- Early sampling-related endogenous blood loss resulted in a 58% depletion of endogenous blood and was associated with the development of bronchopulmonary dysplasia.
- The potential beneficial role of minimising the loss of endogenous blood and thus perinatal endogenous blood components during an early stage of development should be further evaluated.

2 | METHODS

2.1 | Study population and setting

This was a retrospective medical chart study. The study comprised preterm infants treated at two level III referral neonatal intensive care units, one at Sahlgrenska University Hospital in Gothenburg, which geographically covered the Region Västra Götaland and the other at Skane University Hospital in Lund, which geographically covered Southern Sweden. In the corresponding regions, all expected extremely preterm deliveries before 28 weeks gestation were referred to one of these university hospitals, where the infants were delivered and received initial care.

The study group comprised 149 liveborn infants in total. Of these, 51 children were born at less than 28 weeks of gestation in 2013 through 2018 in the Gothenburg hospital. These infants were included in two clinical trials that tested fatty acid supplementations in extremely preterm infants: (NCT02760472 and NCT03201588). In addition, 98 infants born in 2014-2015 in the Lund hospital were included. Infants born outside the hospital were excluded from the study. The clinical characteristics of the included infants are shown in Table 1.

2.2 | Blood sampling and transfusion

The medical records of each patient were reviewed to determine the frequencies and volumes of blood sampling and transfusions performed during postnatal days 1-14. The types of blood tests and the total blood volume of each blood sample were noted. A minimum amount of blood sampled, as required for laboratory analysis, was assumed, with no extra blood drawn for washing tubes. A maximum number of combined analyses performed for each laboratory tube was assumed. Combination analyses were assumed to have occurred when the laboratory analyses were performed at the same time point. The types and volumes of blood transfusions were noted. All data on blood sample volumes for each analysis, and analysis definitions, are shown in Table 2. It was estimated that, on average, infants had a blood volume of 70 mL/kg body weight, based on previous reports of total blood volume in preterm infants (range 62-78 mL/kg).[15,16] This value was used to calculate the percentage of sampled and transfused blood volumes relative to the total blood volume.

2.3 | Morbidities

Clinical diagnoses of bronchopulmonary dysplasia (BPD), necrotising enterocolitis (NEC) and intraventricular haemorrhage (IVH) were retrieved from the clinical records. BPD was defined as a need for

TABLE 1 Clinical characteristics

Clinical characteristics	Total n = 149	Lund n = 98	Gothenburg n = 51
GA, wk; mean (SD)	25.6 (1.5)	25.8 (1.5)	25.1 (1.5)
Birth weight, g; mean (SD)	797 (215)	809 (215)	774 (214)
BW-SDS; mean (SD)	−0.96 (1.37)	−1.12 (1.40)	−0.65 (1.27)
Mortality*, N (%)	17 (11.4)	14 (14.3)	3 (5.9)
Male; N (%)	97 (65.1)	63 (64.3)	34 (66.7)
Morbidities			
IVH grades 3-4; N (%)**	28 (19.0)	15 (15.6)	13 (25.5)
Any IVH; N (%)	51 (34.7)	27 (52.9)	24 (47.1)
NEC; N (%)**	8 (5.4)	4 (4.2)	4 (7.8)
BPD; N (%)***	91 (72.8)	57 (72.2)	34 (73.9)

Abbreviations: BW-SDS, birth weight standard deviation score; GA, gestational age; IVH, intraventricular haemorrhage; N, number; NEC, necrotising enterocolitis; SD, standard deviation.
*During postnatal days 1-14.
**147 individuals had complete data.
***125 individuals had complete data.

TABLE 2 Schematic overview of blood sampling analyses and volumes (mL)[a]

Serum/plasma analyses	
CRP (mg/L)[b]	0.4[c,d]
IL-6 (ng/L)	0.6[c]
ASAT (μkat/L), ALAT (μkat/L), ALP (μkat/L), Creatinine (μmol/L), Urea (mmol/L), Albumin (g/L)	0,4[d]-0.6[c]
Insulin (mIE/L)	0.4-0.6[c]
Bilirubin (μmol/L)	0.4-0.6[c]
Phosphate (mmol/L), Magnesium (mmol/L)	0.4-0.6[c]
Triglycerides (mmol/L)	0.4[d]-0.6
PTH (pmol/L)	0.4[d]-0.6
25(OH)D (ng/L)	0.4-0.6
17α-OHP (nmol/L)	0.4-0.6
TSH (mIU/L), Thyroid hormone (nmol/L)[e]	0.4[d]-0.6[f]
Cortisol (nmol/L)	0.4[d]-0.6
Whole blood analyses	
WBC count (10^9/L), platelets (10^9/L), neutrophils (10^9/L)	0.38[g]-0.5
FFA (mmol/L)	0.5
Blood coagulation analyses	
PR-INR (N/A), D-dimer (mg/L FEU), Fibrinogen (g/L), Anti thrombin (kIE/L)	0.9-1.0
Blood gas	
Blood gas (N/A[h])	0.3[i]
Blood typing/compatibility	
Blood typing (N/A)	0.5
Blood compatibility (N/A)	0.5
Other	
Vancomycin concentration (mg/L)	0.4-0.5
Tobramycin concentration (mg/L)	0.5
Gentamycin concentration (mg/L)	0.4-0.5
Study sampling[j] (N/A)	0.15-0.8
Phenobarbital (μmol/L)	0.5-0.5
PKU	
PKU test (N/A)	0.5
Blood culture	
Blood culture (N/A)	1.0

Abbreviations: 17α-OHP, 17 alpha-hydroxyprogesterone; 25(OH)D, 25-hydroxy vitamin D; ALAT, alanine transaminase; ALP, alkaline phosphatase level; ASAT, aspartate transaminase (ASAT); CRP, C-reactive Protein; FFA, free fatty acids; IL-6, interleukin-6; INR, international normalised ratio; N/A, not applicable; PKU test, phenylketonuria test; PR, prothrombin ratio; PTH, parathyroid hormone (PTH); TSH, thyroid stimulating hormone; WBC count, white blood cell count.

[a]In Lund, additional more infrequent laboratory analyses are not shown. All data available were used in statistical analyses.

[b]When obtained separately.

[c]Combined analyses in Gothenburg, maximum amount of retrieved mL of whole blood corresponds to minimum amount required for one single analysis.

[d]Combined analyses in Lund, maximum amount of retrieved mL of whole blood corresponds to minimum amount required for one single analysis.

[e]Thyroid hormones include both unbound T3 and T4.

[f]Required two tubes per analysis in Gothenburg.

[g]Isolated platelet analyses required 0.25 mL in Lund.

[h]Includes multiple sub-analyses with different units.

[i]Isolated blood glucose analysis bedside required 0.05 mL in Lund.

[j]Blood sampling due to ongoing parallel studies conducted at the neonatal care according to study protocol.

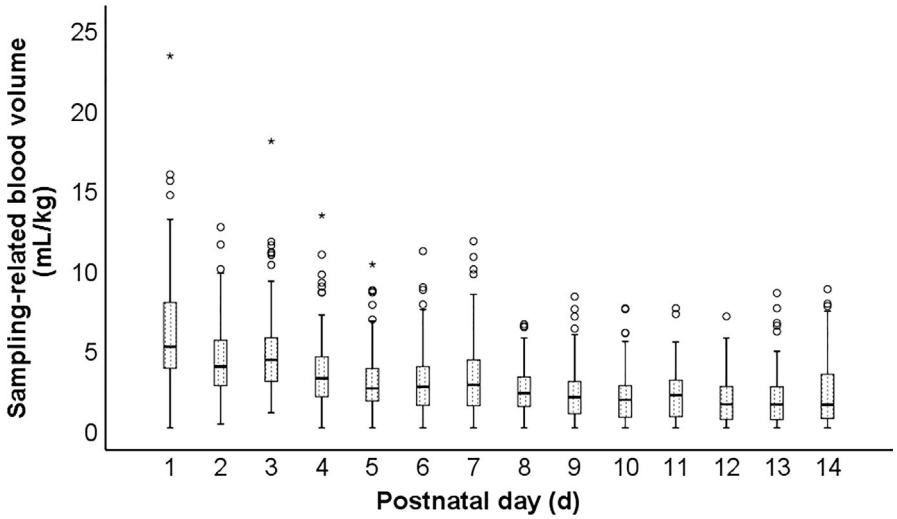


FIGURE 1 Daily volume of blood sampled (mL/kg) in a cohort of 149 extremely preterm infants. During postnatal days 1-14, median (IQR) blood sampling volume was 40.4 (23.9-53.3) mL/kg, which corresponded to 58% of the total endogenous blood volume. The majority of blood samples were drawn during the first week of life and corresponded to a median (IQR) of 24.3 (16.7-33.8) mL/kg, equivalent to 35% of the total endogenous blood volume. Boxes illustrating 25th percentile (bottom), median and 75th percentile (top), whiskers illustrate 1.5 times the IQR, or if no case has a value in that range, minimum and maximum. Outliers illustrated by a small circle and extreme outliers, defined as three times the IQR, illustrated by an asterisk. IQR, interquartile range

supplemental oxygen 36 weeks postmenstrual age (age based on foetal ultrasonography, performed at week 16-18 postmenstruation). NEC was diagnosed based on clinical signs and radiological findings (Bell's stages 2-3). IVH was determined with repeated ultrasound examinations, and it was graded according to the Papile classification (I-IV).[17]

2.4 | Statistical analysis and variable definition

Statistical analyses were performed with SPSS 25 (IBM). Spearman's correlation was used to assess correlations between continuous variables. Longitudinal variables for paired observations were compared with Wilcoxon's signed-rank non-parametric test. Blood sample volumes were corrected for birth weight for postnatal days 1-7 samples and for body weight at postnatal day 14 for postnatal days 8-14 samples. Inclusion criteria for analyses were complete data on blood sample volumes and the associated clinical blood analyses during each study period. 149, 146, 144, 138, 135, 133 and 130 infants were available each day for analyses of days 1-7, respectively. In total, 120 infants had full data days 8-14. Multivariate analyses were evaluated with binary logistics and linear regression. All assumptions for linear regression were fulfilled for included variables. Independent confounding variables included in the full multivariate analysis were GA at birth and birth weight standard deviation score (BW-SDS). In all analyses, *P* values <.05 were considered significant.

3 | RESULTS

For postnatal days 1-14, the median and interquartile range (IQR) of total blood sampling volumes were 40.4 mL/kg and 23.9-53.3 mL/kg, respectively, which corresponded to 58% of the total blood volume. The sampling-related blood volume drawn during postnatal days 1-7 (median 24.3 mL/kg, IQR 16.7-33.8 mL/kg) was significantly higher ($P < .001$) than the blood volume sampled postnatal days 8-14 (median 13.7, IQR 6.2-20.3 mL/kg) (Figure 1). The sampling-related blood volumes (mL/kg) on postnatal days 1-7 and postnatal days 1-14 were correlated with the GA at birth ($r_S = -0.730$, $P < .001$ and $r_S = -0.738$, $P < .001$) (Figure 2). During postnatal days 1-14, the median and IQR of erythrocyte transfusion volumes were 60.7 mL/kg and 24.1-88.0 mL/kg, respectively, which corresponded to 87% of the total blood volume. Erythrocyte transfusion volume was significantly higher during postnatal days 1-7 (median 32.9 mL/kg, IQR 13.8-52.9 mL/kg) than during postnatal days 8-14 (median 24.4 mL/kg, IQR 10.2-36.0 mL/kg) ($P < .001$) (Figure 3). The median and IQR plasma-, platelet- and erythrocyte-transfusion volumes combined were 82.7 mL/kg (IQR 40.2-118.8), 46.8 mL/kg(IQR 24.5-75.4) and 27.6 mL/kg (IQR11.5-43.8 mL/kg), respectively, during postnatal days 1-14, 1-7 and 8-14. The total volume of erythrocytes transfused (mL/kg) during postnatal days 1-7 and 1-14 correlated with the GA at birth ($r_S = -0.575$, $P < .001$ and $r_S = -0.628$, $P < .001$). In the weeks of gestation 22, 23, 24, 25, 26 and 27, the median (IQR) total volumes of erythrocytes transfused during postnatal days 1-14 were 109.3 mL/kg (IQR 96.7-not applicable), 96.0 mL/kg a (IQR 75.2-105.2), 71.2 mL/kg (IQR 56.5-95.5), 71.4 mL/kg (IQR 47.1-90.2), 21.5 mL/kg (IQR 10.2-41.4) and 23.3 mL/kg (IQR 13.0-56.5 mL/kg), which corresponded to 156%, 137%, 102%, 102%, 31% and 33%, respectively, of the total endogenous blood volume. Sampling-related blood volume (mL/kg) was positively correlated with erythrocyte transfusion volume (mL/kg) during postnatal days 1-14 ($r_S = 0.870$, $P < .001$) (Figure 4).

The blood gas analyses required the highest proportion of the blood sample volume (Figure 5), requiring 48.7% during postnatal

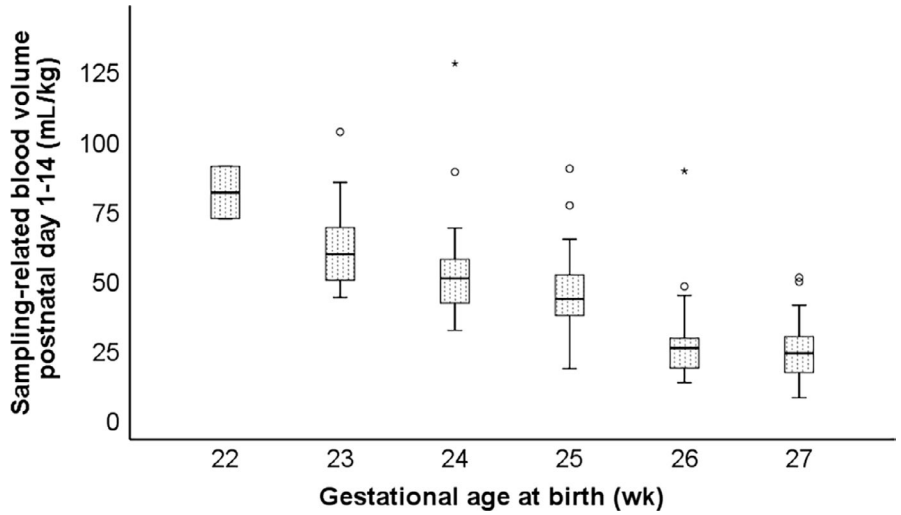
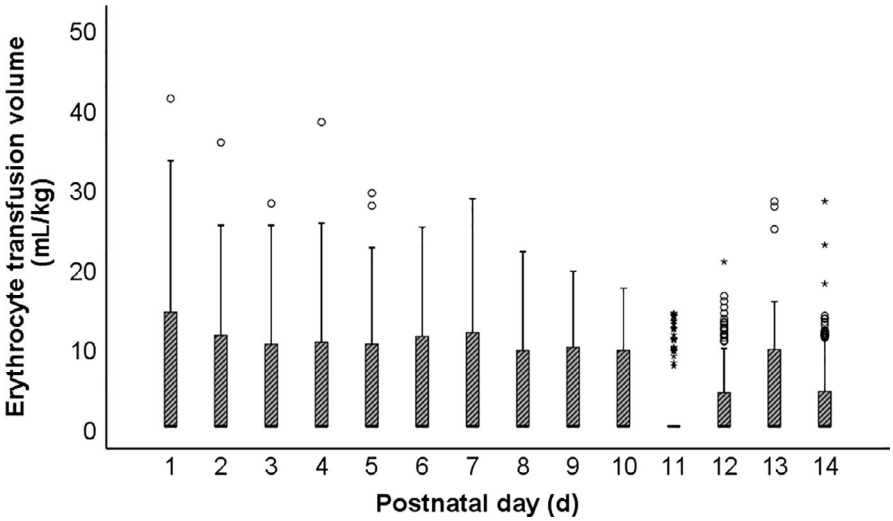


FIGURE 2 Sampling-related blood loss in preterm infants during postnatal days 1-14, according to gestational age at birth in a cohort of 149 extremely preterm infants. At 22, 23, 24, 25, 26 and 27 weeks gestation, sampling-related blood losses comprised 116%, 84%, 71%, 61%, 36% and 33%, respectively, of the total endogenous blood volume. Boxes illustrating 25th percentile (bottom), median and 75th percentile (top), whiskers illustrate 1.5 times the IQR, or if no case has a value in that range, minimum and maximum. Outliers illustrated by a small circle and extreme outliers, defined as three times the IQR, illustrated by an asterisk. IQR, interquartile range

FIGURE 3 The volume of erythrocyte transfusions on postnatal days 1-14 in a cohort of 149 extremely preterm infants. The median (IQR) erythrocyte transfusion volume was 60.7 (24.1-88.0) mL/kg, which corresponded to 87% of the total endogenous blood volume. Boxes illustrating 25th percentile (bottom), median and 75th percentile (top), whiskers illustrate 1.5 times the IQR, or if no case has a value in that range, minimum and maximum. Outliers illustrated by a small circle and extreme outliers, defined as three times the IQR, illustrated by an asterisk. IQR, interquartile range



days 1-14, 44.0% during postnatal days 1-7 and 56.3% during postnatal days 8-14.

3.1 | Blood sampling and morbidities

The blood sample volumes (mL/kg) drawn during postnatal days 1-7 and postnatal days 1-14 were significantly associated with the development of BPD both in univariate analysis, odds ratio (OR) by a 10-unit (mL) increase with a 95% confidence interval (CI), 3.3 and 1.8-5.9 ($P < .001$) and 1.8 and 1.3-2.5 ($P < .001$), respectively, (Figure 6) and in the full statistical model adjusting for both GA at birth and BW-SDS postnatal days 1-7, OR by a 10-unit increase with a 95% CI 2.4 and 1.1-5.4 ($P = .03$). The probability plots for BPD and blood sample volumes (mL/kg) postnatal days 1-7, postnatal days 1-14 and GA at birth are illustrated in Figure 7. The area under the curve (AUC) for blood sample volumes (mL/kg) postnatal days 1-7 and 1-14, respectively, and BPD were 0.80 and 0.77 unadjusted and 0.80 in the full model for postnatal days 1-7. Moreover, the erythrocyte transfusion volumes (mL/kg) administered during postnatal days 1-7 and postnatal days 1-14 were associated with the development of BPD in univariate analysis, OR by a 10-unit increase with a 95% CI 1.6 and 1.3-2.0 ($P < .001$) and 1.3 and 1.1-1.5 ($P < .001$). In the full statistical model after adjusting for GA at birth and BW-SDS associations with erythrocyte transfusion volumes were apparent at postnatal days 1-7, OR by a 10-unit increase with a 95% CI 1.4 and 1.0 - 1.8 ($P = .03$).

No associations were found between the sampling-related blood loss and erythrocyte transfusion postnatal days 1-7 and 1-14 for NEC development in univariate or multivariate analyses. The amount of blood sampled (mL/kg) on postnatal day 1 associated with IVH grade I-IV, OR by a 10-unit increase (95% CI) 3.5 (1.3-9.5), $P = .01$ but not with severe IVH in univariate analysis. No associations were found when adjusting for GA at birth and BW-SDS.

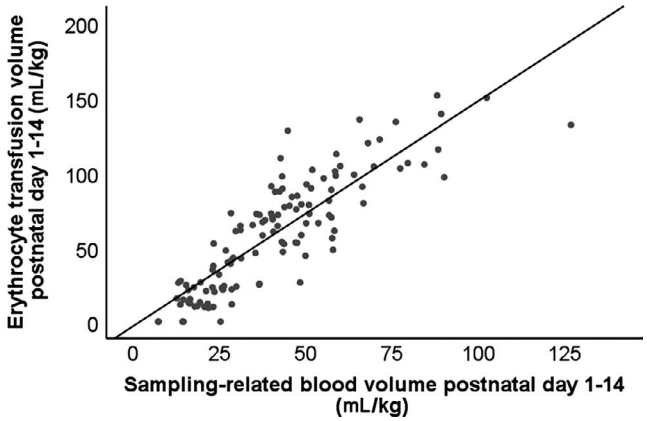


FIGURE 4 Correlation between total sampling-related blood loss and erythrocyte transfusion volume during postnatal days 1-14 in a cohort of 149 extremely preterm infants. The amount of erythrocytes transfused during postnatal days 1-14 was highly correlated with the amount of sampling-related blood loss (mL/kg). rS = 0.870, $P < .001$

The two study sites were compared for differences in blood sample volumes and erythrocyte transfusion volumes. The blood sample volumes between the sites during postnatal days 1-7 and postnatal days 1-14 were significantly different ($P = .008$, $P = .02$), however when adjusting for GA at birth, there was no statistical difference between the study sites at any time period. The erythrocyte transfusion volumes were not different between study centres at any of the three time periods.

4 | DISCUSSION

This study showed that sampling-related blood loss resulted in a depletion of 58% of the endogenous blood volume during the first 2 weeks of life, where a majority was drawn during postnatal days 1-7. This blood loss was strongly associated with the volume of transfusions received with adult blood components. Sampling-related blood losses the first postnatal week were larger in infants that later developed BPD than in those without later BPD. From a world-wide perspective, preterm birth affects over 15 million newborns each year. It is the main contributor to neonatal mortality and morbidity, moreover, this morbidity contributes to 40% of all deaths of children under 5 years of age.[18,19] A Swedish national population-based cohort study 2014-2016 showed an unprecedented high survival (77%) of extremely preterm infants born between 22 and 26 weeks of gestation.[20] One contributing factor to severe morbidity is the chronic lung disease, BPD, which is also a predictor of adverse long-term outcome.

Current treatment for BPD only addresses the symptoms, and the incidence of BPD is approximately 40% in surviving infants born extremely preterm. Various studies have shown that BPD and other neonatal morbidities were associated with anaemia and adult blood transfusions.[21,22] It is well known that sampling-related blood loss during neonatal clinical care is linked to the number of blood transfusions administered.[23] Extremely preterm infant blood contains components unique for foetal development, predominantly foetal haemoglobin. Moreover, the concentration of circulating hematopoietic stem cells was shown to be inversely related to GA at birth.[24] Recently, a Swedish national population-based cohort study showed that extremely preterm infants received a mean of seven adult blood transfusions during the neonatal period, with considerable between-centre variation (3 to 9 transfusionsperinfant).[25] Taken together, those findings suggested that transfusions of adult blood components in extremely preterm infants might potentially dilute important foetal factors during an essential stage of development.

In this study, it was shown that larger volumes of sampled blood relative to body weight were associated with a higher frequency

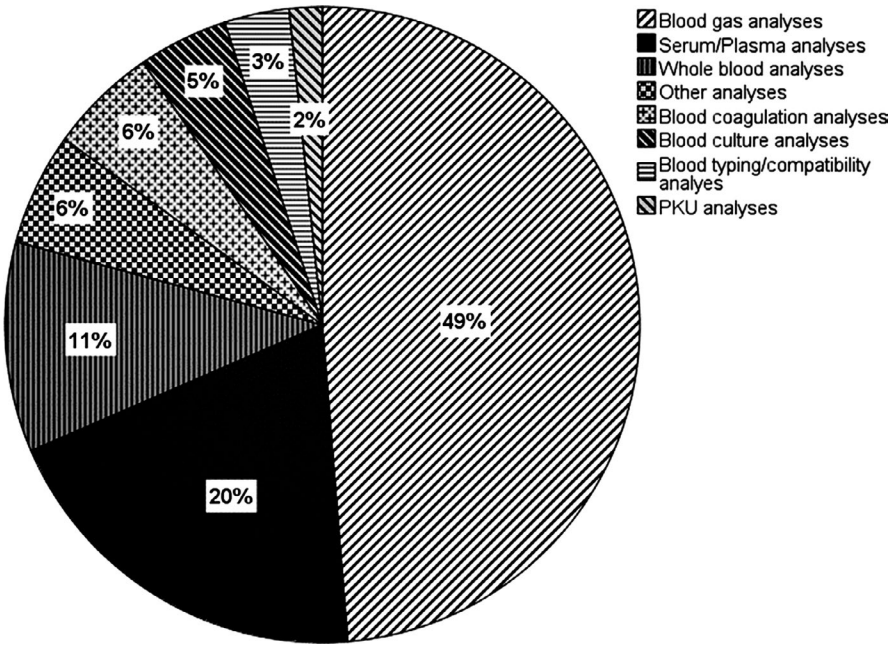


FIGURE 5 Distribution of the proportions of blood sample required for clinical analyses. Each sector represents a different type of clinical test in a cohort of 149 extremely preterm infants. Blood gas analyses accounted for 49% of the total blood volume sampled over postnatal days 1-14. PKU, phenylketonuria test

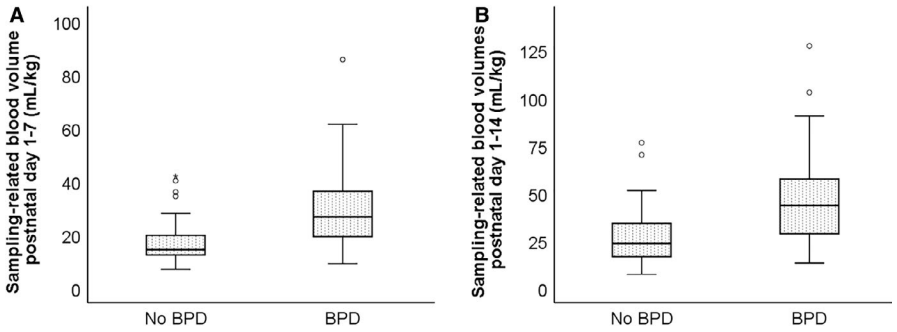


FIGURE 6 Sampling-related blood loss and development of BPD postnatal days 1-7 (A) and 1-14 (B) in a univariate analysis. Sampling-related blood volumes were higher in infants developing BPD in univariate analysis postnatal days 1-7 and 1-14, odds ratio (OR) by a 10-unit increase (95% CI), 3.3 (1.8-5.9), $P < .001$ and 1.8 (1.3-2.5), $P < .001$, respectively, and in multivariate analysis after adjusting for GA at birth and BW-SDS postnatal days 1-7, odds ratio (OR) by a 10-unit increase (95% CI) 2.4 (1.1-5.4), $P = .03$ in a cohort of 149 extremely preterm infants. Boxes illustrating 25th percentile (bottom), median and 75th percentile (top), whiskers illustrate 1.5 times the IQR, or if no case has a value in that range, minimum and maximum. Outliers illustrated by a small circle and extreme outliers, defined as three times the IQR, illustrated by an asterisk. IQR, interquartile range, BPD, bronchopulmonary dysplasia, BW-SDS, Birth weight standard deviation score

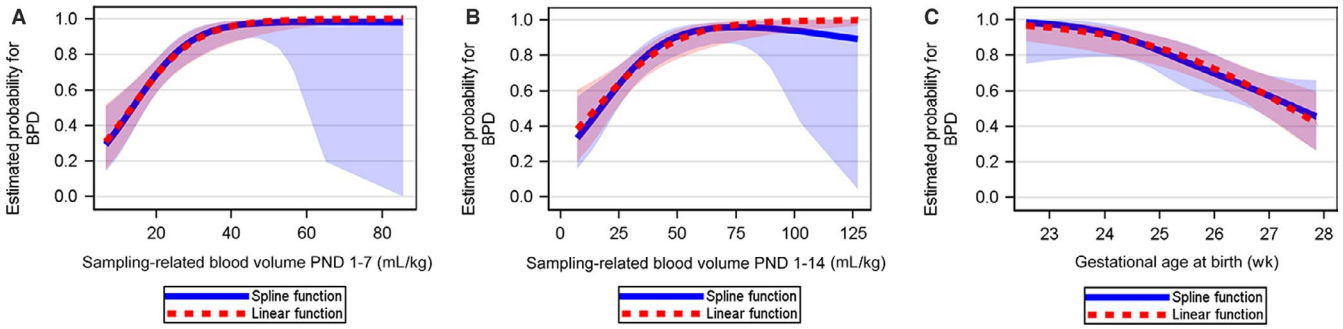


FIGURE 7 Probability plots for BPD and sampling-related blood volume postnatal days 1-7 A, 1-14 (B) and gestational age at birth C, in a cohort of 149 extremely preterm infants. C-statistics for the respective variables were 0.80, 0.77 and 0.74. Shown as linear and spline functions with a 95% confidence interval. BPD, bronchopulmonary dysplasia

of BPD. It was also observed that erythrocyte blood transfusions tended to be associated with morbidity, after adjusting for GA at birth and BW-SDS. Adjusting the multivariate analyses for other factors can reduce, but not exclude, the risk of confounding. The presence of other confounding illnesses, such as maternal or postnatal infection, inflammation or ventilator- or oxygen-related injury might also be taken into account. In this study, the risk of confounding by indication should also be addressed. Infants with more severe acute lung disease are more likely to require a more intensive management and supervision and are at a higher risk of being exposed to more frequent blood gas sampling etc The results in this study add to earlier reports regarding very low birth weight infants (birth weight less than 1500 g) where blood losses due to blood-sampling constitute 11-22 ml/kg/day, where the highest volume loss occurs during the first week of life.[4,26] Further, there has been a concern raised regarding smaller infants being at a higher risk. It should also be noted that in this study, we assumed the lowest amount of blood sampled, only calculating the minimal required amount for laboratory analysis. In very low birth weight preterm infants, blood volumes sampled required for laboratory analysis only constitute 33% of the actual sampling-related blood loss, the rest is discarded as waste or represent hidden blood loss.[27] The study cohort comprised of 149 extremely preterm infants, in two university hospital neonatal intensive care units in Sweden. As there may be local and national differences in intensive care management and maternal and perinatal care, as well as improvements of care over time, the results of our study might not be representative to a general population. Due to the inherent complexity of neonatal intensive care, a larger cohort may be needed to be representative for a general population. It should also be noted that the incidence of NEC in this cohort was relatively low, and thus, this study was statistically underpowered for this outcome.

The effect of blood transfusions on morbidity in preterm neonates has been extensively discussed. Several studies reported positive associations between transfusions of blood from adult donors and the progression of cerebral haemorrhage or the development of NEC, IVH or BPD. However, the mechanisms underlying those associations remain unclear.[21,28-32] Prospective studies have compared transfusion strategies considered liberal or restrictive, based on different haemoglobin thresholds. However, those studies did not show a clear impact on either short- or long-term morbidity.[33] Moreover, a causal relationship cannot be assumed between morbidity outcome and blood transfusions in preterm

infants, because smaller infants have a higher incidence of morbidity, experience more severe morbidities and are the most likely to require blood transfusions.[34]

Anaemia and hypotension are the most common indications for blood transfusions in the neonatal intensive care units. Anaemia is a common condition that can be caused by blood loss during delivery, immaturity of the hematopoietic system (inadequate production of erythropoietin) or iatrogenic blood loss, due to frequent blood sampling. Guidelines at Swedish neonatal units have established reference values of haemoglobin (g/L) at different postnatal ages, which are used as indicators for transfusion therapy. Delayed cord clamping at birth is considered a favourable preventive strategy for anaemia in preterm infants.[35] As shown in a Cochrane meta-analysis, the resulting auto-transfusion of feto-placental blood reduced the number of blood transfusions required and reduced the rates of cerebral IVH and NEC in extremely preterm infants.[36] Those impressive effects of delayed cord clamping strongly support the hypothesis that foetal blood components are essential for preventing morbidity in extremely preterm infants.

Multiple studies have discussed the benefits of a restrictive blood sampling regime in the neonatal period. Significant volumes of blood loss, due to oversampling for laboratory analyses, increased the risk of neonatal anaemia and the need for volume substitution with adult blood components.[37] A range of strategies currently used and under evaluation have been designed to prevent blood loss in the neonate, such as non-invasive monitoring, evidence-based national guidelines on blood transfusion policies and staff training on neonatal care and blood analysis.[38] Prospective intervention studies are needed to accelerate the implementation of effective blood conservation strategies within the neonatal critical care environment. Recent developments in micro-method technologies might facilitate the development of more sophisticated blood analysis methods and substantially reduce sampling-related blood volume loss. In the present study, blood gas analyses were found to be the primary cause of sampling-related blood loss; thus, new analytical methods for analysing blood gases might be an appropriate goal. The potential benefit of collecting and transfusing umbilical cord blood, with high concentrations of foetal haemoglobin (autologous blood transfusion), has been investigated and is currently the subject of a randomised clinical trial (NCT03764813).[39]

5 | CONCLUSION

This study demonstrated that blood sampling was responsible for a 58% loss of total blood volume in extremely preterm infants, within the first two postnatal weeks. The majority of the blood volume sampled was drawn during the first postnatal week. This sampling-related blood volume loss was associated with the development of BPD. The potential short- and long-term effects of exchanging endogenous foetal blood with blood from adult donors currently remains unknown. The potentially beneficial effects of preserving endogenous blood components, such as foetal haemoglobin and stem cells, during early development should be evaluated in larger prospective studies.

ACKNOWLEDGEMENTS

We thank Professor Ann Hellström, MD, PhD, statistician Aldina Pivodic, MSc in mathematics, research nurses Margareta Gebka and Carola Pfeiffer-Mosesson and the staff at the neonatal intensive care units in Gothenburg and Lund for assistance.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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How to cite this article: Hellström W, Forssell L, Morsing E, Sävman K, Ley D. Neonatal clinical blood sampling led to major blood loss and was associated with bronchopulmonary dysplasia. *Acta Paediatr*. 2020;109:679–687. https://doi.org/10.1111/apa.15003