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Patterns of phlebotomy blood loss and transfusions in extremely low birth weight infants

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Abstract

Objective—Characterize frequency and volume of blood draws and transfusions in extremely low birth weight infants in the first 10 weeks of life.

Study design—We included infants with a birth weight <1000 g born 23 0/7–29 6/7 weeks gestational age (GA) and with a length of stay ≥10 weeks, admitted between 2014 and 2016 to a single neonatal intensive care unit.

Results—Of 54 infants, median (25th, 75th percentile) GA and birth weight were 25 weeks (24, 26) and 665 g (587, 822), respectively. Median number of blood draws per infant decreased from 57 (49, 65) in week 1 to 12 (8, 22) in week 10. Median volume of blood extracted was 83 mL (70, 97), and median number of blood transfusions was 8 (5, 10).

Conclusions—This cohort experienced a high number and volume of blood draws. Draw frequency and transfusions decreased over the first 10 weeks of life.

Introduction

Anemia of prematurity is a common complication among premature infants in the neonatal intensive care unit (NICU). This anemia is the result of the combination of transient physiological changes in the settings of prematurity (including lack of third trimester iron stores, decreased red blood cell lifespan, and low circulating erythropoietin [1, 2]) exacerbated by phlebotomy losses for laboratory testing [3–7]. While laboratory studies are important components for monitoring physiologic parameters (e.g., respiratory, electrolyte, hematological, endocrine, and infectious), an excessive number and volume of blood draws can lead to complications, including exacerbation of existing anemia, phlebotomy-induced complications, and an increased number of packed red blood cell (pRBC) transfusions.

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Compliance with ethical standards

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Prior studies demonstrated that an average of 34 mL/kg of blood is removed and 27 mL/kg of blood is transfused during the first 4 weeks of life in infants <28 weeks gestation [8], and other studies have reported even higher phlebotomy blood loss volumes in the first 2 weeks of life [9, 10]. Nearly all extremely low birth weight (ELBW, <1000 g birth weight (BW)) infants need pRBC transfusions in the first few weeks of life [11–13]. Phlebotomy loss is particularly important among this patient group because even small volumes of blood loss are large relative to an ELBW infant's body weight and blood volume.

The number of blood draws and the volume of blood extracted from ELBW infants are underreported in the literature, and the available data are limited to the first 2–4 weeks of life. In this study, we sought to better characterize the frequency and the volume of phlebotomy for laboratory testing and the necessity of blood transfusion requirements in a contemporary cohort of ELBW infants in the NICU setting over the first 10 weeks of life.

Materials and methods

Data source and study population

We conducted a retrospective study of ELBW infants admitted to the Duke University Medical Center (Durham, NC, USA) NICU from 2014 to 2016. To identify the cohort and extract data of interest from electronic health records, we used the Duke Enterprise Data Unified Content Explorer, a web-based query previously described [14]. We included all ELBW infants born between 23 0/7 and 29 6/7 weeks gestational age (GA) with a length of stay $\geq$ 10 weeks. We excluded infants admitted after the first day of life. We collected the following infant characteristics: BW, GA at birth, inborn status, sex, race, daily weight, small, appropriate, or large for GA (LGA) status, presence or absence of an umbilical catheter (venous or arterial), and hospital length of stay (in days). Laboratory data included specific diagnostic studies performed, timing of laboratory draws, and volume (in mL) of blood used for each test (Appendix A). Transfusion data included the number of pRBC transfusions and the volume (in mL) transfused. We collected daily data for the first 10 weeks of life.

Definitions

We defined a laboratory draw as any individual blood sample collection based on the orders entered in the electronic health record with a unique corresponding collection time. We calculated volumes of blood collected based on the specific volumes required by the laboratory to process each of the ordered tests. To avoid overestimating blood volumes, we considered both the number of orders and the collection times for blood draws. When the order number was different than the collection time, we included one draw in 24 h for blood cultures, type, and screen, and two draws in 24 h for basic metabolic panel (BMP) and complete blood count (CBC), based on unit protocols and collection times for blood draws. We excluded neonatal bilirubin levels ordered and collected at the same time as a BMP, given that, in our unit, they were collected in the same tube.

In our unit, the decision to transfuse pRBCs follows standardized protocols that are based on the hematocrit level and clinical condition of the infant. We used leukoreduced, irradiated,

cytomegalovirus-negative, type-specific pRBC for our transfusions. For asymptomatic infants <1200 g, our transfusions guidelines recommend one aliquot of 10 mL/kg of pRBC for a hematocrit <28%. For asymptomatic infants >1200 g, transfusions are recommended for a hematocrit <26% and reticulocytes < 5%; however, transfusion orders are at the discretion of the care team. We defined small for GA (SGA) as a BW below the 10th percentile for GA, and LGA as a BW above the 90th percentile for GA, based on Olsen growth curves [15]. We calculated the volumes of blood collected/transfused (mL/kg) using the infant's weight on the day of collection/transfusion.

Statistical analysis

We summarized the distribution of continuous variables and categorical variables using medians (25th and 75th percentiles) and counts (percentages), respectively. We noted any missing data, but excluded them from the analysis. We compared proportions using the Fisher's exact test, paired proportions using the McNemar's test, paired differences using the Wilcoxon signed-rank test, two independent groups using the Wilcoxon rank-sum test, and more than two independent groups with the Kruskal–Wallis test. We summarized the results for ELBW infants by GA, weight, or week of life. We conducted all the statistical analyses using SAS 9.4 (SAS Institute Inc., Cary, NC, USA), and we considered a $p < 0.05$ statistically significant without multiple comparison adjustment. The Duke University Institutional Review Board declared this study exempt from full review.

Results

We identified 54 ELBW infants with a median (25th and 75th percentiles) GA and BW of 25 weeks (24, 26) and 665g (587, 822), respectively. The majority (52/54, 96%) were inborn, male (29/54, 54%), and black (28/54, 52%). The median hospital length of stay in this cohort was 147 days (110, 175). The proportion of SGA and LGA infants was 13/54 (24%) and 3/54 (6%), respectively.

Out of 21,691 laboratory tests documented in the first 10 weeks of life, the most common were the point-of-care glucose checks (7137/21,691 [33%]), followed by blood gas (3770/21,691 [17%]) and BMP (3337/21,691 [15%]). Of the 3770 blood gas draws, 28% were arterial, 67% capillary, and 5% venous. In the first 10 weeks of life, the median number of blood draws per week was 23 (12, 52), and this number decreased with increasing age of the infant from a median of 57 (49, 65) in the first week of life to 12 (8, 22) in week 10 ($p < 0.001$; Table 1). The median volume of blood extracted for laboratory evaluation in the first 10 weeks of life was 83 mL (70, 97). The median volume of blood drawn (mL/kg) decreased over the 10 weeks in all GA groups, and was inversely proportional to the birth GA (Fig. 1). The volume of blood out (mL/kg) in the first 10 weeks of life was statistically higher in the infants born at 23 weeks GA compared with infants born at 24 weeks GA (median 142 mL/kg vs. 81 mL/kg, $p = 0.01$; Fig. 2).

In the first 2 weeks of life, the median volume of blood necessary for laboratory testing was 48 mL/kg (38, 59) and was higher in infants with lower BW: 73 mL/kg (66, 84) for infants with BW <500 g, 53 mL/kg (44, 62) for infants with BW 500–750 g, and 39 mL/kg (26, 47) for infants with BW >750 g (Fig. 3). Also, SGA infants had a higher volume extracted than

appropriate for GA and LGA infants (median 62 mL/kg (43, 73) vs. 47 mL/kg (37, 56) and 39 mL/kg (25, 54); $p = 0.04$ and $p = 0.11$, respectively).

The median volume of blood extracted from infants before a transfusion was 10 mL/kg (5, 17). Only one infant (2%) received no transfusions in the first 10 weeks of life. The median number of transfusions in the first 10 weeks of life was 8 (5, 10), and varied from 11 (9, 12) for infants born at 23–24 weeks GA to 6 (4, 7) for infants born at 27–28 weeks GA.

The median length of umbilical vascular catheter placement in this cohort was 7 days (5, 9), with a median of 0 (0, 6) days for umbilical venous catheter, and 7 (4, 9) for the umbilical arterial catheter. Three (6%) infants did not have an umbilical catheter placed. The median (25th, 75th percentile) volume of blood extracted in the first week of life in infants with an umbilical catheter was 30 mL/kg (23, 36), similar to the volume extracted from the three infants without an umbilical catheter, 35 mL/kg (28, 38) ($p = 0.39$). In this group, 3/56 (5%) of the infants received erythropoiesis-stimulating agents.

Discussion

During the study period, we report the number and volume of blood draws in this contemporary cohort of ELBW infants. The number of laboratory draws decreased in frequency with increasing age in weeks. The volume of blood drawn from ELBW infants was inversely proportional to the birth GA. As one would expect, transfusions followed similar trends, with higher numbers in the less-mature infants and fewer transfusions towards the end of the 10-week period.

The most common lab draws in this cohort were glucose checks, blood gases, and BMP. Most of the lab draws were at the discretion of treatment team. The guidelines for regularly scheduled lab draws include: bilirubin check at 12 h, CBC, BMP, newborn screen and bilirubin at 24 h, and twice a week electrolytes while on total parenteral nutrition. Glucose levels are followed closely after admission and while on parenteral nutrition (checked at intravenous fluid initiation and with any change in glucose infusion rate >1 mg/kg/min). If any glucose from a line is <100 or >250 , it has to be confirmed with a heel stick. Feeding intolerance, septic workup, increased apnea/bradycardia, and glycosuria are also reasons to check glucose levels.

Estimates of the laboratory phlebotomy loss in premature infants in the first few weeks of life have been shown to approximate the volume of red blood cells (RBCs) transfused during that same period [4, 16, 17]. Similarly, in our group, infants had a median phlebotomy loss of 10 mL/kg (5, 17) before a transfusion was given.

Prior reports estimate blood volumes of 89–110 mL/kg in the first 2 weeks of life [18–20]. In the current report, more than 50% of infants' total blood volume (median of 48 mL/kg (38, 59)) was extracted during this initial period for laboratory draws. Physiologic changes in hematocrit and hemoglobin concentration during the neonatal period in infants born at early GA are difficult to interpret, due to the confounding issues of periodic phlebotomy losses and blood transfusions [21]. With an increase in the survival of periviable infants, and with evidence that high blood volumes are being drawn for laboratory testing in this most

vulnerable population, providers need to develop strategies to minimize blood draws and maintain acceptable hematocrit and hemoglobin levels.

In a study of 14 very low BW infants (BW < 1500 g), it was estimated that an average of >50% of the hemoglobin present at birth was removed during the first 30 days of life, and the transfused hemoglobin amount was approximately twice the blood loss from phlebotomy [18]. A study of 98 ELBW infants by Wang et al. reported that pRBC transfusions have a negative impact on survival, increase the risk of retinopathy of prematurity, and affect late neurodevelopment; this particular study found the number of pRBCs transfusions in the first 60 days of life (11.3 ± 4.5) [22] to be higher than what we report in our current study (eight in the first 70 days of life [5, 10]). Wang et al. did not report the number or volume of blood draws in their ELBW population.

Blood draws from heel sticks are one of the most common invasive procedures performed in the NICU, and infants might have as many as 86 during the first 2 weeks of hospitalization [23]. The majority of infants in our cohort had an umbilical catheter in place (94%), for a median duration of 7 days (5, 9), similar to other reports [24]. Nevertheless, in the ELBW infants included in the current study, the presence of umbilical catheters was not associated with an increased number of draws when compared with infants without umbilical catheters.

Our study had several strengths. We extracted the data using high-quality web-based queries, and using detailed orders and collection data to describe the timing and volumes of blood draws and transfusions. During the study period, standardized guidelines on laboratory draw volumes and transfusion were followed. All infants were tracked in the same unit for the entire duration of the study.

Our study had a number of limitations. We did not quantify the impact of blood sampling on hematocrit or hemoglobin levels and did not attempt to separate the impact of blood loss through sampling from the effect of neonatal illness; however, our findings suggest that this level of sampling was often associated with the need for transfusion. Although transfusion guidelines were consistent throughout the study period, transfusion was left to the discretion of the attending physician, and it is possible that our NICU's transfusion guidelines were not always strictly followed. The volume of blood drawn and reported in this manuscript is underestimated since the volume lost in the gauze or syringe was not accounted for. Furthermore, more blood than necessary is frequently collected. For the two outborn infants that were transferred shortly after delivery, we did not account for any blood drawn prior to their admission to our unit. In an attempt to control for neonatal illness, we decided to only include infants with a length of stay of at least 10 weeks, and excluded infants that were transferred or died before 10 weeks of age. As deaths can occur soon after birth and all the way up to several weeks or months of age, the "noise" in this group of patients would make assessment of laboratory draws difficult. Nonetheless, by excluding deaths, we understand that there is the possibility that our reported number and volumes of laboratory draws is lower than in the entire ELBW cohort.

Reduction in the extensive blood draws experienced by ELBW infants is the most promising clinical intervention associated with a reduction in transfusions. Strategies to develop more

restrictive guidelines for laboratory drawing could lead to a reduction in pRBC transfusions [5, 9, 25, 26]. Other methods to reduce pRBC transfusions in the neonatal period could include delayed cord clamping at delivery [27, 28], introduction of more restrictive transfusion guidelines [29, 30], use of erythropoiesis-stimulating agents [31], use of a rounding checklist to review the need for laboratory testing, and decreasing phlebotomy losses by reducing laboratory testing [32], as suggested by our current study. Reducing phlebotomy losses can be achieved by using bedside or in-line laboratory analyzers, implementing a customized blood drawing schedule, decreasing the duration of umbilical catheter insertion [5, 9, 10], and obtaining initial blood tests from the umbilical cord at delivery.

Our study focused on describing the number and volume of blood draws and transfusions during the first 10 weeks of life in a cohort of ELBW infants admitted to a tertiary neonatal unit. We concluded that this fragile population undergoes a high number and volume of blood draws; the trends for the number of blood draws and transfusions were toward a decrease in the first 10 weeks of life, and the number of blood draws decreased as the birth GA increased. The results of this retrospective study strongly support the role of laboratory phlebotomy loss as a main cause of anemia leading to RBC transfusion in the first 10 weeks of life. After implementing more restrictive blood drawing guidelines, a prospective follow-up study using quality-improvement methodology could be beneficial. Our study emphasizes the need for thorough reflection prior to ordering blood sampling in critically ill ELBW infants. Avoiding excessive phlebotomy blood losses that can result in unnecessary blood transfusions remains an important goal for clinicians caring for ELBW infants admitted to the NICU.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Volume of blood drawn by week of life. Volume of blood drawn by week of life in the first 10 weeks of life

Fig. 2.
Volume of blood drawn by gestational age. Volume of blood drawn by gestational age in the first 10 weeks of life

Fig. 3. Volume of blood drawn by birth weight. Volume of blood drawn by birth weight in the first 2 weeks of life

Table 1

Number and volume of blood draws by week of life

Week of life	Number of draws Median (25th, 75th percentile)	Volume of blood (mL/kg) Median (25th, 75th percentile)
1	57 (49, 65)	30 (24, 36)
2	56 (38, 74)	20 (13, 28)
3	48 (29, 67)	17 (10, 24)
4	29 (18, 65)	12 (7, 21)
5	20 (16, 37)	8 (5, 12)
6	16 (11, 28)	6 (4, 9)
7	14 (9, 22)	5 (3, 8)
8	14 (9, 22)	4 (2, 8)
9	12 (8, 18)	3 (2, 6)
10	12 (8, 22)	3 (2, 6)