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ORIGINAL ARTICLE

Using umbilical cord blood for the initial blood tests of VLBW neonates results in higher hemoglobin and fewer RBC transfusions

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OBJECTIVE: We previously described a method for reducing early phlebotomy losses from very low birth weight (VLBW) neonates by obtaining the initial blood tests from otherwise discarded fetal blood from the placenta. In the present study we sought to; (1) measure the feasibility of performing this method in actual practice, (2) test the hypothesis that this method would result in higher hemoglobin concentrations and lower erythrocyte transfusion rates in the first week after birth.

METHODS: We conducted two studies in three Intermountain Healthcare NICUs. The first was a feasibility analysis involving 96 VLBW neonates, measuring the success of obtaining the NICU admission laboratory blood tests this way. The second study used case–control methodology to test the hypothesis that this method would result in a higher blood hemoglobin 12 to 24 h after birth, and a lower proportion receiving an erythrocyte transfusion in the first week.

RESULT: In 91 of 96 VLBW neonates (95%) the initial blood tests were successfully obtained with this method. The success rate was not diminished by delayed cord clamping or cord milking, as it was successful in 35 of 36 (97%) such instances. Cases and controls were well matched on demographic and level of illness comparisons. Among cases the hemoglobin generally increased between birth and 12 to 24 h later, but among controls the hemoglobin generally decreased ($P < 0.05$). In the week following birth fewer cases received vasopressors ($P < 0.01$) and erythrocyte transfusions ($P < 0.001$).

CONCLUSION: We judge that it is feasible to collect the initial blood tests of VLBW neonates using otherwise discarded umbilical cord/placental blood, in that this can be accomplished in about 95% of VLBW deliveries. This method, which can be used in addition to either delayed clamping of the umbilical cord or cord milking, results in higher hemoglobin concentrations, less vasopressor use and fewer transfusions in the first week.

INTRODUCTION

Very low birth weight (VLBW, <1500 g) premature neonates are routinely phlebotomized within the first hours after birth.[1–3] These early blood tests generally include a blood culture, complete blood count with differential and platelet count, state metabolic screen, blood gas, blood glucose determination and occasionally other tests such as coagulation tests, type and cross match, genomic microarray or karyotype. For the smallest patients the initial phlebotomy might equal up to 10% of their blood volume.[4,5] The initial and subsequent phlebotomies during the first days in the NICU can result in a lower blood hemoglobin concentration, and on that basis can cause some to qualify for and receive an early erythrocyte transfusion.

We previously described a method for obtaining all NICU admission laboratory tests using otherwise discarded fetal blood from the umbilical vein, immediately following placental delivery, thereby drawing no blood initially from the neonate.[6,7] We showed that this blood is equivalent to blood drawn from the neonate for all complete blood count parameters.[7] However the feasibility of obtaining blood using this technique in actual practice has not been tested, nor is it clear whether this method results in a higher blood hemoglobin concentration or fewer early transfusions.

We now report a three-center study in Intermountain Healthcare level III NICUs, where we sought to obtain all admission blood tests of VLBW neonates using cord/placental blood, thereby drawing no blood initially from the neonate. We aimed to determine the proportion of VLBW deliveries where attempts to draw blood this was would be successful. We also aimed to determine whether drawing blood this way, thereby initially drawing no blood from the neonate, would result in higher hemoglobin concentrations and fewer erythrocyte transfusions during the week after birth.

METHODS

The study was performed at three Intermountain Healthcare level III NICU's; McKay Dee Hospital, Ogden, Utah Valley Regional Medical Center, Provo, and Dixie Regional Medical Center, St George, Utah, from August 2009 through February 2012. It was accomplished according to a protocol approved by the Intermountain Healthcare Institutional Review Board. Several staff members from each of the participating NICU (generally bed-side NICU nurses) were trained to draw fetal blood from the umbilical vein using the methods detailed in Supplementary Material S1. Training was provided for individuals who worked day shifts and others who worked night shifts. When one of these trained individuals was present at the delivery of a VLBW neonate they made an attempt to draw the

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laboratory blood studies using this method, thereby drawing no blood initially from the neonate. These neonates became the 'cases' in this report, whether or not the attempt was successful (intent to treat analysis). During this same period of time, at the same NICUs, if an individual trained in umbilical vein drawing was not present at the delivery the initial laboratory studies were drawn in the usual way, from the neonate, and these neonates were in a pool from which the matched Controls were subsequently identified.

In deliveries where the new method was to be attempted, the obstetrician placed the placenta in a sterile basin with the umbilical cord clamped. If there were multiples, one clamp was placed on the placental end of the umbilical cord for baby A, two for baby B, and so on. The placenta was then given to the NICU staff for phlebotomy. The umbilical vein at its insertion on the placenta was prepped with povidone iodine and allowed to set for about 60 s (see Supplementary Material S1 for details and illustrations). A sterile 18-gauge needle attached to a 10-ml syringe was used for the phlebotomy. The needle was inserted bevel down to prevent collapse of the vessel wall as the blood was drawn into the syringe. Generally 6 to 7 ml were drawn into the syringe, the appropriate laboratory tubes were filled, a sterile transfer device was used to inoculate the blood culture bottle, generally with 2 to 3 ml, and the spots on the metabolic screen card were filled.

Feasibility of the blood drawing procedure was judged according to whether the blood needed for the initial testing was obtained as planned. Feasibility was associated with the variables of gestational age, type of delivery (vaginal or cesarean section), singleton vs multiple, whether or not a placental abruption was identified, and whether delayed cord clamping or cord milking was performed prior to cutting the umbilical cord.

'Cases' (VLBW deliveries where the intent was to draw the baseline laboratory studies from cord/placental blood and not from the neonate) and 'controls' (no attempt was made to draw the baseline laboratory studies this way) were matched 1:1 on the basis of birth weight ± 200 grams, gestational age ± 2 weeks, gender, severity of illness (SNAPPE II) scores ± 10 (ref. 8) and maternal receipt of antenatal steroids.

Blood hemoglobin concentrations measured at the time of delivery were compared with repeat values obtained 12 to 24 h later. The proportion of neonates that received treatment with a vasopressor (dopamine or dobutamine) and the proportion that received one or more erythrocyte transfusions in the first seven days, and the number of erythrocyte transfusions per neonate in the first seven days, were compared between the cases and controls. Transfusions were given according to established guidelines, and compliance with these guidelines has been measured at $>95\%$ in the Intermountain Healthcare system.[9,10] The erythrocytes transfused were supplied by the American Red Cross Blood Center, Salt Lake City, UT and were irradiated, leukoreduced, stored in CPDA-1 and not washed before transfusion.

Means and s.d. were used to express values in groups that were normally distributed, mean with interquartile range in those that were not. Differences in categorical variables were assessed using a χ^2 test or Fisher's exact test, or a Mann–Whitney U test. Statistical significance was set as $P < 0.05$.

RESULTS

Drawing the admission laboratory blood tests using this method was successful in 91 of 96 (95%) VLBW deliveries where it was attempted, including eight of nine born at 23 to 24 weeks gestation. The gestational ages of the five with unsuccessful draws was 26 ± 1.4 weeks and the 91 with successful draws was 27.9 ± 2.8 weeks, $(P = 0.160)$. Thirty-four of the 96 cases were twins or triplets and 31 (91%) of these had successful draws. Seventy-two of the 96 had a Cesarean section delivery, 67 (93%) of which had successful draws. Twenty-four were vaginal deliveries and 11 had a placental abruption, and all of these had successful draws. Delayed clamping of the umbilical cord or cord stripping was practiced in 36 cases, and drawing all admission laboratory tests from the placenta was successful in 35 (97%) of these.

As shown in Table 1, the cases and controls were well matched on birth weight, gestational age, gender, race, SNAPPE II score and maternal receipt of antenatal steroids. The initial blood hemoglobin concentrations did not differ between cases and controls. A subset of 36 of the 96 cases had either delayed cord clamping or cord stripping performed before the attempt to obtain the initial

Table 1. Adequacy of the case/control matching process, using demographic and level of illness indicators

	Cases n = 96	Controls n = 96	P-value
Birth weight (g)	1005 ± 289	1000 ± 315	0.910
Gestation (w/d)	28 ± 3	28 ± 3	0.800
Male (%)	51 (53%)	51 (53%)	1.000
White (%)	76 (79%)	79 (82%)	0.583
Snappe II score	21 ± 19	22 ± 19	0.834
Maternal steroids (%)	87 (90%)	87 (90%)	1.000

Abbreviations: d, days; w, weeks.
The cases were VLBW infants where the intent was to draw the blood tests for NICU admission (blood culture, complete blood count with differential count and platelet count, and state metabolic screen) from the umbilical vein near the placenta, with no blood drawn from the neonate. This method was accomplished as planned in 91 of the 96 (all 96 are included in the intent-to-treat analysis). The controls were VLBW infants during the same time period where the NICU admission blood tests were drawn from the neonate. Data are shown as mean ± s.d. or percent.

blood tests using this new method (Table 2). A follow-up hemoglobin was obtained 12 to 24 h later in 33 of these 36, and was about $2\,g\,dl^{-1}$ higher than it had been at birth, however their 33 matched controls had a hemoglobin about $1\,g\,dl^{-1}$ lower than at birth (controls had no delayed clamping or milking and no attempt to draw the initial blood sample from the cord/placenta). Similarly, the cases who did not have delayed cord clamping or cord stripping performed had a higher hemoglobin 12 to 24 h later than did their matched controls (Table 2).

Also shown in Table 2, during the first seven days following birth, the cases were treated less commonly with vasopressors and with erythrocyte transfusions. This was so among the cases who had been subjected to delayed clamping/milking, and also among the cases who had not.

Eighty-nine of the 96 cases, and 95 of the 96 controls, had one or more head ultrasound examinations prior to hospital discharge (the others had no head ultrasound examinations ordered). Twelve percent of the cases (11/89) had a severe (grade $\geqslant$ 3) IVH compared with 21% (20/95) of the controls ($P = 0.115$). Bilateral severe IVH was identified in 10% (9/89) of the cases vs 18% (17/95) of the controls ($P = 0.096$).

DISCUSSION

Erythrocyte transfusions can provide critical benefits to NICU patients, but they also carry risks.[11] Indeed, safely reducing blood transfusions for neonates, children and adults is an international priority.[12,13] VLBW neonates often need transfusions owing to their small blood volume and the number of blood tests ordered to assist critical care decisions. Previous techniques shown to reduce transfusion rates among VLBW neonates include delayed clamping of the umbilical cord,[14–17] 'stripping' or 'milking' of the umbilical cord,[18–20] implementing written guidelines for transfusions,[1,21] limiting phlebotomy losses[4,22] and early recombinant erythropoietin administration.[1,21,22,23] The present study tested yet another method; drawing all initial blood tests from otherwise discarded fetal blood in the placenta, thereby initially drawing no blood from the VLBW neonate.[5–7,11]

We found this technique for initial phlebotomy to be feasible in actual practice, because it was accomplished in 95 percent of the VLBW deliveries where it was attempted. We recognize that this was accomplished using trained personnel, and to have this same level of success in other centers, training and practice would surely be needed (see Supplementary Material). We also found that sufficient blood remains in the umbilical vein for drawing after delayed clamping or stripping. Thus, it appears to us that one

Table 2. Cases (initial blood tests drawn from placenta/cord) were matched 1:1 with controls (initial blood tests drawn from neonate)

	Cases with delayed clamping or milking	Matched controls	P-value	Cases with no delayed clamping or milking	Matched controls	P-value
Change in hgb in the first 12 to 24 h after birth (mean, interquartile range)	+2.0 g dl^{-1}; −0.2 to 3.5 ($n=33$)	−1.0 g dl^{-1}; −1.9 to −0.1 ($n=33$)	<0.001	+0.5 g dl^{-1}; −0.7 to 2.0 ($n=55$)	−0.5 g dl^{-1} −1.3 to 0.7 ($n=55$)	<0.05
Vasopressors	17% 6/36	61% 22/36	<0.001	8% 5/60	30% 18/60	0.003
One or more erythrocyte transfusions	25% 9/36	64% 23/36	<0.001	25% 15/60	42% 25/60	0.05
Number of erythrocyte transfusions per patient (mean; interquartile range)	0.6; 0 to 0.5	2.2; 0 to 4	<0.001	0.4; 0 to 0.5	1.2; 0 to 2	0.001

Abbreviation: hgb, blood hemoglobin concentration.
Comparisons were; (1) change in blood hemoglobin concentration between birth and 12 to 24 h later, (2) proportion that received vasopressors in the seven days following birth, and (3) proportion that received erythrocyte transfusions in the seven days following birth. Data from all cases were included (intent-to-treat analysis) even though the procedure was unsuccessful in five. Cases subjected to delayed cord clamping or cord milking are compared with their matched controls. Similarly, cases not subjected to delayed cord clamping or milking are compared with their matched controls.

or the other of these two placental transfusion techniques (delayed clamping or stripping), plus our method of drawing the initial blood tests, might be additive in the benefits of keeping the hemoglobin higher and the early transfusion rate lower.

We found that when the initial blood samples were drawn from the cord/placenta and not from the neonate, vasopressors were used less commonly in the first days after birth. This is similar to the reports of improved hemodynamic stability after delayed cord clamping and after cord milking,[14–20] which we assume to be on the basis of slightly higher blood volume. Although validation is needed for the technique we describe in this report, including repeating the experience in other centers, it seems to us that it is a simple and practical way to reduce early transfusions in the VLBW population.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Journal of Perinatology website (http://www.nature.com/jp)