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Is There a Role for Autologous/Placental RBC Transfusions in the Anemia of Prematurity?

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Abstract

Because most extremely preterm infants with birth weight <1,000 g need red blood cell transfusions, many attempts have been made to collect, process and store placental blood (i.e., umbilical cord blood) for autologous transfusions. Although it is feasible to do this, multiple problems in doing so including insufficient volumes collected, clotting, hemolysis, bacterial contamination, failure to significantly supplant need for allogeneic transfusions, and high costs have led many to question whether, on balance, autologous/placental RBC transfusion offers clinically significant benefits.

Keywords

placental blood; umbilical cord blood; neonatal RBC transfusions; neonatal/infant autologous RBC transfusions

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The short answer to the question posed by the title of this paper as to whether there is a role for autologous/placental RBC transfusions in the anemia of prematurity is “Little, at best.” The more complete and accurate answer at present is “It depends on several factors and what is desired to be achieved.” This paper will critically assess published information pertaining to these “several factors and desired achievements.”

Need for RBC Transfusions

Preterm infants with birth weight <1,000 g (commonly designated as extremely low birth weight, or ELBW, infants) have completed ≤ 29 weeks gestation, and nearly all will need RBC transfusions during the first weeks of life. Every week in the United States, approximately 10,000 infants are born prematurely (i.e., <37 weeks gestation) with 600 (6%) of these infants being ELBW (1). Approximately 90% of ELBW neonates will receive at least 1 RBC transfusion (2,3). Physiological and non-physiological factors related to prematurity are responsible for this high transfusion rate, with laboratory blood loss as perhaps the biggest contributor (4). Because of efforts to minimize the amounts of blood drawn from neonates for laboratory testing (5), and to transfuse more conservatively (i.e., to accept lower pretransfusion hematocrit values), the number of RBC transfusions given to preterm infants has dropped over the years (2,6), with the mean value $\pm$ SD during years 2000 to 2005 of RBC transfusions given

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to each transfused ELBW infant at the University of Iowa Hospitals & Clinics being 5.4 compared to 1.1 for premature per infant with birth weights from 1,001 to 1,500 g (Table 1). Thus, the 600 ELBW infants born each week in the U.S. (1) receive approximately 3,240 RBC transfusions during their hospitalization, with 60 to 80% of these given within three to four weeks following birth.

The vast majority of RBC transfusions given to ELBW infants are “small volume” and consist of 10 to 20 mL per kg (of the infant's weight on the day of transfusion) of allogeneic RBCs stored in preservative solution at an hematocrit of ~55% (42-day storage permitted in AS-1, AS-3, AS-5 solutions) or ~70% (35-day storage permitted in CPDA solution). Although the known infectious risks of RBC transfusions from each donor exposure are extremely small, and decreasing over time with improvements in donor screening and laboratory infection surveillance, efforts have been made to limit transfusions and consequent donor exposures to the fewest number possible (3,7,8). Following this rationale/philosophy to limit exposure to allogeneic donors, it is logical to explore whether some small-volume RBC transfusions, or even all for some infants, might be given as autologous/placental RBCs.

Placental Blood Collection & Storage

Although attempts have been made since the 1970s to collect, store and transfuse blood from the placenta/umbilical cord, most technical advances have been made via systematic investigations to collect hematopoietic/immunologic stem cells from placental/umbilical cord blood for transplantation. In initial studies of autologous/placental blood transfusions, collection and storage methods were quite variable, and several significant problems occurred including collection of insufficient volumes of placental blood for meaningful transfusions, clots forming both during collection and/or storage, and bacterial contamination. Large clots that occur in needles and tubing during collection prevent obtaining sufficient volumes for processing and transfusion. Small clots, of course, can be removed at the time of transfusion by filtration, but the possibility exists that activated hemostatic and fibrinolytic factors might be infused and cause adverse effects. Highly variable rates of bacterial contamination ranged from zero to 28% of collections (9-21) in reports through the year 2000. Some institutions experienced a “learning curve” as the highest rates occurred during initial collections, but were reduced by refinements of technique including donor selection (10,19). However, even in reports after 2000, bacterial contamination was detected in up to 13% of units (22-25). Thus, it is critically important to carefully consider the threat of bacterial contamination whenever transfusing placental blood/RBCs and to take appropriate steps for appropriate case selection and for quality assurance/control (e.g., surveillance cultures of collected units) (26).

The rate at which sufficient volumes of quality placental blood have been collected successfully for subsequent processing, storage and transfusion has varied greatly. As expected, total/actual volumes collected are greater with term than preterm neonates. However, when expressed as milliliters per body weight, the expected volume is about 20 mL/kg of whole blood with a hemoglobin concentration varying from 12 to 16 g/dL, depending on gestational age (13,14, 21,24,25). Volumes collected successfully from the placenta vary greatly among individual infants, particularly for the smallest of preterm neonates who are the most challenging. Most successful collections followed vaginal delivery, while the placenta is still *in utero*, are accomplished by cleaning the cord surface, inserting a needle into the umbilical vein, and then draining the placental blood via gravity into a collection bag containing citrate anticoagulant. Following Cesarean section, the placenta is usually delivered and placed on a sterile surface before cord cleansing, needling of the umbilical vein and drainage of placental blood by gravity. In addition to gravity drainage, many investigators have utilized additional steps of aspirating blood from umbilical cord vessels into syringes containing anticoagulant. When adequate volumes are collected without inducing clotting and/or hemolysis, *in vitro* studies of RBC

biochemistry and function demonstrate satisfactory storage (12,27). More sophisticated studies of post-transfusion short- and long-term RBC survival in the circulation and microvascular flow of placental RBCs in human infants have not been reported.

Transfusion of Placental Blood/RBCs to Human Infants

When considering the possible merits of collecting placental blood for autologous transfusion, it is important to remember that most ELBW infants with body weight < 1,000 g need multiple RBC transfusions, whereas most infants cared for in the NICU with body weight >1,000 g are not transfused (Table 1). Moreover, when ELBW infants are transfused, they often need three to five (sometimes even more) RBC transfusions of 15 ± 5 mL/kg volume during the first 3 to 4 weeks of life (sometimes even longer). Thus, in our view, to really make a clinically significant difference among the ELBW infant group, “success” should be defined as the ability to collect, process, store and transfuse enough placental RBCs to satisfy all needs of the infant from whom the placental blood was collected or, at least, the amount needed for two transfusions. Based on infants with birth weights from 1,000 to 1,500 g having a 5-fold lower RBC transfusion requirement (Table 1), success is more readily achievable in this group in which 35 to 55% of infants are transfused.

In one of the earliest studies, neonates who were hypotensive at or shortly after delivery received placental blood transfusions, up to 12 hours following birth, that had been collected from the placenta/umbilical vein into heparinized syringes (20). Although details in this report are somewhat sketchy, approximately 50 mL of placental blood were available for each infant, with 25 mL/kg being successfully transfused to treat shock without apparent adverse effects.

Subsequent clinical studies report varying success (13,15,21,24,25), and four will be discussed further (13,15,25,28). Brune et al. reported two clinical studies, but it is not clear if the infants were entirely separate in the two reports or overlap. In the first report (13), a preclinical study was first performed in 141 term and preterm infants to establish the ability to collect placental blood and to estimate success in providing a 10 mL/kg RBC transfusion, if needed. It was estimated that one 10 mL/kg transfusion would have been possible for 72.5% of the 131 infants for whom placental blood could be obtained. In only 16% of infants was enough placental blood collected for two transfusions. Of the 22 infants who actually were transfused following the preclinical study, 11 (50%) received only autologous/placental RBC transfusions; the other 50% needed additional allogeneic transfusions (13).

In their later report (28), Brune et al. reported 52 infants who received autologous/placental RBC transfusions. Every neonate (100%) with a birth weight <1,000 g and 91% of infants requiring surgery for necrotizing enterocolitis received allogeneic RBC transfusions in addition to their autologous/placental RBCs. Only 41% of infants with birth weight 1,000 to 2,500 g received exclusively autologous/placental RBCs (i.e., 59% needed allogeneic RBC transfusions). Autologous/placental RBCs were stored for 23 ± 12 days before transfusion, and the transfusions were efficacious and safe. However, the need for allogeneic RBC transfusions by the majority of infants raised questions about the merits of collecting, processing, storing and transfusing placental RBCs in this particular group of infants, some of whom required surgery for necrotizing enterocolitis (28).

Eichler et al. (15) attempted collection of placental blood from 43 preterm deliveries and was successful in 35 (81%). Three of the 35 were contaminated with bacteria, leaving 32 (74%) available for possible autologous transfusion. RBC transfusions were given to 21 infants with a birth weight of $1,286 \pm 584$ g and gestational age 30.0 ± 3.5 weeks. Of the subset of infants with birth weight 670 to 1,000 g, 46 allogeneic and only 2 autologous/placental RBC transfusions were given. Of infants with birth weight 1,001 to 1,500g, 9 allogeneic and only 1 autologous/placental RBC transfusion were given. Of infants with birth weight 1,501 to

3,310 g, 7 allogeneic and 1 autologous/placental RBC transfusion were given. Overall, no infants were supplied exclusively with their own autologous/placental RBCs! Importantly, most infants with birth weight >1,400 g did not need any RBC transfusions. The authors rightfully concluded that the preparation of placental RBCs for autologous transfusion is feasible, but major concerns exist as to their actual clinical benefits or from a cost-effectiveness perspective (25).

In 2008, Khodabux et al. (25) attempted placental blood collection in 176 deliveries of neonates with gestational age <32 weeks. Of the attempts, 101 (57%) yielded ≥ 15 mL/kg of placental blood (excluding anticoagulant) and thus were deemed sufficient to permit further processing and storage. When all volumes of placental whole blood were included, 16 ± 15 mL/kg was collected for neonates with birth weight <1,000 g, 18 ± 18 mL/kg for neonates 1,000 to 1,250 g, and 20 ± 23 mL/kg for neonates >1,250 g. Of the 101 collections that could be processed, only 64 of the 176 deliveries (36%) yielded satisfactory units for transfusion (25). For neonates most likely to need RBC transfusions (<1,000 g birth weight or gestational age <29 weeks), only 17% of placental blood collections were available for autologous RBC transfusions. Among 67 neonates who were given an average of 2.5 transfusions per infant, use of autologous/placental RBCs decreased need for allogeneic RBC transfusions by only 15%. The authors concluded that, although sufficient placental blood could be collected to theoretically replace 27% of allogeneic RBC transfusions, clinical benefit could not be determined because so few of the autologous/placental RBC units actually were transfused (25).

Conclusions

Because nearly all preterm ELBW infants with birth weight <1,000 g (gestational age <29 weeks) receive RBC transfusions, it is logical to consider whether some of these transfusions could be supplied by autologous/placental blood collected at delivery, processed and stored for transfusion within the first weeks of life. Clearly, it is possible to collect placental blood from both vaginal and Caesarean deliveries and to store it for short periods of time, e.g., up to 28 d (27), while maintaining satisfactory quality. However, problems with obtaining sufficient volumes, with clotting and hemolysis, and with bacterial contamination are frequent – especially, until experience/skill is developed with the technique. These problems are particularly frequent in the most premature/smallest ELBW neonates – the very ones most likely to need RBC transfusions. In the reports with the greatest number of study infants, autologous/placental transfusions could supplant only a minority of RBC transfusions needed by the infants, and the cost of autologous/placental RBC transfusion ranged from 6.5 to 15 times higher than allogeneic RBC transfusions! (25)

As an alternative to collecting, processing and storing placental blood for later autologous transfusions, several reports suggest the feasibility and benefits of delayed clamping – rather than immediate – of the umbilical cord (29,30). Advantages for delayed cord clamping reported by some, but not all studies, include higher hematocrit or RBC volume/mass, higher blood pressure, fewer RBC transfusions, and lower rates of intraventricular hemorrhage in neonates experiencing delayed clamping. Delayed clamping of the umbilical cord can be technically difficult in very preterm neonates, particularly those requiring immediate resuscitation. As an alternative to delayed clamping, brief “milking” of the cord has been reported as a safe measure to increase neonatal hemoglobin values and to decrease RBC transfusions (31).

In the more distant future, it is possible that other scientific advances may make autologous transfusion with placental blood effective from both clinical and cost perspectives. For example, if laboratory phlebotomy losses can be significantly reduced by emerging point-of-care testing coupled with nanotechnology and/or non-invasive testing of critical analytes, then the relatively small volumes of autologous/placental blood available at delivery may be

sufficient in providing all of the RBC transfusion needs of significantly more very preterm infants. It is also possible that expansion of autologous hematopoietic progenitors *ex vivo* may someday become a more plentiful source of autologous RBCs. While the first of these two possibilities relies on safely obtaining adequate volumes of placental blood as described above, the expansion of autologous hematopoietic progenitors does not. It seems likely that neither of these possibilities will occur in the near future.

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Table 1

RBC Transfusions Administered to Infants from 2000 to 2005 for the University of Iowa Children's Hospital

	<u>2000</u>	<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>	<u>Total for 2000-2005</u>
<u>Infants ≤ 1.0 kg</u>							
Number of Infants	69	57	78	61	69	83	417
Number (%) of Infants receiving ≥ 1 transfusion	63 (91%)	50 (88%)	70 (90%)	55 (90%)	57 (83%)	64 (77%)	364 (87%)
Mean number of transfusions per infant	3.9	6.1	6.4	5.9	5.6	5.0	5.4
<u>Infants 1.0-1.5 kg</u>							
Number of Infants	63	67	54	70	79	69	402
Number (%) of Infants receiving ≥ 1 transfusion	34 (54%)	32 (48%)	20 (37%)	30 (43%)	28 (35%)	27 (39%)	171 (42%)
Mean number of transfusions per infant	1.1	1.5	1.0	1.1	1.0	1.2	1.1
<u>Infants 1.5-2.5 kg</u>							
Number of Infants	208	232	231	208	243	259	1,382
Number (%) of Infants receiving ≥ 1 transfusion	36 (17%)	22 (10%)	31 (13%)	18 (9%)	14 (6%)	10 (4%)	132 (9.5%)
Mean number of transfusions per infant	0.38	0.43	0.37	0.47	0.26	0.17	0.34
<u>Infants ≥ 2.5 kg</u>							
Number of Infants	1,147	1,268	1,338	1,388	1,485	1,510	8,141
Number (%) of Infants receiving ≥ 1 transfusion	58 (5.1%)	58 (4.6%)	68 (5.1%)	51 (3.7%)	22 (1.5%)	6 (0.4%)	263 (3.2%)
Mean number of transfusions per infant	0.24	0.26	0.28	0.40	0.11	0.03	0.21