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Posttransfusion 24-hour recovery and subsequent survival of allogeneic red blood cells in the bloodstream of newborn infants

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Abstract

Background—The feasibility, efficacy, and safety of transfusing stored allogeneic RBCs has been demonstrated for small-volume transfusions given to infants. We measured the posttransfusion recovery and intravascular survival of allogeneic RBCs stored up to 42 days to further elucidate their efficacy.

Study Design and Methods—Preterm infants were transfused with 1.0 mL of biotinylated RBCs plus 15 mL per kg of unlabeled allogeneic RBCs. Posttransfusion infant blood samples obtained at 10 minutes, and at 1, 2, 4, 7, 10, 14, and 21 days were used to determine the 24-hour posttransfusion recovery (PTR₂₄), mean potential life span (MPL), and time to disappearance of 50 percent of biotinylated RBCs (T₅₀).

Results—No significant differences were found between allogeneic RBCs stored 1 to 21 days versus 22 to 42 days for PTR₂₄, MPL, or T₅₀, indicating comparable posttransfusion circulation, regardless of storage age. Although MPL and T₅₀ values in infants using biotinylated RBCs were short, compared to those expected using chromium-labeled RBCs in adults, they agreed with results reported by others using biotinylated RBCs.

Conclusions—Satisfactory posttransfusion RBC recovery and survival, measured with biotinylated RBCs, support earlier clinical trials that established the efficacy and safety of stored allogeneic RBCs for small-volume transfusions given to infants. The relatively short MPL and T₅₀ values in some infants may underestimate true survival due to ongoing erythropoiesis and infant growth with commensurate increase in blood volume during the time of RBC survival studies. Because values in infants differ from those expected using chromium-labeled RBCs in adults, and the number of posttransfusion determinations was few, additional studies are needed to define the mechanisms involved.

Most extremely preterm infants (<1.5kg birth weight) receive red blood cell (RBC) transfusions during the first few weeks of life—particularly, those weighing less than 1.0kg with cardiopulmonary illnesses.^{1,2} Although many factors contribute to the anemia of prematurity,³ the major mechanism responsible for RBC transfusions given during the 1st month of life is the inability to compensate for blood drawn for laboratory testing. Concerted efforts to minimize volumes of blood taken for laboratory testing,⁴ to increase erythropoiesis with combined recombinant EPO (rEPO) plus iron therapy,⁵ and to transfuse RBCs conservatively⁶ have diminished the number of RBC transfusions given to some infants.

Nonetheless, allogeneic RBC transfusions remain the mainstay of therapy for the anemia of prematurity.

To decrease donor exposure and, thereby, to lower allogeneic transfusion risks, several groups of investigators have recommended that small-volume RBC transfusions ($\cong 15$ mL/kg infant weight) be issued as small aliquots from a single unit of RBCs reserved for a specific infant and stored for up to 42 days.⁷ The feasibility, efficacy, and safety of allogeneic RBCs obtained from stored units for multiple small-volume transfusions have been documented to be indistinguishable from fresh RBCs—the latter defined as RBC units stored no more than 7 days after collection. Specifically, the posttransfusion increases in blood Hct levels, changes of pretransfusion versus post-transfusion blood chemistry results, and rates of transfusion reactions—the last being remarkably rare—were comparable whether stored or fresh allogeneic RBCs were transfused.⁷

In the current report, the efficacy of transfusing stored allogeneic RBCs was further elucidated by measuring the 24-hour posttransfusion recovery (PTR_{24}) and subsequent intravascular survival of RBCs obtained from blood bank units, labeled with biotin^{8,9} and then transfused into preterm infants for measurements of circulating kinetics.

Materials and Methods

Study subjects

Infants studied with biotinylated RBCs were a subset of preterm infants previously reported¹⁰ as a randomized, partially-blinded trial that established the equivalent efficacy and safety of small-volume transfusions of allogeneic RBCs obtained from either the biologic parents of study infants or unrelated blood center donors. To summarize briefly, the study was approved by the Institutional Review Board, and parents gave written consent. Donor RBCs were collected either from biologic parents or unrelated adults and were stored for up to 42 days in AS-3 preservative solution (Leukotrap RC System, Medsep, Covina, CA). As reported earlier,¹⁰ posttransfusion increases in blood Hct, changes in blood chemistry results, and clinical safety were comparable with RBC units obtained from parents versus units from unrelated donors, and, importantly, results were similar to other studies comparing transfusions of fresh versus stored RBCs collected from standard blood center donors.^{7,11,12} For example, the posttransfusion increase in blood Hct (mean $\pm$ SD) after a transfusion of 15 mL per kg of fresh RBCs (stored ≤ 7 days after collection) from unrelated donors was 11.9 ± 5.1 percent versus an increase in Hct of 11.7 ± 4.4 percent from RBCs stored up to 42 days.¹¹ A similar increase in Hct occurred after the transfusion of stored RBCs obtained from biologic parents, 11.6 ± 4.6 percent (paternal) and 11.8 ± 3.9 percent (maternal).^{10,11} Nearly identical increases in Hct ($12 \pm 5\%$ versus $12 \pm 4\%$) were found comparing transfusions of RBCs stored 0 to 21 days versus RBCs stored 22 to 42 days in AS-3 preservative solution.⁷ Thus, extensive data support the overall clinical efficacy of stored RBCs and refute the need to use fresh RBCs when small-volume transfusions are given to infants.

Fifteen of the 40 infants (38%) enrolled in the previously reported clinical trial¹⁰ were studied using biotinylated RBCs to assess posttransfusion circulating kinetics for the current report. Technical issues precluded study of all 40 infants—specifically, the length of time required to biotinylate an aliquot of allogeneic RBCs before transfusion and the need to coordinate interlaboratory shipping of blood samples, as described in the following section, mandated that all study transfusions be performed during regular working hours. Thus, the timing of the transfusions was the only determining constraint, with the clinical condition of study infants not being a selection criterion for the biotinylated-RBC studies.

Of the 15 infants studied, one was excluded subsequently because posttransfusion blood samples were hemolyzed to preclude analysis. PTR₂₄ was determined for all 14 remaining infants. None of the 14 received a second transfusion within 24 hours after the study transfusion—the time during which blood samples were obtained for PTR₂₄ analysis (an experimental critical factor)—because a second transfusion during sampling would confound the measurement. Results of posttransfusion RBC survival beyond the first 24 hours will be reported for 8 of the 14 infants. The other six infants, for whom RBC survival will not be reported, were given additional RBC transfusions during the 3 weeks after infusion of biotinylated RBCs, precluding accurate determination of the T₅₀ and mean potential life span (MPL)—the two measures used to determine posttransfusion, long-term RBC survival. The rationale for exclusion is that subsequent transfusions of allogeneic nonbiotinylated RBCs would dilute the circulating biotinylated RBCs transfused earlier to artifactually shorten RBC survival results. Infants were not excluded if they experienced phlebotomy blood losses during the period of study because blood sampling removed biotinylated and unbiotinylated RBCs in equal proportions and, thus, did not alter RBC survival as determined by measuring the percent of biotinylated RBCs circulating in the bloodstream after transfusion. None of the infants received rEPO, which might have accelerated erythropoiesis, even beyond that occurring naturally, to greatly increase the number of endogenous unbiotinylated RBCs in the bloodstream.

Studies using biotinylated RBCs

Biotinylation of RBCs—The method to biotinylate RBCs has been previously reported,⁸ including modifications for preterm infants.¹³ Use of this method for short-term and long-term RBC survival has been validated against ¹⁴C-cyanate in sheep¹⁴ (and unpublished data) and ⁵¹Cr in adult human volunteers.⁹ Briefly, the RBC wash solution was prepared by the addition of 4 mL of 50-percent dextrose (Baxter, Deerfield, IL), 20 mL of 8.4-percent sodium bicarbonate (American Reagent Laboratories, Shirley, NY), and 1 mL sodium phosphate (American Reagent Laboratories) to 1 L of 0.9-percent sodium chloride. Osmolarity for this solution is 356 mOsm per L. A 0.04-mg-per-mL solution of sulfo-N-hydroxysuccinimide biotin (sulfo-NHS biotin; Pierce, Rockford, IL) was prepared in wash solution and filter-sterilized immediately before use. One mL of sulfo-NHS biotin solution was added to 1 mL of washed RBCs that had been resuspended in wash solution to the original Hct. The mixture was incubated at room temperature for 30 minutes. The RBCs were washed 4× to remove unreacted biotinylating reagent.

The exact weight of biotinylated RBCs infused was determined gravimetrically. After allowing 10 minutes for mixing within the infant's circulation, a 0.2-mL sample of venous blood was taken by venipuncture or from the unwarmed heel of a limb, other than the one used for infusion of biotinylated RBC, using a standardized capillary sampling device (Tenderfoot, International Technidyne, Edison, NJ). The number of biotinylated RBCs, as a percentage of total RBCs in the sample (biotinylated plus unbiotinylated RBCs), was measured by flow cytometry to enumerate the biotinylated RBCs remaining in the circulation.⁸ Flow windows were set to exclude the few cells exhibiting features of cell fragments, and the standard number of RBCs counted per each determination was 200,000. The overall process of using RBCs prepared and detected as described above to determine RBC survival was granted United States Patent #5,536,643, July 16, 1996, titled “Non-radioactive method for determining circulating red cell volume, total blood volume, and red cell survival.”

RBC survival—RBC survival is a general term for the persistence of RBCs within the circulation. In this study, three measures of RBC survival were determined: 1) post-transfusion recovery after 24 hours (PTR₂₄); 2) mean potential RBC life span (MPL); and 3) time to disappearance of 50 percent of biotinylated RBCs (T₅₀). Infant blood samples were obtained

at 10 minutes after transfusion and at approximately 1, 2, 4, 7, 10, 14, and 21 days thereafter. Survival variables were determined from these measurements as follows:

PTR₂₄: PTR₂₄ reflects the intravascular recovery of RBCs 24 hours after transfusion. PTR₂₄ was calculated as the percentage of biotinylated RBCs circulating 24 hours after transfusion minus the percentage of biotinylated RBCs circulating 10 minutes after transfusion divided by the percentage of biotinylated RBCs circulating 10 minutes after transfusion.

MPL: In the steady state of a healthy adult subject (i.e., an individual with stable body size, unlike a rapidly growing infant with constantly changing body size), an equal number of RBCs are produced and removed from circulation per unit of time. Accordingly, the population distribution for the age of RBCs is even. If all RBCs are uniformly labeled, survival curves will demonstrate a linear decline. The percentage of biotinylated RBCs was measured, expressed as a percentage of the value at Day 0 (10-min sample) and plotted versus time. Data were fitted by least squares. The value obtained by extrapolation of this linear disappearance curve to the time axis is referred to as the MPL. The MPL reflects the average life span from the time that the RBCs are infused into circulation until they are removed.

T₅₀: Time to disappearance of 50 percent of the biotinylated RBCs is denoted T₅₀. T₅₀ was determined from the 50-percent point of the linear regression line described above for MPL. In essence, the MPL and T₅₀ provide similar information, but expressing both results permits more complete comparison with other reports in the literature.

Statistics

Overview of clinical trial—The major objective of the reported¹⁰ randomized clinical trial was to determine whether RBCs collected from biologic parents and stored up to 42 days in AS-3 could satisfy all RBC needs of preterm infants as safely as RBCs collected from unrelated blood donors and stored identically. The hypothesis tested was that changes in laboratory results would not differ after transfusions of RBCs from parental versus unrelated donors. We wished to detect differences in mean values of analytes equal to or greater than their SDs at an alpha equal to 0.05 and a statistical power of at least 0.70. Per these assumptions, 40 preterm infants were enrolled, 20 into each of the two study arms.

Biotinylated-RBC studies—As explained previously, only certain RBC transfusions given during the clinical trial included biotinylated RBCs. Student's t test was used to determine significance of differences in results of PTR₂₄, T₅₀, and MPL between RBCs stored 1 to 21 days versus RBCs stored 22 to 42 days.

Results

Transfusions of biotinylated plus unlabeled RBCs

Each RBC transfusion consisted of 1.0 mL of biotinylated RBCs infused plus unlabeled allogeneic RBCs given per institutional transfusion practice guidelines at a dose of 15 mL per kg infant body weight. The biotinylated RBCs were prepared from the same allogeneic unit from which the unbiotinylated RBCs were obtained. All donor RBC units were either group O or of identical ABO group with the infant. The RBC unit age (i.e., median days of storage after collection) on the day of transfusion was 24 days (range, 3-42 days). Of the 14 transfusions, 7 consisted of RBCs stored for the relatively brief period of 1 to 21 days, and 7 consisted of RBCs stored for the longer duration of 22 to 42 days.

Median postpartum age of the infants at the time the study transfusion was 40 days (range, 16-54 days). Mean infant weight at the time the study transfusion was 1.424 kg (range,

0.768-2.160 kg)—compared to a mean birth weight of 0.948 kg. For the eight infants undergoing determinations of posttransfusion T_{50} and MPL, growth—defined as the percentage of body weight increases per day from the day biotinylated RBCs were transfused (Day 0) until the last blood sample was drawn (Day 14-27)—were 0.71 to 2.38 percent (mean, 1.88%; median, 2.22%) (Table 1). All infants experienced phlebotomies for laboratory testing during the biotinylated-RBC study, but none were given additional RBC transfusions during that time.

Posttransfusion circulating RBC kinetics

The storage age, posttransfusion survival data, and rate of growth are presented in Table 1 for all eight transfusions with determination of T_{50} and MPL. There was no apparent relationship between RBC survival and either the duration of RBC storage or infant growth. No significant differences were found between allogeneic RBCs stored 1 to 21 days versus 22 to 42 days (Table 2) for PTR_{24} , T_{50} , or MPL after small-volume transfusions. Mean values of the two groups were similar (Table 2). Pooled data (mean $\pm$ SD) for all RBC transfusions, regardless of RBC storage duration, were $PTR_{24} = 97.8 \pm 5.8\%$ ($n = 14$), $T_{50} = 42.6 \pm 10.7$ days ($n = 8$), and $MPL = 85.2 \pm 21.5$ days ($n = 8$).

Discussion

No significant differences of posttransfusion RBC 24-hour recovery and survival were found when transfusions of allogeneic RBCs stored for the relatively brief period of 1 to 21 days were compared to transfusions of RBCs stored for the longer duration of 22 to 42 days. Although the number of transfusions studied was too few to confidently exclude the possibility that small significant differences might have gone undetected (i.e., a beta-type error), the actual mean values were quite similar between the two groups and, importantly, did not suggest diminished survival of RBCs stored for the longer duration (i.e., T_{50} and MPL values actually were slightly greater for RBCs stored 22-42 days vs. 1-21 days). These results, using biotinylated RBCs to directly measure posttransfusion RBC circulating kinetics in the bloodstream of infants, support the clinical and laboratory observations of earlier reports that stored RBCs are safe and efficacious for neonatal small-volume RBC transfusions.^{7,11,12}

Our results of PTR_{24} document the satisfactory quality of RBCs stored up to 42 days, which, by FDA requirements for approval, must exhibit 75-percent recovery at 42 days of storage.^{15,16} Our value of approximately 97 percent agrees with our earlier studies of normal adults⁹ and with the value of 97 percent reported for baboons using fresh biotinylated RBCs.¹⁷ Results with biotinylated RBCs are higher than those using chromium as the RBC label—mean values being approximately 83 percent for human chromium-labeled RBCs stored 42 days^{15,16} and 92 percent for fresh baboon RBCs labeled with chromium.¹⁷

We have no proven explanation for the apparent difference between results obtained using chromium versus biotin-labeling methods but speculate that, during the biotinylation procedure used to label RBCs for posttransfusion kinetic studies, those RBCs damaged during storage and destined to be removed from the bloodstream within the first 24 hours after transfusion are, instead, removed *ex vivo* by the multiple washing steps of the biotinylation process.^{8,9} Thus, they are never infused, and only the relatively undamaged biotinylated RBCs are transfused and studied during posttransfusion kinetic experiments. Alternative mechanisms include: 1) alteration of the RBC surface by biotin molecules (e.g., “coating”) to block the rapid removal storage damaged RBCs from the circulation; 2) RBC injury by chromium to accelerate their removal from the circulation during the first 24 hours after transfusion and artifactually reduce the PTR_{24} ; and/or 3) factors intrinsic to the *in-vivo* condition and/or environment of infants that differ from adults to favor RBC recovery (e.g., decreased

reticuloendothelial function in infants resulting in failure of RBCs damaged during storage to be removed quickly from the circulation).

The results of our posttransfusion RBC survival studies were consistent with T_{50} and MPL values reported using fresh biotinylated RBCs in baboons (45 and 95 days, respectively).¹⁷ However, our MPL values are modestly shorter than those reported for stored human RBCs, which range from 103 to 116 days in adults, depending on the RBC-labeling method.^{9,15,18,19} Because we performed a total of only eight studies (Table 1), the shorter MPL values may not reflect a genuine difference in posttransfusion survival compared with the results of others. The difference may simply be a manifestation of the differences between results using biotinylated versus chromium-labeled RBCs.¹⁷ Alternatively, because the posttransfusion survival studies reported by others were performed in adults,^{9,15,18,19} our modestly shorter MPL values may be related to an undefined in-vivo factor unique to infants.

It is widely accepted that the life span of RBCs is shorter in the circulation of infants than in adults—a finding ascribed to intrinsic physical and biochemical differences between infant and adult RBCs.²⁰⁻²² However, factors intrinsic to RBCs that are responsible for the shortened survival of RBCs produced endogenously by infants can not explain the shortened MPL of transfused allogeneic RBCs collected from adult blood donors. Therefore, other dynamic factors that might influence infant physiology during the time infant blood samples are being taken for posttransfusion RBC kinetic studies may influence the results—especially for the relatively long-term measurement of MPL. The most likely dynamic factors are rapid somatic growth with commensurate expansion of the infant's blood volume linked to ongoing erythropoiesis.^{23,24} In this scenario, two factors may interact to underestimate posttransfusion RBC survival. First, the consequent increase of erythropoiesis and release of endogenous infant RBCs into the bloodstream will dilute the transfused donor biotinylated RBCs, thus lowering the calculated MPL values independently of true RBC survival. Second, the expansion of blood volume commensurate with increasing body weight, likewise, lowers the calculated RBC MPL results independently of true RBC survival. Consistent with this speculation, the eight infants involved in the T_{50} and MPL measurements were studied at a median postpartum age of 40 days, and their mean weight had increased from 0.948 kg at birth to 1.424 kg at the time of the study. Importantly, all of them experienced an increase in body weight during the period when blood samples were drawn for the RBC survival studies. However, there was no clear relationship between the magnitude of growth and the T_{50} and MPL results. Thus, other factors must be involved.

In conclusion, results of satisfactory posttransfusion RBC recovery and survival measured with allogeneic biotinylated RBCs support the findings of clinical trials that established the efficacy and safety of donor RBCs stored up to 42 days for small-volume transfusions given to neonates and infants. Compared to values reported for normal adults, posttransfusion survival of transfused allogeneic donor RBCs, assessed by MPL, was shortened similarly to MPL values reported by others for autologous neonatal RBCs. However, MPL measurements in rapidly growing infants may be spuriously underestimated and may not reflect true survival of either allogeneic or autologous RBCs. To this end, additional studies are needed that take into account rapid infant growth, ongoing erythropoiesis, and the effects of RBC transfusions.

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Abbreviations

MPL	mean potential life span
PTR ₂₄	24-hour posttransfusion recovery
rEPO	recombinant EPO

TABLE 1
Storage age of RBC units, posttransfusion survival of all RBC transfusions (n = 8), and rate of growth during RBC survival studies

Storage age (days)	T ₅₀ (days)	MPL (days)	Growth* (%)
3	56	111	0.71
4	32	64	2.34
11	35	69	1.80
22	50	99	2.34
27	50	99	2.09
29	27	53	2.35
31	41	81	2.38
42	53	105	1.02

* Growth expressed as the percentage of body weight increase per day from the day biotinylated RBCs transfused until the final blood sample drawn for T₅₀ and MPL determinations.

TABLE 2
Comparison of posttransfusion circulating kinetics of relatively fresh RBCs versus RBCs stored 1 to 21 days versus RBCs stored 22 to 42 days in AS-3 and transfused into infants

Measurement	RBCs stored 1-21 days*	RBCs stored 22-42 days*	p values
24-hr posttransfusion recovery (%)	98.6 ± 0.8 (98.6)	96.9 ± 8.4 (99.5)	0.30
Number	7	7	
Posttransfusion survival (T ₅₀)	40.6 ± 12.9 (34.4)	43.8 ± 13.1 (49.6)	0.36
Number	3	5	
Posttransfusion survival (MPL)	81.2 ± 25.8 (68.8)	87.5 ± 26.1 (99.2)	0.36
Number	3	5	

* Results expressed as mean ± SD (median) values; p determined by t test.