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Allogeneic Umbilical Cord Blood Red Cell Concentrates: An Innovative Blood Product for Transfusion Therapy of Preterm Infants

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Key Words
Umbilical cord blood transfusion · Preterm infants · Availability of umbilical cord blood · Safety of umbilical cord blood · Adult red blood cells

Abstract
Background: Preterm infants often receive blood transfusions early in life. In this setting, umbilical cord blood (UCB) might be safer than adult blood (A) with respect to infectious and immunologic threats. ***Objectives:*** To evaluate, as a first objective, the feasibility of fulfilling transfusion needs of preterm infants with allogeneic UCB red blood cell (RBC) concentrates and, as a secondary objective, to assess the safety of allogeneic cord blood transfusions. ***Methods:*** At the Neonatal Intensive Care Unit and the UNICATT Cord Blood Bank of 'A. Gemelli' Hospital in Rome, a prospective study was carried out over a 1-year period, enrolling newborns with gestational age ≤30 weeks and/or birth weight ≤1,500 g requiring RBC transfusions within the first 28 days of life. At first transfusion, patients were assigned to receive UCB-RBCs or A-RBCs depending on the availability of ABO-Rh(D)-matched UCB-RBC units. The same regimen (UCB-RBC or A-RBC units) was thereafter maintained, unless ABO-Rh(D)-matched UCB-RBC units were not available. ***Results:*** Overall, 23 UCB-RBC units were transfused to 9 patients; the requests for UCB-RBC units were met in 45% of patients at the first transfusion and in 78% at the subsequent transfusions. At a median follow-up of 57 days (range 6–219), no acute or delayed transfusion-related adverse events occurred. Hematocrit gain after transfusion and time intervals between transfusions were similar in the UCB-RBC and A-RBC group, as well. ***Conclusions:*** Transfusing allogeneic UCB-RBC units in preterm infants appears a feasible and safe approach, although the transfusion needs of our study population were not completely covered. More data are necessary to validate this novel transfusion practice.

Introduction

Preterm infants frequently require transfusion. All newborns experience a progressive decline of the red blood cell (RBC) count during the first weeks of life, re-

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sulting in the so-called 'physiological anemia of infancy'. Nevertheless, in prematurely born infants, this decline is significantly more rapid and pronounced [1]. Repeated RBC transfusions are acknowledged risk factors for retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC) and bronchopulmonary dysplasia (BPD) [2–6]. Several approaches have been explored to prevent or even to reduce the threshold and the frequency of RBC transfusions. Among these, umbilical cord blood (UCB) collection and processing to obtain RBC products for autologous transfusion have been extensively investigated [7–12]. The refinement of techniques of collection, processing and storage of UCB allowed the production of UCB-RBC units suitable for clinical use [13, 14]. However, the small volume of UCB collected does not allow an adequate coverage of transfusion needs of preterm infants and this practice has nowadays been abandoned [12]. We assumed that to replace RBC transfusions from adult blood donors with UCB-RBC transfusions obtained from healthy full-term neonates could be advantageous for preterm infants. In fact, UCB is privileged with respect to both immunologic and infectious threats, and, in addition, it contains the same kind of hemoglobin as that of recipients, i.e. fetal hemoglobin. We have previously shown that the automated processing of UCB collected from full-term neonates produces valid units of packed RBCs in terms of both quality and yields [15, 16]. Indeed, in this study, we firstly report clinical data on allogeneic packed UCB-RBC transfusion in premature infants.

Table 1. Decisional criteria for RBC transfusion in preterm infants admitted to the NICU

1	Hct ≤20% or Hb <4.3 mmol/l even in the absence of symptoms if reticulocytes <5%	
2	Hct ≤30% or Hb <5.6 mmol/l if:	
	a	Oxygen with FiO_2 <0.35
	b	CPAP or IPPV with MAP <6 cm H_2O
	c	Apnea and bradycardia clinically relevant, although treatment with xanthenes
	d	HR >180 or <80 bpm for >12 continuous hours
	e	Increase of weight <10 g/day for >4 days, with a caloric intake equal to 100 kcal/day
	f	Planned surgery
3	Hct ≤35% or Hb <7.4 mmol/l if:	
	a	Oxygen with FiO_2 >0.35
	b	Orotracheal tube with CPAP or IPPV with MAP >6–8 cm H_2O

Hct = Hematocrit; Hb = hemoglobin; CPAP = continuous positive airway pressure; IPPV = intermittent positive-pressure ventilation; MAP = mean airway pressure; HR = heart rate; bpm = beats per minute.

Patients, Materials and Methods

Study Design and Patient Population

This prospective study was carried out at the Neonatal Intensive Care Unit (NICU) and at the UNICATT Cord Blood Bank of 'A. Gemelli' Hospital in Rome. The first aim of our study was to evaluate, during a 1-year period, the feasibility of fulfilling transfusion needs of preterm infants admitted to the NICU with gestational age ≤30 weeks and/or birth weight ≤1,500 g with allogeneic UCB-RBC units within the first 28 days of life. As a secondary objective, we focused on the safety of allogeneic cord blood transfusions. Patients with maternal-fetal immunization, hydrops fetalis, major congenital malformations associated or not with genetic syndromes, hemorrhage at birth due to placental hemorrhage and/or loss from cord blood with neonatal hemoglobin <7.4 mmol/l, congenital viral infections [cytomegalovirus (CMV) and parvovirus B19] and outborn infants were excluded. The study was approved by the Local Ethics Committee. Informed consent was obtained from parents at NICU admission. At the time of the first transfusion, patients were assigned to receive UCB-RBCs or adult RBCs (A-RBCs) on the basis of the availability of UCB-RBC units matched for ABO and Rh(D). For the subsequent transfusions, patients in the UCB-RBC group (intervention group) continued to receive ABO- and Rh(D)-matched UCB-RBC units, if available. The patients in the A-RBC group (control group) continued to receive only A-RBC units. Decisional criteria for RBC transfusion are illustrated in table 1 and constitute the current operative procedure adopted at the local NICU [17]. According to NICU procedures, anemia of newborns was avoided by restricted phlebotomy practices, iron supplementation and erythropoietin. The anticipated hematocrit of A-RBC and UCB-RBC units administrated was between 50 and 70%. Both A-RBC and UCB-RBC units were administered at a dose of 20 ml/kg by continuous infusion (Alaris pump infusion set; CareFusion, San Diego, Calif., USA). During transfusions and for 6 h after transfusions, all patients were continuously monitored for O_2 saturation, heart rate, transcutaneous measure of PO_2 and PCO_2 and for the onset of fever. Blood pressure was monitored before, during and 2 h after the end of transfusion. Hematocrit values were obtained by automated capillary blood sampling before and 2 h after transfusion. The occurrence of transfusion reactions and adverse events as well as morbidities and deaths were recorded. The proportion of patients receiving UCB-RBC units as a first transfusion and the proportion of patients assigned to the UCB-RBC group receiving UCB transfusions at subsequent transfusions were considered as feasibility outcomes.

RBC Unit Processing

UCB-RBC units were obtained after informed consent and processed at the UNICATT Cord Blood Bank according to UNICATT Cord Blood Bank standard procedures and national regulations [18]. Eligible criteria for UCB collection were: ≥37 weeks of gestation, absence of ongoing infections in the mother and/or fever within 24 h of delivery and no staining of the amniotic fluid. In both vaginal and caesarean deliveries, the placenta

was still in utero when blood was harvested. Maternal blood samples were also collected to perform serological and/or molecular testing for transfusion-transmitted infections, including CMV antibodies. UCB was collected in CPD (citrate-phosphate-dextrose) and maintained at 2–6°C until processing, which was performed within 24 h of collection. The units with a volume of >60 ml, total nucleated cell content of $\leq 1.5 \times 10^9$, erythroblasts ≤20%, no signs of clots or hemolysis and negative direct antiglobulin test were processed as previously reported [16]. Briefly, a buffy coat-depleted packed cord red cell suspension was obtained by centrifugation and then subjected to automated separation (Compomat G4®; Fresenius HemoCare, Bad Homburg, Germany). Packed RBCs were then suspended in SAG-mannitol (ratio blood:SAG-mannitol 2:1) and cultures for bacterial and fungal contamination were performed. Units were stored at 2–6°C for 14 days at a maximum in order to permit γ-irradiation (^{137}Cs). Poststorage filtration was performed using the Purecell® NEO Neonatal High Efficiency Leukocyte Reduction Filter (Pall, East Hills, N.Y., USA). UCB-RBC units were considered eligible for allogeneic transfusion when microbiologic analysis (bacterial and fungal cultures, serological and molecular testing for HBV, HCV, HIV and syphilis test) was proven negative.

Statistical Analysis

Continuous variables were expressed as mean values ± standard deviations (SD) if they were normally distributed or as median values with ranges if they were not normally distributed. Continuous variables were analyzed with the Mann-Whitney U test and dichotomous variables with the χ^2 test. A p value <0.05 was considered statistically significant. Statistical analysis was performed using the SPSS software.

Table 2. Characteristics of UCB-RBC units processed and released for transfusion

Processed units, n	128
Unsuitable units, n (%)	16 (12.5)
Positive microbiology test	5 (3.9)
Positive DAT or erythroblastosis	5 (3.9)
Technical problems[a]	6 (4.6)
Suitable units, n (%)	112 (87.5)
Mean unit volume ± SD, ml	92.3±18.3
Blood group distribution	
Rh(D), positive/negative	103/9
O positive/O negative	51/5
A positive/A negative	39/2
B positive/B negative	11/2
AB positive/AB negative	2/0
Transfused units[b], n (%)	23 (20.5)
Rh(D) positive/negative	21/2
O positive/O negative	13/2
A positive/A negative	8/0
B positive/B negative	0/0
AB positive/AB negative	0/0
Expired units[b], n (%)	89 (79.5)

DAT = Direct antiglobulin test. [a] Technical problems consisted of clots or inadequate recovery. [b] Data refer to suitable units.

Results

The study started on March 1, 2013. Among 93 patients admitted to the NICU over a 1-year period, we observed 63 neonates with a gestational age ≤30 weeks and/or a birth weight ≤1,500 g and consent to participate in the study was obtained for 62 of them. Among them, 20 (32%) preterm infants required RBC transfusion within the first 28 days of life and they were included in the study. The first patient was transfused on April 18, 2013, and the last one on February 26, 2014.

RBC Unit Processing and Release

During the study, 128 UCB units were processed: 112 of them (87.5%) were considered eligible for transfusion and 23 (18%) were transfused, which amounts to 20.5% of suitable units. The characteristics of UCB-RBC units are shown in table 2. On the whole, 51 total transfusion events were recorded: in the UCB-RBC group, 9 patients received 23 UCB-RBC units and 4 A-RBC units, while in the control group, 11 patients received 24 A-RBC units (table 3). At the first transfusion request, an UCB ABO-Rh(D)-matched unit was available only for 9 patients (table 3). Seven out of 11 patients with unavailable UCB-RBCs were Rh(D) negative (35% of the entire series; table 3). Indeed, at the first transfusion event, the availability of UCB units in our inventory allowed us to support 45% (9/20) of all patients and 70% (9/13) of Rh(D)-positive patients. All patients, except 1, received subsequent transfusions. In the UCB-RBC group, 6 out of 9 patients were transfused only with UCB-RBCs, whilst 3 patients received also A-RBCs for a total of 4 units. Overall, matched UCB-RBC units were supplied in 78% (14/18) of the requests subsequent to the first transfusion. Finally, the storage time of UCB-RBCs was significantly longer than that of A-RBCs (table 3).

Clinical Findings

The preterm infants receiving UCB-RBCs or A-RBCs had a similar sex and age distribution, gestational age, birth weight, Apgar scores, hematocrit and hemoglobin levels at birth (table 3). The triggers for transfusion were similar in the two groups (table 3) and A-RBC and UCB-RBC transfusions produced a similar raise of the hematocrit. Both groups of patients received a similar number of transfusions in the first 28 days of life and the intervals between transfusions were comparable between the two

Table 3. Clinical and hematological findings of enrolled patients

	Cord blood group (n = 9)	Adult blood group (n = 11)	p value
Males, n (%)	5 (55)	8 (72)	0.64
Gestational age, weeks	26.7±3.1	26.1±1.4	0.59
Age at first transfusion, days	7 (3–17)	5 (2–19)	0.799
Weight, g	840±282.4	830±207.9	0.93
Twins, n (%)	2 (22)	2 (18)	1
Apgar[1]	5.2±2.2	4±2.2	0.23
Apgar[5]	7.7±1.7	7±1.8	0.34
Hct at birth, %	48±5.5	45.5±6.9	0.38
Hb at birth, mmol/l	9.5±1.14	9±1.6	0.39
O/A/B/AB, n	5/3/0/1	6/4/1/0	1
Rh(D) negative, n (%)	0	7 (64)	0.004
Total transfusions[a], n	27[b]	24	0.239
Transfusions per patient, n	3±1.7	2.18±1.9	0.966
Hct before transfusion, %	31.6±2.55	31.6±3.4	0.92
Hct after transfusion, %	43.5±5.1	44.5±5.3	0.49
ΔHct[c], %	11.9±5	13±5	0.43
Blood losses between two consecutive transfusions, ml	10.5±6.5	10.6±7.5	0.98
Interval between transfusions, days	9.7±9	11±9.3	0.515
Mean storage time, days	7 (3.2–10)	3.5 (1–6)	0.001

Data are expressed as mean values ± SD or as median values with ranges in parentheses unless otherwise indicated. Apgar[1] and Apgar[5] denote Apgar scores at 1 and 5 min, respectively. Hct = Hematocrit; Hb = hemoglobin. [a] Total transfusions performed within the first 28 days of life. [b] Four out of 27 transfusions in this group consisted of A-RBC units because of the lack of ABO-Rh(D)-matched cord blood units. [c] Mean Hct increase between two consecutive transfusions.

groups (table 3). No acute transfusion reactions and adverse events related to transfusions were recorded among patients of both groups, including fever, hemolysis, allergic reactions or transfusion-related acute lung injury (TRALI). Among delayed adverse events, no transfusion-associated graft versus host diseases or CMV infections were observed. CMV infection was excluded by serology on mothers' samples and molecular biology on neonate urine. At a median follow-up of 57 days (range 6–219), the incidence of ROP, NEC, BPD, sepsis or intraventricular hemorrhage was similar in the two groups (table 4).

Discussion

Our study investigates for the first time the use of allogeneic UCB-RBC transfusion in preterm infants and reports data on 23 UCB-RBC transfusions performed in 9 patients with a gestational age ≤30 weeks and/or with a birth weight ≤1,500 g, within the first 28 days of life. In fact, in the past, other authors have described the clinical feasibility of cord blood for the therapy of anemic neonates, but only for autologous use [7–11].

The primary aim of this study was to evaluate if the unit inventory of our cord blood bank was potentially able to fulfill the transfusion needs of preterm infants admitted to the NICU. We could cover RBC needs only in 45% of patients at first transfusion and in 78% of cases at subsequent transfusions. Rh(D)-negative patients were severely disadvantaged for receiving UCB-RBC transfusions. Comparing the prevalence of the Rh(D)-negative phenotype of our population with the Rh(D) distribution in Caucasians, we observed an imbalance between the unusually high prevalence among enrolled patients (35%) and the low prevalence among collected UCB units (8%). Although this discrepancy can be partly explained by the exclusion of Rh(D)-negative women from donation because of a positive direct antiglobulin test, this study highlights the difficulty to support anemic Rh(D)-negative preterm infants with matched UCB-RBCs.

As a secondary aim, we focused on the safety of allogeneic cord blood transfusions. As previously reported in

Table 4. Clinical findings of patients grouped according to the RBC products during the whole period of follow-up until the date of discharge

	Cord blood group (n = 9)	Adult blood group (n = 11)	p value
Mean follow-up (range), days	57 (6–40)	57 (6–219)	0.958
Total transfusions, n	48	42	0.500
Deaths, n (%)	2 (22.2)	3 (27.2)	1
ROP, n (%)	2 (22.2)	2 (18.1)	1
BPD, n (%)	4 (44.4)	3 (27.2)	0.642
NEC, n (%)	0	2 (18.1)	0.478
IVH, n (%)	3 (33.3)	3 (27.2)	1
Sepsis, n (%)	4 (44.4)	5 (45.4)	1

IVH = Intraventricular hemorrhage.

the SHOT study, neonatal adverse events are often underreported and/or underdiagnosed mainly due to concomitant critical illness: in 2011, no TRALI were reported in neonatal populations [19]. On this basis, a careful hemovigilance system was applied for this new protocol and any adverse reactions which could be related to transfusion were registered. No febrile reactions, respiratory distress, hemolysis or allergy were recorded among neonates receiving UCB units.

Furthermore, considering that all UCB units were required to have negative bacterial and fungal testing before the release, patients in the UCB-RBC arm received blood products with a significantly longer storage time than those receiving standard RBCs. The in vitro RBC storage lesions include a wide range of cell abnormalities, affecting cell deformability and adhesion, oxygen delivery and free iron and microparticle production. These changes have been alleged to impair nitric oxide availability, immune regulation, inflammatory response and coagulation [20]. Despite the different storage times, in our preliminary findings, there were no differences in acute and delayed reactions between UCB and adult RBCs. On the other hand, also recent prospective data show that in premature, very-low-birth-weight infants the transfusion of RBCs stored for less than 1 week did not affect the incidence of major neonatal morbidities, including NEC, ROP, BPD and intraventricular hemorrhage [21].

Preterm infants receiving transfusions from adults inevitably undergo the 'unnatural switching' of fetal-to-adult hemoglobin, resulting in an abnormal delivery of oxygen to tissues and developing organs. Although the effect of oxygen release to tissue is not completely understood, this phenomenon possibly contributes to the pathogenesis of various illnesses of prematurity [2–6]. Normally, in full-term neonates, the fetal-to-adult hemoglobin switch occurs within a few months after birth, so that, for preterm infants, UCB-RBC units might represent the ideal RBC product. In addition, UCB-RBCs have the advantage of having been obtained from donors fully inexperienced in infectious and immune stimuli, including CMV infection. The main limitation of UCB resides in the small amounts available. For this reason, in contrast to blood from adult donors, one UCB unit cannot be processed and stored in pedipaks, i.e. several small satellite bags [22]. On the other hand, this technique, aimed to reduce the adult donor exposure among neonate patients, often conflicts with the storage time of fractionated units, not allowing the irradiation of the blood products. Future studies on large series of patients receiving UCB-RBCs should evaluate if the strategy of selecting immunologically naive donors is advantageous due to a lower adult donor exposure. This might result in a lower rate of TRALI and transfusion-associated immunomodulation.

Cord blood units without clots or signs of hemolysis, when fractionated, have red cells with acceptable biochemical and functional properties during storage [13, 16]. Accordingly, hematocrit gain after transfusion and time intervals between transfusions were similar in UCB-RBCs and A-RBCs. Moreover, at a median follow-up of 57 days (range 6–219), no acute or delayed transfusion-related adverse events occurred.

There is an increasing awareness that transfusion of blood products in preterm infants is an independent predictor of adverse outcome [23, 24]. The implementation of more stringent transfusion guidelines, restraint of phlebotomy losses, iron supplementation and erythropoietin administration are all recommended approaches to reduce the frequency of transfusions in these patients [1]. Our preliminary observations are limited to a small number of patients. In particular, in our series of preterm infants, only 32% of patients needed transfusions. This low proportion probably results from the anemia-preventing strategies adopted in our NICU, including restrictive phlebotomy practices, iron supplementation and use of erythropoiesis-stimulating agents. Nonetheless, the evidence gathered on our small series of preterm infants paves the way for future studies evaluating the impact of UCB-RBC transfusions on the prognosis of this extremely fragile set of patients.

Since RBC transfusions are still unavoidable in several clinical circumstances, many patients could benefit from allogeneic cord RBC transfusions. UCB-RBC units may be recovered in cord blood banks after collection, since

almost half of the UCB units eligible for transplantation according to donor selection and microbiological testing are actually considered ineligible due to a low content of total nucleated cells [25]. Thus, it is reasonable that through the cooperation among more cord blood banks, a large inventory of UCB-RBCs could be provided to preterm infants, also in those NICUs not having a local cord blood bank. Moreover, a higher availability of UCB-RBC units will allow the enrollment of a larger number of patients to evaluate the efficacy and long-term effects of this innovative transfusion approach.

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Disclosure Statement

The authors declare that they have no competing financial interests.

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