



Use of allogenic umbilical cord blood for red cells transfusion in premature infants: utopia or reality?

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ABSTRACT

Extremely low birth weight (ELBW) infants almost always receive blood transfusions early in life. Newborn infants are currently transfused with leukocyte-depleted, irradiated red blood cells (RBCs) obtained from adult donor, which contains adult hemoglobin. Adult hemoglobin affinity for oxygen is lower than fetal, therefore red cell transfusion could be responsible for increased oxygen delivery to tissues increasing the risk of the “oxygen radicals disease of the newborn”. Though clinical studies have demonstrated that autologous cord blood transfusions in newborns is feasible, the clinical use of umbilical cord blood (UCB) for RBC transfusion purposes is still limited, especially because of the small volumes achieved after processing of the UCB unit. The preliminary results of the first clinical study assessing the feasibility and the effectiveness of a transfusional program in preterm infants with packed RBCs obtained from allogenic UCB are shown.

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1. Introduction

Extremely low birth weight (ELBW) infants represent a category of patients with very high transfusion requirements [1]. Blood transfusions are a clinical practice almost indispensable in preterm ELBW newborns because they are subject to anemia due to decreased half-life of red blood cells (RBCs) containing fetal hemoglobin, impaired erythropoietin response to anemia and iatrogenic blood loss. Despite the use of restrictive transfusion protocols, the reduction of phlebotomy loss and the use of erythropoietin, the transfusion rate remains very high and in Italy it is estimated that 70–80% of infants weighing <1500 g receive RBCs transfusion, most of which is carried out in the first weeks of life.

2. Autologous cord blood transfusion for anemia of prematurity

According to national and international guidelines newborn infants are currently transfused with leukocyte-depleted, irradiated RBCs obtained from adult donor in a small volume (10–20 ml/kg). The improvement of transfusion practices has ensured that the risks associated with the use of RBCs is minimized. The screening of adult donors and the monitoring of infectious diseases of blood components dramatically reduced the risks of transfusion by single donor. However to further limit the risks associated with multiple exposure to allogeneic donor, efforts have been made to verify the feasibility of autologous placental blood transfusions. The increased

collection of cord blood as a source of haematopoietic progenitor cells and the development of modern techniques for the processing and storage of blood products has raised the question as to whether the RBCs discarded by the process of separation could not be a useful blood product for autologous transfusion of premature newborns in the early stages of life.

Umbilical cord blood (UCB) availability as a prospect for transfusional use was first reported in 1939 [2]. The preparation of autologous RBCs from the UCB of preterm infants was negatively affected in the past by the difficulties of collection of UCB units and storage. Blood clotting was a main problem during the collection of cord blood units [3]; clots prevent to collect adequate volumes of blood to be processed and separated in different blood components. Blood clotting can be also responsible of activating coagulation cascade in the RBCs unit. Refinements in techniques of umbilical blood processing for the purpose of recovering umbilical cord stem cells has gradually improved collection and storage of UCB and several clinical trial have been performed with the aim to verify the coverage of transfusion need of preterm and the feasibility of autologous RBC transfusion.

Clinical studies have demonstrated that autologous cord blood transfusions in newborns, although feasible, are not sufficient to entirely cover the early neonatal blood requests because of the small volumes achieved after processing of the UCB unit, too often not adherent to the transfusion requirements of preterm infants [4]. Khodabux et al. [5] described the attempt to collect and process UCB in 176 deliveries <32 weeks' GA into autologous RBC products, aiming to reduce allogenic transfusion. He declare that 57,6% of the collected UCB reached volumes >15 mL, able to be

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processed into RBC products and that after processing and quality control only 36,4% of suitable autologous products were available for transfusion. Considering low availability of autologous products due to a low number of successful UCB collections this randomized clinical study was stopped before the enrollment of the sample size planned to demonstrate the primary outcome.

In addition, the high rate of bacterial contamination (1,9–8,6%) of the harvested UCB units in the published clinical studies, probably attributed mostly to non-sterile procedures for the collection of cord blood units, has been considered a major limitation for the actual use of these blood components [3–5].

3. Allogenic cord blood-derived RBCs for anemia of prematurity

The neonatal blood inside the placenta and the umbilical vessels was initially used as a source of blood for adult allogeneic transfusions during the Second World War. In some hospitals in New York was used until the end of the sixties and, currently, it is reported its use in particular contexts, such as in developing countries [6]. No experience with allogeneic cord blood (ACB) RBC transfusion has been described until the preliminary results of a study carried out to assess the feasibility of an ACB RBCs transfusion program for premature newborns in terms of preparation and yield of valid ACB RBCs units [7]. The authors collected ACB units, that were not suitable for processing and storage for allogeneic transplant cord blood, in delivery ≥ 37 weeks' GA, with absence of infection in the mother and no staining of the amniotic fluid. Forty-three percent of the 76 collections attempted was not suitable for subsequent processing because of the insufficient volume or of the presence of blood clots. The median volume after fractionation (31.2 ± 8.2 ml) of the remaining units appears to be greater than the volume of RBCs unit from UCB for autologous use reported from literature and then it is mostly sufficient to provide the coverage of a single transfusional event of a ELBW infant. Biochemical, hematological parameters and microbiologic testing performed on the ABC RBC units proved that all units could be considered eligible for transfusion. The authors conclude that the preparation of RBCs from ACB is feasible and convenient. This method does not reduce the risks associated with allogeneic transfusion but certainly allows to bypass the limits of cord blood collection for autologous use firstly the insufficiency of blood volumes harvested at low gestational ages. The collection of cord blood for allogeneic transfusion in deliveries of term neonates would then have the advantage to ensure a wider coverage transfusion. This method could also reduce the risk of post-transfusion CMV infection that is currently connected to transfusions from adult donor, due to the guarantee of the search for antibodies against CMV, always performed on serum from the mother. The use of neonatal blood, although allogeneic, could theoretically result in other benefits when administered to ELBW infants. Currently, newborns are transfused with RBSs from adult donor, which contains adult hemoglobin. Adult hemoglobin affinity for oxygen is substantially lower than fetal hemoglobin, therefore red cell transfusion could be responsible for increased oxygen delivery to tissues increasing the risk of the "oxygen radicals disease of the newborn". Many of the major complications of preterms, such as ROP, chronic lung disease, IVH, necrotizing enterocolitis have been associated with oxidative cellular damage mediated by oxygen radicals. In particular RBCs transfusions in the first month of life of pretermatures are one of the major risk factor for developing retinopathy [8].

4. Our experience

At our NICU is ongoing a single center case control that aims to define the feasibility and the effectiveness of a program of transfusion therapy of preterm infants with packed RBSs obtained from UCB allogeneic.

4.1. Methods

Subject to acceptance of proper informed consent, packed RBSs are elected to transfuse from UCB (ECC) infants with gestational age ≤ 30 weeks and/or birth weight ≤ 1500 grams candidates for transfusion therapy within four weeks after birth or up postnatal age of the $\hat{=}$ 32 weeks, in agreement with the national recommendations [9]. In the absence of availability of group compatible, cord blood infants are assigned to receive packed RBSs from adult donor (ECA). For each assignment group the characterization and biological qualification of blood units (obtained from donor and UCB) are carried out in accordance with the procedures in our Blood Transfusion Service and current legislation. Are excluded from this study infants with: isoimmunization maternal-fetal, fetal hydrops, congenital malformations and acute hemorrhage at birth.

4.2. Statistical analysis

Normally distributed continuous variables were expressed as mean and standard deviation (SD).

The statistical evaluation was conducted using the software SPSS data mining, using for the analysis of continuous variables the Mann-Whitney U test and Fisher's exact test for dichotomous variables.

The level of significance is for values of $p < 0.05$.

4.3. Results

From 1 April 2013 to 1 July 2013 were elected to receive cord blood transfusions 16 infants. Of these were enrolled, because needed of transfusion, 8 infants of which 3 are assigned to the ECC group and 5 assigned to the ECA (Table 1).

The amount of blood transfused was 20 ml/kg at each event transfusion. The characteristics of the pockets of RBSs from UCB reflect those described by Bianchi et al. [7].

The feasibility, understood as the fulfilling of transfusion requirements of patients included in the study, is currently at 54.5%.

Currently the assessment of effectiveness can be performed only using the changes in hematocrit as a result of each transfusional event. The hematocrit after transfusion, show no statistically significant differences between the two groups (Table 2).

There were no adverse events referable to the transfusion of RBSs from UCB.

Table 1
Characteristics of the enrolled infants.

	Cord group	Adult group	P value
N	3	5	
Male	2	4	1
EG	27.2 \pm 3.7	27.1 \pm 1.2	1
PN	794.2 \pm 287.9	873 \pm 216.8	0.45
Twins	1	1	1
APGAR 1	5.3	3.8	0.2
APGAR 5	8	6.6	0.34
SGA	0	1	1

Table 2
Hematological values (media \pm SD).

	Cord group	Adult group	P value
Δ Ht (%)	13.1 \pm 4.2	14.1 \pm 4.4	0.59
Ht at born (%)	54 \pm 5.2	57 \pm 8.4	0.65
Blood loss by phlebotomy before each transfusion (ml)	15.2 \pm 13.5	18.2 \pm 13.1	0.39

4.4. Conclusions

From the data available so far we can state that transfuse homologous RBSs from cord blood is an eventuality possible. In our reality, with the collaboration of UNICATT Cord Blood Bank with, respect to transfusion requirements of infants the availability of RBSs from UBC can cover the 55.5%. With regard to transfusional effectiveness, from currently collected data, we can state that the RBCs from UBC lead to an increase of the post-transfusion hematocrit comparable to that produced by transfusions of RBSs from adult donor. The data represent a preliminary evaluation waiting to extend the analysis to a larger sample.

Conflict of interest

The authors have no conflict of interest to declare.

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