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Toward clinical use of allogeneic red cell concentrates from umbilical cord blood: feasibility and process optimization

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Background - Umbilical cord blood has clinical applications beyond hematopoietic stem cell transplantation, making it possible to use donations more efficiently. Cord blood (CB)-derived red cell concentrates (CB-RCCs) may offer physiological advantages for extremely preterm infants (born <28 weeks' gestation), who commonly require transfusion during the first weeks after birth. Prior to clinical implementation, CB-RCC collection and processing protocols must be validated within the blood bank to ensure consistent quality, safety, efficacy, and adequate supply.

Materials and methods - We conducted an open-label, nonrandomized, single-centre pilot trial between September 13, 2023, and July 12, 2025, evaluating the use of CB-RCCs for transfusion in extremely preterm infants. The present manuscript does not report the clinical safety or efficacy outcomes of the trial. Instead, it focuses on CB-RCC availability, inventory management, and the processing workflow, including fractionation, leukoreduction, storage, and pretransfusion irradiation. We also described the characteristics of the final product with predefined quality controls (volume, hematocrit, hemolysis, residual leukocyte content, and sterility assurance procedures).

Results - During the study period, 161 CB units were processed for CB-RCCs, producing 187 aliquots after fractionation. The availability of the product for clinical application was 78.6% of all requested units. Median final volume of CB-RCC units released for clinical use was 25.3 mL [IQR: 23.9-26.8]. After processing, 159/187 aliquots met all acceptance criteria, corresponding to an overall release rate of 85%. The most common cause of discard was failure to meet microbiological safety requirements.

Discussion - The implementation of an internal cord blood bank protocol demonstrated that CB-RCC units can be processed in a feasible and reproducible manner, with high release rates and sustained availability, supporting the potential for large-scale production to meet transfusion needs in extremely preterm infants.

Keywords: cord blood, extremely preterm infants, fetal hemoglobin, red blood cell transfusion, transfusion medicine.



INTRODUCTION

Cord blood (CB) is usually collected after delivery of full-term healthy neonates as a source of allogeneic hematopoietic stem cells for transplantation in children and adults with cancer, bone marrow failure syndromes, hemoglobinopathies and other genetic metabolic disorders^{1,2}. The strict cellular criteria for transplantation are met by only a small fraction of the umbilical cord donations that are collected. As a result, a large proportion of collected donations are discarded³. In addition to stem cells, CB contains foetal blood components such as platelets, plasma and red blood cells (RBCs) that can be useful in addressing other clinical conditions⁴.

Anemia of prematurity is a prevalent condition in extremely preterm infants (born <28 weeks' gestation). There are multiple physiological contributors, including hematopoietic immaturity, the shortened half-life of erythrocytes, and frequent blood draws for clinical monitoring⁵. Traditionally, anemia in these patients has been treated through transfusions of adult donor-derived red cell concentrates (A-RCCs). However, these are associated with risks, such as transfusion reactions, alloimmunization and transmission of infections. In addition, replacing foetal hemoglobin (HbF) with adult hemoglobin (HbA) can affect tissue oxygenation and has been associated with complications such as retinopathy of prematurity (ROP)⁶⁻⁸ and bronchopulmonary dysplasia (BPD)^{9,10}. CB has unique characteristics that may benefit preterm infants, being rich in HbF, which has a higher affinity for oxygen and offers advantages for the oxygenation of developing tissues^{11,12}. Moreover, CB has lower immunogenicity, potentially reducing the risk of adverse reactions and alloimmunization¹³. Recently, Teofili *et al.* conducted a multicentre, double-blinded, randomized, controlled trial to assess the impact of CB-RCC transfusion on ROP in extremely preterm infants. Their results suggest that this transfusion approach has the potential to reduce the risk of severe ROP compared with standard A-RCC transfusions^{14,15}. Despite this growing interest in the clinical use of CB-RCCs, its implementation in neonatal practice is hampered by the lack of robust evidence addressing real-world supply sustainability, quality assurance and feasibility. Prior to widespread clinical adoption, the entire process, from collection and processing to storage, release, and

subsequent transfusion, needs to be validated within an integrated transfusion pathway.

To date, evidence on CB-RCCs processing for transfusion purposes is scarce and largely confined to methodological descriptions, leaving a gap in evidence regarding operational feasibility, stock management, and readiness for clinical implementation. Earlier studies investigating automated and semi-automated CB-RCCs fractionation methods provided limited data on final product characteristics and were lacking in transfusion-oriented quality controls¹⁶⁻¹⁹. More recently, Bianchi *et al.* described an automated fractionation protocol capable of producing CB-RCC units with hematocrit levels comparable to A-RCC units, acceptable residual white blood cell content, low microbial contamination rates and a storage period of up to 14 days under standard blood bank conditions^{11,14,20}. At the same time, the All-cord study group explored other storage conditions and managed to obtain satisfactory results in terms of compliance with international quality standards for a storage period of 21 days²¹.

The present study was conducted within the framework of a broader pilot clinical trial evaluating CB-RCC transfusion in extremely preterm infants. However, this manuscript does not report the clinical safety or efficacy outcomes of that trial. It focuses instead on the operational feasibility, product availability, and stock management of CB-RCC units collected and processed at the public cord blood bank Concordia Program at the Banc de Sang i Teixits (BST) for transfusion in extremely preterm infants. We also aimed to describe the characteristics of the final CB-RCC product in line with international standards (including volume, stability, and sterility).

MATERIALS AND METHODS

Study design

This study was conducted within an open-label, nonrandomized, single-centre pilot clinical trial (NCT05612919) performed at Hospital Clínic de Barcelona between September 13, 2023, and July 12, 2025. The clinical safety and efficacy outcomes of the trial are outside the scope of the present manuscript. To ensure product availability for transfusion in a clinical trial setting involving extremely preterm infants, this study evaluated the CB-RCCs production workflow in the processing centre, along with associated quality parameters and

sterility assurance. Before the study commenced, a proof of concept phase was performed in order to establish processing conditions and quality thresholds²². The protocol was approved by the Ethics Committee for Research with Medicines of Hospital Clínic de Barcelona (HCB/2021/0161).

In the course of the study period, CB units collected through the Concordia-BST cord blood bank programme were processed to produce CB-RCC units. All the processing steps, quality-control procedures, and storage conditions were recorded prospectively, and product availability was defined prospectively as maintaining at least a one-week stock of two compatible CB-RCC units, using only group O units.

In parallel, transfusion activity in extremely preterm infants from a single neonatal intensive care unit (NICU) was monitored to assess the use of CB-RCC transfusions.

Red blood cell processing

CB donations were conducted in the context of the Concordia-BST cord blood bank Program, an inter-regional cooperative model for public umbilical CB donation, coordinated by the BST, which brings together six regions of Spain and Andorra with the aim of optimizing availability of units for therapeutic use in accordance with international quality standards²³. CB donations were eligible if they met the following

criteria: signed informed consent including use for this purpose, health questionnaire, infectious screening eligibility, term gestation (≥ 37 weeks' gestation), collection within the previous 48 hours, net volume greater than 50 mL (100 g of gross weight), and absence of visible clots (see process flowchart in **Figure 1**). The donations were collected by trained healthcare professionals using conventional techniques and dedicated bags with 28 mL citrate phosphate dextrose (CPD) as anticoagulant (Macopharma, Tourcoing, France); units of CB were eligible for fractionation if they had a gross weight exceeding 100 g and 0% hemolysis, assessed quantitatively before processing. Fractionation was performed in a closed system using a commercially available kit (Solutran Hemo Bionest ABC, Meditalia Industriale, Lovero, Italy) in a Class D cleanroom under a Class A laminar airflow cabinet. After centrifugation at 2,000 g for 15 minutes, the platelet-poor plasma was transferred to the satellite bag and 2 mL of buffy coat was extracted using a Halkey-Roberts luer for sampling, ensuring closed circuit, included in the processing kit of Solutran Bionest ABC (Meditalia Industriale). The RBCs were then connected to the leukoreduction kit (Solutran Hemo Bionest EF, Meditalia Industriale), which includes a small-volume polybutylene terephthalate filter, and a saline-adenine-glucose-mannitol (SAGM) bag was

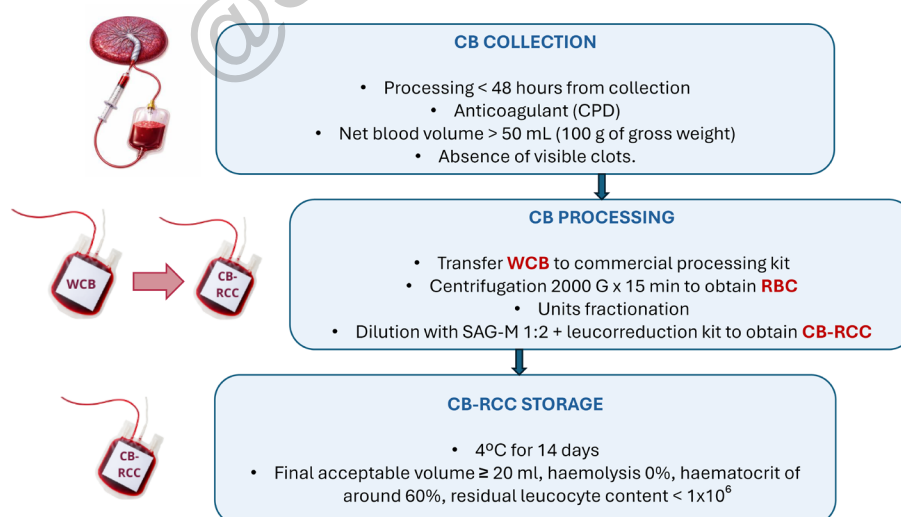


Figure 1 - Processing flowchart of cord blood red cell concentrates

CB: cord blood; CPD: citrate phosphate dextrose; WCB: whole cord blood; RBC: red blood cell; CB-RCC: cord blood-derived red cell concentrate.

connected to the other end of the kit. The volume of SAGM was calculated based on the weight of the CB-RCC mass to obtain a final hematocrit of approximately 60%±10%. Once diluted and filtered, the final CB-RCC was sampled for quality parameters, such as hemogram, hemolysis, and sterility. All CB-RCC units were fully processed within 48 hours of collection. CB-RCCs were stored at 4°C. The final acceptable volume of CB-RCCs was established to be at least 20 mL, with negligible hemolysis, a hematocrit of around 60% (±10%) and an acceptable residual leukocyte content of less than 1×10^6 /unit. The product had a shelf life of 14 days. Our research group previously validated the production and quality assurance phases of CB-RCCs, demonstrating that, under defined storage and irradiation conditions, CB-RCC units are comparable in terms of stability and quality to standard A-RCC units^{22,24}. Lastly, RBC irradiation was conducted at 30 Gy within 6 hours before transfusion.

Quality controls

Complete blood counts (CBC) for the initial CB units were obtained using an XN-1000 hematology analyzer (Whole Blood mode; Sysmex Europe GmbH, Norderstedt, Germany). For the CB-RCC, the same equipment was utilized via the specialized Blood Bank mode to determine residual white blood cell (rWBC) and platelet (rPLT) counts, hemoglobin (Hb) levels and hematocrit (Hct). The percentage of hemolysis was calculated using the following equation: $(\text{plasma Hb} \times (100 - \text{CB Hct})) / \text{CB Hb}$.

After release for transfusion, HbF quantification was performed using dried blood spot samples analyzed by capillary electrophoresis with a commercial kit designed for the Sebia Capillarys 3 DBS system (Capillarys Neonatal Hb Kit, Sebia Inc., Lisses, France). Microbiological sterility was assessed through a validated strategy that includes blood culture on each aliquot using the BACT/ALERT® system in iFAPlus and iFNPlus bottles, with a total incubation period of 14 days at 37°C, and the addition on day 4 of a rapid real-time PCR assay for *Cutibacterium acnes* in cases where the blood culture was not positive for fast-growing bacteria at that time. This method was validated according to European Pharmacopoeia guidelines^{23,24}. Therefore, units with negative results were provisionally released and made available for transfusion between days 4 and 14. After that period, the units were definitively released and withdrawn from stock if not used.

Serological and molecular testing were performed on maternal and CB plasma samples for the following infectious diseases: triple nucleic acid testing (NAT) for hepatitis B and C viruses, human immunodeficiency virus; and antibody and antigen markers for cytomegalovirus, syphilis, hepatitis B virus, *Toxoplasma gondii*, and human T-lymphotropic virus types I and II. Additional testing was also performed when a risk was detected for West Nile virus, *Trypanosoma cruzi*, or *Plasmodium*²³.

Statistics

Statistical analysis was performed using Stata (version 14.2, StataCorp LLC, College Station, TX, USA). Continuous variables were reported as median and interquartile range (IQR). Categorical variables were reported as frequency and percentage.

RESULTS

Process development

During the study period, 161 CB units were collected for CB-RCC production at a median gestational age of 39 weeks and 4 days. Units were processed in a closed system within the standard 48-hour post-collection window, with a median collection-to-processing time of 30 hours and 37 minutes [IQR: 29.1-32.1]. Twenty-six CB units (16%) with a gross volume exceeding 120 mL were split into two kits. As shown in **Figure 2**, a total of 187 aliquots were processed. Blood group distribution and causes of release failures are also indicated.

CB-RCC product characteristics

The characteristics of CB-RCC volumes, blood components and microbiological testing are shown in **Table I**. RBC volumes decreased in a predictable manner during processing, from a median initial whole cord blood (WCB) volume of 100.7 mL [IQR: 86.0-129.5] to a final CB-RCC volume of 25.3 mL [IQR: 23.9-26.8] per aliquot ready for release. The weight of the RBC mass decreased from 32.9 g [IQR: 23.0-46.9] in WCB to 18.1 g [IQR: 17.78-19.0] in the final CB-RCC product, corresponding to a median recovery of 56%. The RBC prefiltration volume was 50.2 mL [IQR: 48.5-51.8], while RBC post filtration volume was 27.3 mL [IQR: 25.6-28.9] per unit. The filter dead (retained) volume was 19.1 mL [IQR: 13.3-24.7]. The retained RBC mass represented 35% [IQR: 19.8-59.7] of the prefiltration RBC mass.

Leukoreduction resulted in near-complete removal of white blood cells. Median final hematocrit after filtration was 60%. Detectable hemolysis was observed in eleven fractionated units (5.8%); in all these units, hemolysis had been 0% in WCB before processing. The total Hb content per CB-RCC unit was 5.66 g [IQR: 2.19-9.28].

HbF levels were assessed only in products released for

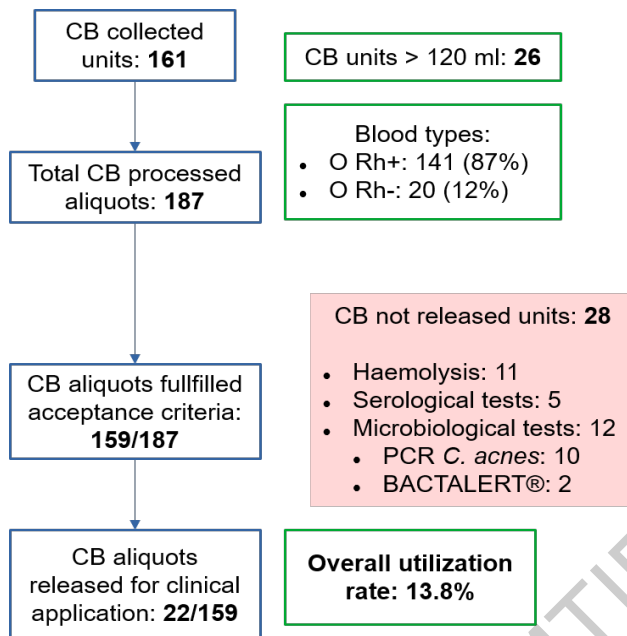


Figure 2 - Process development

Total number of CB-RCC units released in relation to the total number of CB samples and aliquots processed, distribution by blood group of the CB samples, reasons for non-release and overall utilization rate. CB: cord blood; C. acnes: *Cutibacterium acnes*.

Table I - Volume and hematologic characteristics of whole cord blood units before processing and cord blood-derived red blood cell aliquots ready to release

	WCB	CB-RCC
Volume (mL)	100.7 (86.0-129.5)	25.3 (23.9-26.8)
HCT (%)	37 (32-42)	60 (59-64)
Hb (g/dL)	11.7 (11.5-11.9)	18.8 (18.7-19.0)
White blood cells ($\times 10^6/\text{mL}$)	10.8 (10.4-11.2)	0.0
RBC ($\times 10^{12}/\text{L}$)	3.4 (2.9-3.5)	5.3 (5.3-5.9)
Hemolysis (%)	0.0	0.0 (0.00-0.19)

WCB: whole cord blood; CB-RCC: cord blood-derived red blood cell concentrates; HCT: hematocrit; Hb: hemoglobin; RBC: red blood cells. Values are expressed as median and interquartile range.

transfusion (No.=22/159), as required by the clinical trial. The median HbF ratio (measured on 22 CB-RCCs released for clinical use) was 83.7% [IQR: 81.7-85.7].

All CB-RCC units underwent microbiological testing. Among the 161 CB units processed, microbiological contamination was detected in 12 units (7.4%). Two aliquots (1.2%) were positive after incubation with BACT/ALERT® blood culture system, one for *Escherichia coli* and the other for *Bifidobacterium catenulatum*. The time to detection was 9.6 and 118.3 hours, respectively. Real-time PCR detected *Cutibacterium acnes* in ten units (6.2%), always before the fifth day of incubation.

Pilot study on CB-RCC availability and stock output

After processing, 85% of the products fulfilled the acceptance criteria (No.=159). This represents a median available stock of 1.97 units per week [IQR: 1.8-2.1]. Reasons for discarded units for release are shown in **Figure 2**, with microbiological contamination being the most common. There was availability of compatible CB-RCCs in 22 of 28 requests in the clinical trial (78.6%). Among the six occasions when compatible CB-RCC units were unavailable, three involved RhD-negative recipients (A- or O-). Although group O units were in stock, only RhD-positive (O+) units were available and therefore could not be transfused due to RhD incompatibility. In the remaining three cases, stock shortages were attributable to a high transfusion demand over a short period of time. As shown in **Figure 3**, these events were concentrated during the first five weeks of the study and during weeks 33-37.

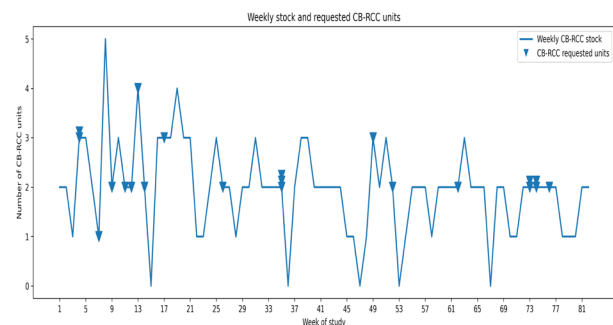


Figure 3 - Blood bank stock output of cord blood red cell concentrates

The image shows CB-RCCs requested for transfusion in relation to CB-RCCs in stock available for release per week. CB-RCC: cord blood-derived red cell concentrates.

DISCUSSION

This study analyzed the preparation of CB-RCC units for transfusion within an open-label, nonrandomized, single-centre clinical pilot study in extremely preterm infants, demonstrating not only the feasibility of the process, but also a significant improvement in product availability compared with previous studies. In fact, the developed blood component met predefined quality and safety-release criteria in a high number of processed units. Experience in developing CB-RCCs for transfusion purposes remains limited. Few research groups, including ours, have published a validated method for CB-RCCs production and quality assurance. Therefore, whether CB-RCC units can be consistently produced and managed to meet the transfusion needs of preterm infants is still an open question. In the present study, CB-RCC units were produced in accordance with our already published workflow²², which predefined quality requirements in terms of leukocyte depletion, hemolysis, stability, and sterility, as recommended by international guidelines²³. The final CB-RCC aliquot volume was 25.3 mL [IQR: 23.9-26.8], which showed limited variability between units and aligned with transfusion volume requirements for preterm infants. This finding was comparable to the data on post-leukoreduction volumes reported by Bianchi *et al.*²⁰, producing CB-RCCs with a median volume of 22 mL [IQR: 17-28]. Recently, the BORN trial reported a higher median final CB-RCC volume of 39 mL [IQR 30-50]²⁵. However, this result should be interpreted in the context of different CB unit selection criteria, including higher initial volumes and hematocrit, and different processing methods, including filtration of whole blood units, which limit direct comparability with our results. In this context, optimizing the initial CB unit volume may be an effective strategy to increase the final CB-RCC yield²⁶. In our study, collection was performed within the established cord blood donation program, but collection procedures were not refined or evaluated prospectively with the specific aim of increasing unit volume. Future implementation studies are needed to assess whether optimizing existing collection procedures can further improve CB-RCC yield and availability.

Processing-related factors may also influence final CB-RCC volume. Following fractionation, the median recovery of RBC mass on WCB versus the final CB-RCC

release observed in our study was 56%, which is slightly higher than the 38% reported by Bianchi²⁰. This result may be partly explained by dead volume retained in the filter and sampling for quality control. In our approach, leukoreduction was performed after fractionation and was highly effective, resulting in near-complete removal of white blood cells. Nevertheless, improvements in leukoreduction technology may increase the final CB-RCC volume, potentially making this product available for use in a larger neonatal population.

In conclusion, future implementation studies must also determine whether CB-RCC-specific quality thresholds are needed, since current hemolysis requirements are largely based on adult RCC component standards. In the present study, hemolysis was 0.03%, meeting predefined quality requirements and remaining lower than the 1.3% reported by Bianchi *et al.*²⁰.

Other groups have also published protocols differing in processing timelines, additive solutions, storage conditions, and irradiation practices. The All-Cord study compared different dilution approaches (pre- vs post-filtration), additive solutions, and storage bag materials, reporting that pre-filtration dilution adversely affected product quality and that post-filtration dilution with PAGGSM stored in non-DEHP bags resulted in lower hemolysis during storage (0.30 ± 0.09)²¹. Similarly, Henriksson *et al.* investigated the impact of extended storage time before processing, proposing that delayed processing could increase logistical flexibility; however, their results also suggested a reduction in RBC deformability, which may compromise cell function²⁷. Finally, the high proportion of HbF found in our final CB-RCC product is consistent with neonatal physiology and comparable to previous reports^{20,27}.

Regarding microbiological safety, the overall contamination rate in our cohort was 7.4%, in line with other published series which have reported contamination rates ranging from 1 to 8%^{20,24,28,29}. The variability in collection practices, the time from collection to processing, sampling volumes, and sterility testing protocols across centres may further contribute to differences between studies. In parallel, methodological factors, such as the use of highly sensitive molecular techniques including PCR may increase the detection of low-level bacterial contamination compared with conventional

culture-based approaches. To achieve a lower contamination risk, it is essential to implement continuous quality monitoring and targeted corrective actions along the entire collection-to-processing pathway.

Clinical experience with CB-RCC transfusion remains limited and has so far only been reported by a few groups. In this context, our pilot study provides additional clinical feasibility data, showing that most processed CB-RCC units were suitable for release and could be consistently available for transfusion in the NICU. In contrast, Teofili *et al.*'s multicentre randomized controlled trial, which aimed to evaluate the impact of CB-RCC transfusion on ROP in extremely preterm infants, reported a high rate of protocol deviations due to CB-RCC unavailability¹⁵. In that multicentre study, CB units were processed across seven different blood banks, which may have contributed to variability in production capacity, logistics, and product availability. These findings underscore the critical operational requirement of sustained CB-RCC availability for broader implementation. In our study, the implementation of a validated protocol, together with continuous stock monitoring and close coordination between the blood bank and the NICU, were key factors in maintaining a readily available inventory and high product availability throughout the study period. This integrated approach supports the operational reproducibility of CB-RCC production and establishes a practical basis for scaling up to a multicentre regional supply model. In Spain, transfusion data from Barcelona suggest that CB-RCC production could provide adequate, and potentially even greater, coverage to meet local clinical needs. The sustained availability achieved in our pilot study therefore supports the feasibility of scaling up this model to the regional level by using centralized processing and standardized logistics.

Beyond its potential clinical benefits for preterm newborns, demonstrating the feasibility of CB-RCC production also supports the broader concept of multi-component cord blood banking. Currently, more than 80% of collected CB units are discarded for hematopoietic stem cell transplantation due to insufficient stem cell counts. An international proof-of-concept exercise involving a network of 12 public cord blood banks established a preliminary standardized framework for the routine production of cord blood platelet concentrates, cord

blood platelet-poor plasma, and CB-RCCs for therapeutic use²². Our results further support this international strategy aimed at maximizing the clinical value of CB-derived components with wide therapeutic potential, in addition to reducing ethical concerns about the current high cord blood disposal rate and improving the economic sustainability of public cord blood banks. Coordinated implementation across public blood banks could facilitate extension of this approach nationwide. At a national level, future CB-RCC inventory networks would require centralized coordination, continuous stock monitoring, early shortage alerts, emergency planning, and harmonized activity reporting to support standardized inventory management and equitable access across centres.

We identified several study limitations. Our high availability results should be interpreted in light of the fact that the inventory relied exclusively on group O units, and RhD incompatibility accounted for 50% of stock-out events, occurring when only O+ units were available for RhD-negative recipients. Future implementation may therefore benefit from a blood group-stratified approach and the inclusion of A units in order to further reduce unavailability while preserving operational feasibility. In parallel, based on our previous validation results²², a maximum storage time of 14 days was selected to ensure stability due to irradiation, as hemolysis increased beyond this period. Future research focused on extending shelf-life and incorporating additional markers of RBC aging (e.g., ATP) and hemolysis susceptibility, as well as validating different storage methods such as freezing, may enable longer stocking times and improved availability. In addition, the product is currently limited to a maximum of 12 hours after irradiation. Although current guidelines recommend irradiation for transfusions in very low birth weight newborns²³, further evaluation of the risk-benefit balance between the very low incidence of transfusion-associated graft-versus-host disease and the potential advantages of increased immediate availability may be warranted, depending on local clinical practice and patient risk profiles. Reported cases of neonatal graft-versus-host disease have occurred almost exclusively in the presence of additional risk factors such as intrauterine or exchange transfusion, congenital immunodeficiency, or transfusion from blood relatives,

and were mainly described before the implementation of universal pre-storage leukodepletion. In the absence of these risk factors, graft-versus-host disease is exceedingly rare, and consequently the most recent guidelines for graft-versus-host disease prevention no longer recommend irradiation for neonates with no known or suspected defect in cellular immunity³⁰. Lastly, it was not possible to extract CB-derived platelets from WCB during processing⁴, resulting in a portion of CB material being unused. It is well known that CB-derived platelets might have therapeutic use for ophthalmic³¹ and cutaneous applications³². Refining this component of the process could improve the overall utilization of CB.

CONCLUSIONS

In conclusion, the development and implementation of CB-RCC production is feasible within an integrated transfusion pathway when supported by a validated processing protocol and coordinated logistics between the blood bank and NICU. In this pilot clinical study, CB-RCC units met predefined quality and safety criteria in a high proportion of cases, and could be maintained as a readily available inventory, supporting consistent access for transfusion in extremely preterm infants. Importantly, our findings provide operational evidence that centralized processing and structured stock management can improve product availability, although blood group compatibility also needs to be addressed in future scalability strategies. Overall, these results establish a robust foundation for broader clinical evaluation and support the potential for regional implementation of CB-RCC transfusion programs.

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Role of the funder/sponsor

The funder had no role in the design and conduct of the study; collection, management, analysis, and

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Authorship contributions

G-GE, SD and A-CM had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: G-GE, A-CM, SD, F-SJ, QS, A-NE. Study development (processing): SD, FE, VE, AC, C-FN, M-LN, S-GM, CM, AG. Acquisition, analysis, or interpretation of data: G-GE, GdAM, F-SJ, SD, HN, A-CM. Drafting of the manuscript: G-GE, SD, F-SJ, A-CM. Critical revision of the manuscript for important intellectual content: all Authors. Statistical analysis: G-GE. Obtained funding: QS, G-GE, A-CM, SD. Administrative, technical, or material support: QS, F-SJ. Supervision: A-CM, SD, F-SJ.

Conflict of interest disclosures

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