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Received: 13 March 2024 | Revised: 4 June 2024 | Accepted: 20 August 2024

DOI: 10.1111/trf.18007

TRANSFUSION

ORIGINAL RESEARCH

Blood Components

Storage properties of platelet concentrates from umbilical cord blood prepared using three different methods

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Funding information
Griffini-Miglierina Grant; Ministero della Salute

Abstract

Background: Thrombocytopenia, common in preterm newborns, may increase bleeding risk and is often treated with transfusions. Recent studies reveal that transfusing platelets at a high threshold worsens outcomes, possibly due to a "developmental mismatch" between adult-derived platelets and neonatal hemostatic system. Cord blood-derived platelet concentrates (CBPCs) could be an alternative for newborns. Our study aims to produce and evaluate the quality parameters of CBPCs during storage.

Study Design and Methods: Cord blood was collected from placentas after near-term and full-term pregnancies. Several production methods were attempted to obtain CBPCs, varying centrifugation settings, filtration, and dilution procedures. Adult-derived platelet concentrates (PCs) processed with the same methods, and standard PCs from five buffy-coats were used as controls. Storage tests were performed on days 2, 4–5, 7 from the collection.

Results: CBPCs parameters were compared with adult-derived PCs, and no significant differences were found for mean platelet volume (MPV), swirling, morphology, glucose, lactate, pCO_2, and pO_2. pH and bicarbonate were lower

Abbreviations: 5BC-PC, 5 buffy coats platelet concentrate; CB, cord blood; CBPC, cord blood platelet concentrate; CPD, citrate-phosphate-dextrose; ELBW, extremely low birth weight; IVH, intraventricular hemorrhage; MMP, mitochondrial membrane potential; MPV, mean platelet volume; NICU, neonatal intensive care unit; UCB, umbilical cord blood; WBC, white blood cell.

in CBPCs. Some significant differences between methods in CD62P expression and JC-1 ratio were observed. Compared with standard PCs, CBPCs showed lower platelet concentration, pH, and JC-1. Additionally, both in CBPCs as well as in control PCs, the apoptosis marker phosphatidylserine was elevated.
Discussion: CBPCs were of comparable quality to control PCs during storage. However, apoptosis markers in both groups were elevated, suggesting processing and storage of low volumes of PCs require further optimization. Also, filtration of low volumes leads to significant platelet loss, an issue that requires remedy.

KEYWORDS
neonatal transfusion, platelet transfusion, preterm newborn, umbilical cord blood

1 | INTRODUCTION

Thrombocytopenia, defined as a platelet count $<150 \times 10^9$/L, is a common finding in preterm neonates, as it may occur in 18%–35% of infants admitted to the Neonatal Intensive Care Unit (NICU) and 73% of extremely low birth weight (ELBW) infants.[1,2] The extent to which thrombocytopenia and platelet hyporeactivity, typical of ELBW, affect this population's bleeding risk is unknown.[3,4] Major bleeding, including intracranial hemorrhage (mainly intraventricular hemorrhage [IVH]), is a severe issue in NICUs, affecting approximately 6%–11% of neonates admitted, most of whom are preterm infants.[4–8] Thrombocytopenia is often considered a risk factor for bleeding, as well as respiratory and hemodynamic instability.[2,6–8] Although they are frequently temporally related, thrombocytopenia and IVH have never been proven to be causally related.[5,9]

Neonatologists often prescribe platelet transfusions, especially in preterm neonates, in an effort to avert or lessen the risk of bleeding. Approximately 80% and up to 98% of platelet transfusions are given prophylactically to newborns who do not bleed, but evidence for their value is limited and controversial.[10–12] Thresholds for platelet transfusions are highly variable worldwide, due to the lack of consensus and considerable variation in international guidelines.[5,9,13,14]

Recent research has shown that transfusing platelets at a higher threshold does not prevent bleeding and may even have adverse effects, including raising the risk of bleeding and the incidence of bronchopulmonary dysplasia.[4,15–18] Therefore, the dogma that prophylactic platelet transfusions prevent bleeding in this patient group may be more intricate than we have assumed. Due to all the differences between neonatal and adult platelet activity and functionality, which can be summarized in neonatal platelet hyporeactivity, counterbalanced by higher hematocrit levels, mean corpuscular volume, von Willebrand factor (VWF) concentrations, and longer VWF polymers, transfusing adult platelets to preterm infants could potentially be harmful.[1,19–22] A mismatch between adult transfused platelets and the newborn hemostatic system, as well as volume overload, are potential underlying mechanisms.[4,15–17] In fact, since platelets from neonates exhibit a reduced ability in activating immune cells compared with platelets from adults, platelet transfusions from adult donors may act like a pro-inflammatory and pro-thrombotic trigger and lead to the "developmental mismatch" between neonatal and adult blood.[3,16] The developmental mismatch involves the disruption of the normal neonatal balance and adult "hyperreactive" platelets which may lead to thrombotic complications and fail to prevent bleeding episodes in neonatal blood.[23]

Therefore, as well as studying the possible further reduction of the transfusion threshold, research should focus on new transfusion products, which may be more appropriate for preterm neonates, such as blood products derived from umbilical cord blood (UCB). In general, UCB's principal application is as a source of hematopoietic stem cells for children and adults affected by hematological diseases. However, due to insufficient stem cells in around 80% of collections, donated units are often discarded.[24,25]

Recently, blood products derived from UCB have been studied and developed for other several clinical applications.[24–27] UCB has been regarded as a source of red cells for transfusion in infants due to its high hemoglobin concentration, a rise in hematocrit or hemoglobin comparable with adult-derived transfusions, and no documented transfusion-related side effects.[28–31] Prematurity-related complications (bronchopulmonary dysplasia, IVH, necrotizing enterocolitis, and respiratory distress syndrome) were reduced, possibly due to the fetal

hemoglobin, which has a higher oxygen affinity and a lower oxygen release to tissues than adult hemoglobin (HbA).[24,28,29,32–34]

Platelet-rich plasma (PRP) made from UCB has been utilized successfully as a restorative product for applications such as wound healing and ulcers as a platelet gel or lysate.[24–27,35–37] In the NICU context, a potentially effective product for transfusing thrombocytopenic infants is platelet concentrates (PCs) made from UCB. The aim of our study was to assess the best method to process PCs obtained from UCB for transfusion purposes in preterm babies and to evaluate the storage properties of the UCB platelet concentrates (CBPCs) over time.

2 | MATERIALS AND METHODS

2.1 | Cord blood collection

We collected UCB from both vaginal and cesarean deliveries after near-term (≥35 weeks of gestational age) and full-term uncomplicated pregnancies. For vaginal deliveries, the collection occurred before the placenta delivery. In contrast, for cesarean deliveries, UCB was collected after the placenta delivery, in both cases by cannulation of the umbilical vein with a dedicated collecting system (CB Collect, T2950, Fresenius Kabi, Bad Homburg, Germany). Collection was performed by gravity in the bags containing 27 mL of citrate-phosphate-dextrose (CPD) anticoagulant. The amount of CPD was reduced during the experiment to 10 mL, as dilution was noticed in some cases. We decided to set a threshold of a minimum weight of 55 grams (including the weight of the collection bag, about 35 mL of blood including anticoagulant) and a starting platelet count of 120×10^9/L to consider UCB suitable for processing. UCB was transported and stored at controlled room temperature until processing within 36 hours from collection.

2.2 | Methods for platelet isolation

We compared three different preparation methods to obtain CBPCs (Figure 1). In Method 1, whole blood first underwent a centrifugation step at 200 × *g* for 4–6 min, depending on the starting volume and hematocrit (Sorvall RC12BP+, Thermo Scientific, Waltham, MA), and the PRP was manually separated using a plasma clamp and transferred through a leukoreduction filter to a second container (GT526NL, Bioflex CS, Fresenius). Before filtration, the filter was primed with platelet additive solution type E (PAS-E, T-PAS+, Terumo BCT, Lakewood, CA). After filtration, the filter was gently washed with a mixture of PAS-E and plasma from the UCB (ratio of 2:1) to increase platelet recovery. After filtration, a second centrifugation phase was performed with a hard spin

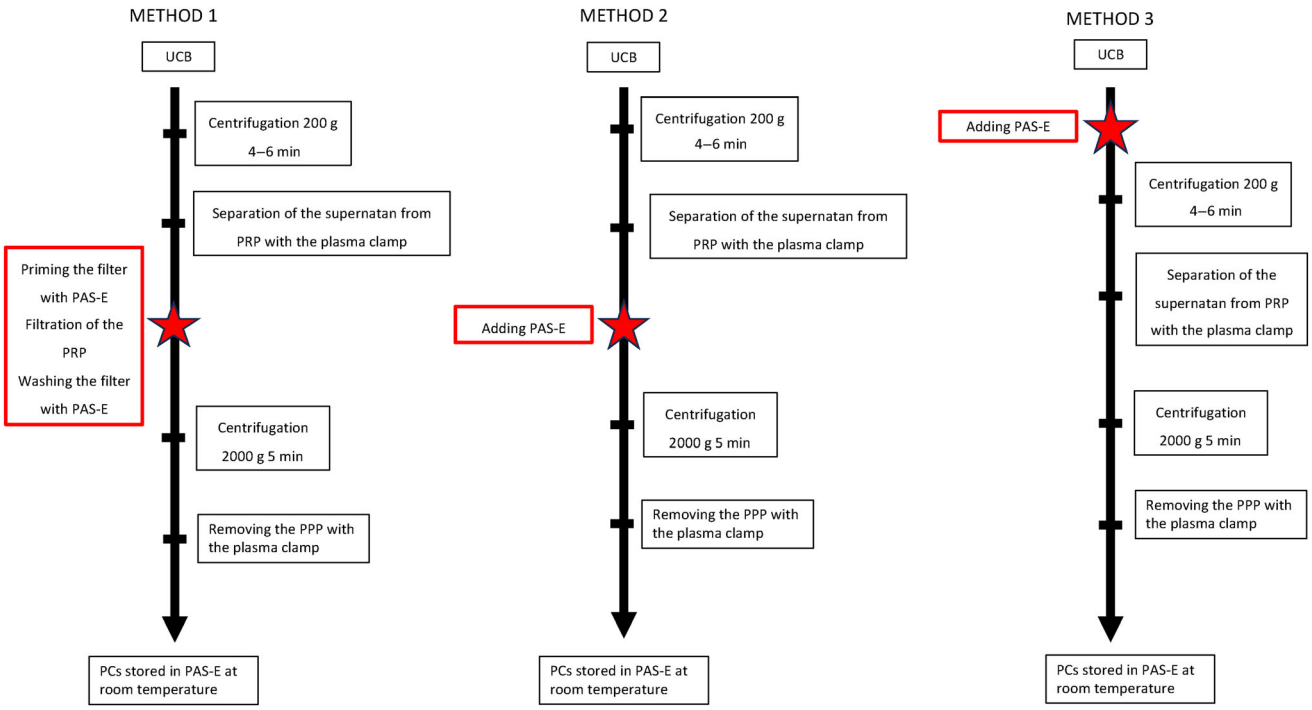

FIGURE 1 Flow-chart of the study. PAS-E, platelet additive solution type E; PCs, platelet concentrates; PPP, platelet-poor plasma; PRP, platelet-rich plasma; UCB, umbilical cord blood. [Color figure can be viewed at wileyonlinelibrary.com]

(2000 × *g* for 5 min). Removal of the platelet-poor supernatant allowed to obtain a PC, by resuspension of platelets in a smaller volume of 65% PAS-E/35% plasma. After processing, PCs were stored in PAS-E at room temperature in a dedicated platelet incubator in 150-mL bags manually sealed to reduce the size (EQ06A0E, Fresenius).

To increase the platelet recovery, as we noticed that the platelet concentration dropped off during the process, we decided to try Method 2, which was identical to the first one apart from the filtration step, which was skipped.

In Method 3, we added PAS-E at the beginning of processing, before the first centrifugation step, instead of after it, as higher starting volume would increase further platelet recovery. Also, no filtration step was included here.

Adult-derived PCs obtained with all three methods and with the same average starting whole blood volume were processed and served as controls. These whole blood units were discarded for routine use due to a low collection volume.

We also performed a comparison between the CBPCs obtained and "standard" PCs from five buffy coats (5BC-PCs), as described in detail earlier.[38]

2.3 | Quality parameter assessment

After collection, sampling for *in vitro* analysis was performed on days 2, 4–5, and 7 (depending on weekdays and weekends). Before sampling, the PCs were weighed to determine the volume, and swirling was visually assessed (0 = no swirl, 1 = poor swirl, 2 = good swirl, 3 = excellent swirl). Sampling was performed aseptically, and sample volume was kept to a minimum (750 microliter). We performed complete cell count, mean platelet volume (MPV) (Sysmex XN1000, Sysmex, Kobe, Japan), and blood gas analysis (pH, pCO_2, pO_2, HCO_3, lactate, glucose; Radiometer ABL90 FLEX, Radiometer, Copenhagen, Denmark).

Morphology was assessed after fixation with glutardialdehyde by determination of the platelet shapes under a light microscope (EVOS XL Microscope) based on the method by Kunicki et al.[39]

Flow cytometry assays (FACS Canto II, BD Biosciences) were used to assess P-selectin expression (CD62P), a platelet activation marker, with FITC-labeled anti-CD62P (Beckman Coulter, ref. 200,048), phosphatidylserine exposure by fluorescently labeled Annexin A5, and the mitochondrial membrane potential (MMP) with the dye JC-1. The methods are described in more detail elsewhere.[40]

2.4 | Statistical analysis

An unpaired Student's *t*-test was used to compare adult-derived and CBPC characteristics in each Method (GraphPad Prism 9.1.1, San Diego, CA, and Microsoft Excel software). A value of $p < .05$ was considered statistically significant.

Differences between the three methods were analyzed with a one-way analysis of variance (ANOVA) followed by a Turkey-Kramer multiple comparison post-test (Instat version 3.06, GraphPad). A Kruskal–Wallis analysis was performed with Dunn's post-test in case of a non-normal distribution in one or more groups.

3 | RESULTS

3.1 | Baseline characteristics

The baseline characteristics of whole blood and PCs derived from UCB or adult blood are shown in Table 1, divided according to the processing Method used. No statistically significant differences were found in the baseline features of the adult and UCB-derived products, except for the hematocrit of the starting product, which was significantly higher in adult blood in Methods 2 and 3. In Method 1, the platelet count and volume were significantly lower in CBPCs compared with the PCs from adult whole blood. As expected, platelet recovery was lowest in Method 1 and seemed specific for UCB. Removal of the filtration step in Method 2 increased the recovery. If the starting volume upfront by adding PAS-E to UCB in Method 3 was higher, the platelet recovery increased to 70%–85% (Table 1).

However, filtration is necessary to remove white blood cells (WBCs). As shown in Table 1, in the CBPCs processed without filtration, WBCs were mainly above the threshold of 1×10^6/U (89%–100%) and 5×10^6/U (44%–75%).

3.2 | Quality parameter assessment

The *in vitro* quality and storage parameters of PCs obtained with Method 1 are shown in Figure 2. No statistically significant differences between CBPCs and controls were found, except for pH and bicarbonate. The MPV in CBPCs tended to increase over time, with no statistically significant difference with PCs from adult blood. Based on the high pO_2 and low pCO_2, the gas exchange capacity of the storage bag in relationship to platelet content was very high and sufficient. Similar results with Methods 2 and 3 were obtained (results not shown), but

TABLE 1 Baseline characteristics of whole blood and platelet concentrates derived from umbilical cord blood (UCB) and adult blood.

	Whole blood			Platelet concentrates		
Method 1	**UCB ($n = 6$)**	**Adult ($n = 6$)**	***p*-Value**	**UCB ($n = 6$)**	**Adult ($n = 6$)**	***p*-Value**
Volume (mL)	65 ± 28	61 ± 12	.80	7 ± 3	13 ± 3	.019
Platelet concentration ($\times 10^9$/L)	226 ± 65	233 ± 14	.81	266 ± 114	350 ± 79	.17
Platelet count ($\times 10^9$/U)	15.7 ± 10.4	14.3 ± 2.6	.75	1.8 ± 0.7	4.5 ± 1.4	.002
Hematocrit (%)	36.3 ± 6	37.6 ± 3.2	.64	n.a.	n.a.	
Platelet recovery (%)				24 ± 19	32 ± 9	
	Whole blood			**Platelet concentrates**		
Method 2	**UCB ($n = 9$)**	**Adult ($n = 6$)**	***p*-Value**	**UCB ($n = 9$)**	**Adult ($n = 6$)**	***p*-Value**
Volume (mL)	65 ± 19	58 ± 17	.50	9 ± 4	12 ± 3	.52
Platelet concentration ($\times 10^9$/L)	214 ± 46	205 ± 28	.68	420 ± 130	410 ± 194	.91
Platelet count ($\times 10^9$/U)	14.5 ± 6.6	11.7 ± 2.9	.36	3.6 ± 1.8	3.9 ± 1.7	.77
Hematocrit (%)	32.2 ± 6.4	37 ± 1.4	.09	n.a.	n.a.	
Platelet recovery (%)				49 ± 17	33 ± 12	
White blood cells (10^6/U)				2.46 (15.84)	10.24 (10.31)	
Units with WBCs < 1 × 10^6/U (%)				1/9 (11%)	2/6 (33%)	
Units with WBCs < 5 × 10^6/U (%)				5/9 (55%)	2/6 (33%)	
	Whole blood			**Platelet concentrates**		
Method 3	**UCB ($n = 8$)**	**Adult ($n = 3$)**	***p*-Value**	**UCB ($n = 8$)**	**Adult ($n = 3$)**	***p*-Value**
Volume (mL)	65 ± 8	43 ± 5	.50	14 ± 3	15 ± 3	.46
Platelet concentration ($\times 10^9$/L)	186 ± 53	212	.44	362 ± 109	351 ± 4	.87
Platelet count ($\times 10^9$/U)	8.9 ± 3.9	9.2 ± 1.1	.90	4.9 ± 1.4	5.4 ± 1	.61
Hematocrit (%)	30.7 ± 2.8	34.3	.06	n.a.	n.a.	
Platelet recovery (%)				78 ± 4	66 ± 7	
White blood cells (10^6/U)				6.53 (5.08)	3 (3.14)	
Units with WBCs < 1 × 10^6/U (%)				0/8 (0%)	0/3 (33%)	
Units with WBCs < 5 × 10^6/U (%)				2/8 (25%)	2/3 (75%)	

Note: Results are expressed as mean ± SD except white blood cells which are expressed as median (interquartile range).
Abbreviation: WBCs, white blood cells.

the flow cytometry assays did show differences, as shown in Figure 3. Best storage conditions were found in CBPCs with a minimum final volume of 12–15 mL and with a high platelet count (>400 × 10^9/L): they showed the lowest values of activation and apoptotic rates and kept relatively high mitochondrial activity, indicating optimal balance between plastic surface and platelet suspension. On the other hand, some of these "best" PCs also had a high content in WBCs. Otherwise, lower volumes of PCs (<8 mL) showed the highest activation at flow cytometry assays and a rapid decrease in mitochondrial activity over time.

Table 2 compares the storage parameters of CBPCs obtained with the three methods. The only remarkable difference is in platelet count and number, which is significantly lower in Method 1 than in Methods 2 and 3, respectively. As measured by Annexin A5 staining, phosphatidylserine exposure was lower in Method 2 compared with Method 1 on D4–5 and D7. pO2 and pCO2 resulted higher and lower in Method 1, respectively, than in Method 3 (Table 2).

In the previous experiments, PCs from adult whole blood processed the same way as CBPCs and stored in small bags were considered as controls. In an additional analysis, we used standard 5BC-PCs stored under routine conditions in 1300 mL containers as controls. The platelet concentration was significantly higher in the standard PCs (see Figure 4 and Table S1). pH and pCO_2 were significantly lower in CBPCs (combined results of all three methods), and pO_2 and glucose were higher (all

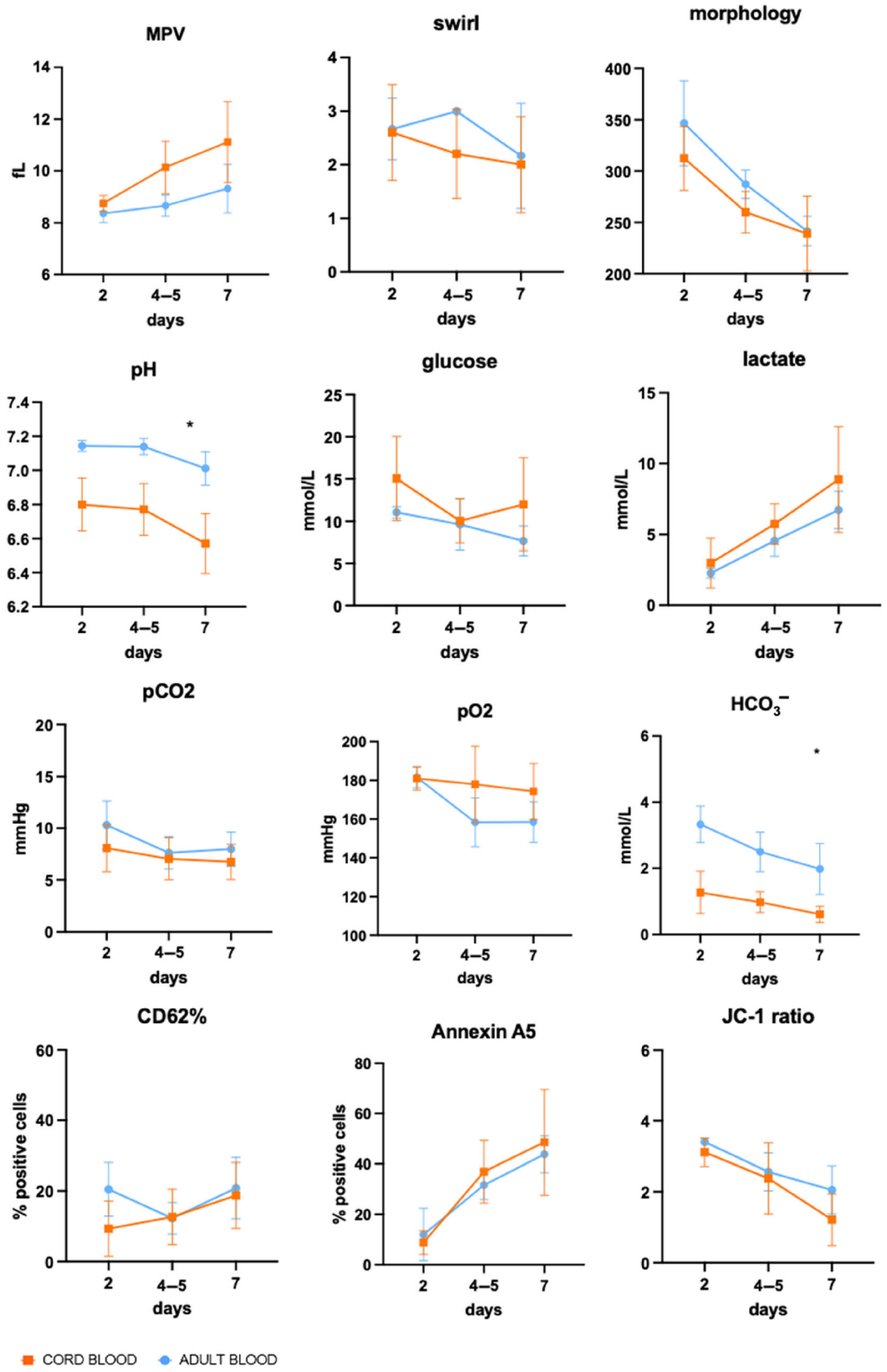

FIGURE 2 Quality parameters of cord blood-derived platelet concentrates (orange line) and adult-derived platelet concentrates (blue line) processed with Method 1. Statistically significant differences are indicated with asterisk (*). MPV, mean platelet volume. [Color figure can be viewed at wileyonlinelibrary.com]

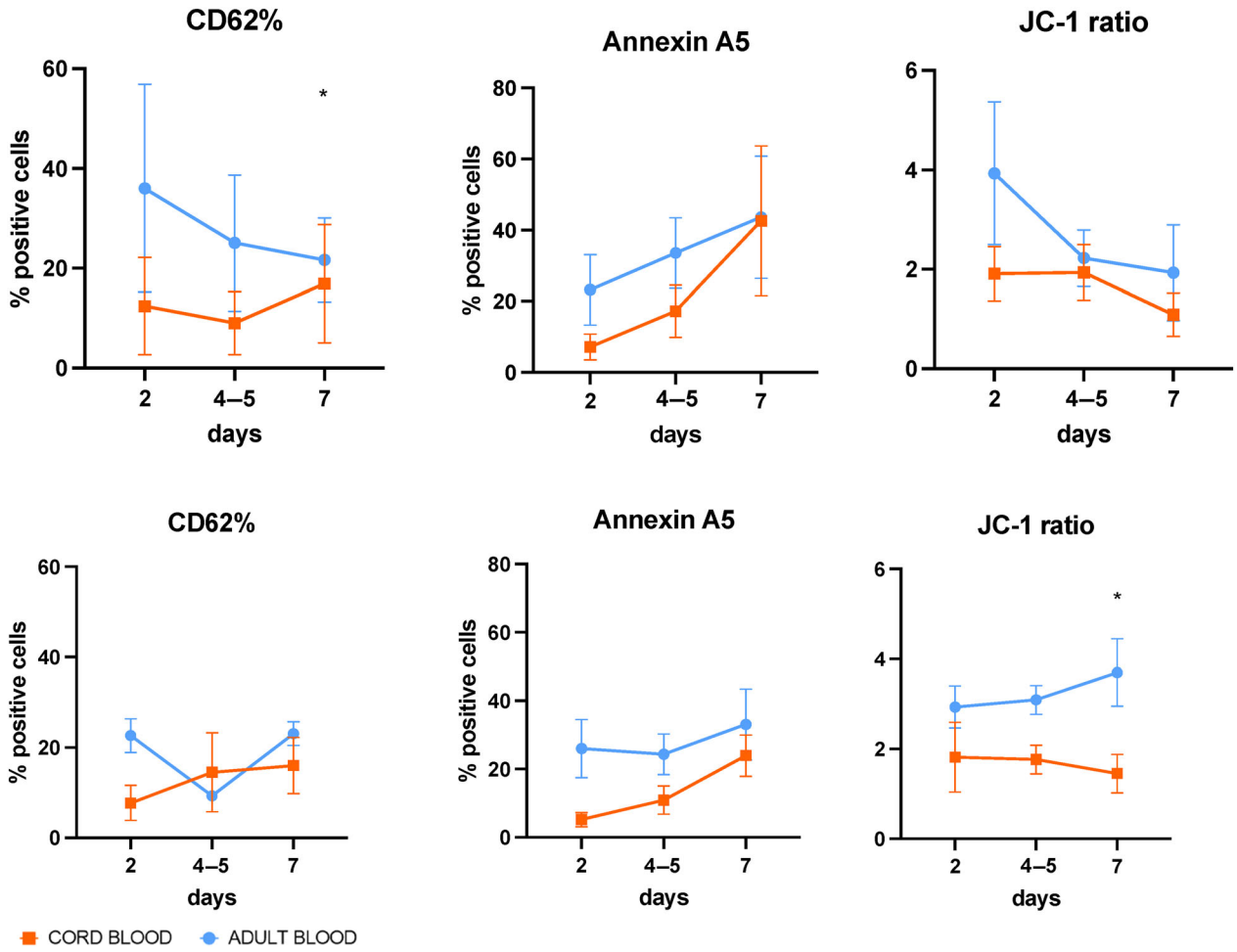

FIGURE 3 Quality parameters of cord blood-derived platelet concentrates (orange line) and adult-derived platelet concentrates processed with Method 2 (upper line) and Method 3 (lower line). Statistically significant differences are indicated with asterisk (*). [Color figure can be viewed at wileyonlinelibrary.com]

determinations). The lactate concentration and the increase over time were similar between the two groups (Figure 4 and Table S1). Starting levels of CD62P and phosphatidylserine exposure (Annexin A5) were higher in CBPCs and increased much more in CBPCs than in 5BC-PCs.

Table S2 compares time points (day 2 vs. day 4–5 vs. day 7) within the same Method for CB and adult-derived PCs. As expected, pH and bicarbonate decrease over time, as well as lactate concentration increases, with all the three methods, both for CB and adult-derived PCs. Morphology assessment worsens significantly over time. Regarding flow cytometry assays, phosphatidylserine exposure has a statistically significant increase over time for all methods, while the JC-1 ratio shows a tendency to decrease without a uniform statistical significance. CD62P, which represents platelet activation, sometimes is higher on D2 than on D4–5. This might reflect a residual activation from processing stress, which lowers in the following determinations.

4 | DISCUSSION

Similarly to what is happening with red blood cells, PCs derived from UCB might be a promising component for transfusing thrombocytopenic newborns. Therefore, we developed a protocol to obtain CBPCs and assess their storage properties, as an alternative platelet product for this patient group, instead of the (single-donor) apheresis platelets now in use.

We started processing CBPCs with a filtration step to eliminate WBCs, whose presence in blood products increases the risk of immune reactions. For this reason, the maximum number of WBCs allowed in a unit of a standard PC is 1×10^6/U. However, neonatal immune system has tolerogenic features and previous studies on non-leukoreduced whole cord blood transfusion did not demonstrate any adverse[24,28,41,42]; thus, the clinical application of unfiltered products might be considered in the future. In fact, in our experiment filtration resulted in a low platelet recovery, especially for UCB-derived

TABLE 2 Comparison between means of cord blood-derived platelet concentrate parameters obtained with the three processing methods (Method 1 vs. Method 2; Method 1 vs. Method 3; Method 2 vs. Method 3).

	Method 1			Method 2			Method 3		
	D2	D4–5	D7	D2	D4–5	D7	D2	D4–5	D7
Volume (mL)	7.9	5.7	5.4	11	7.9	7.5	14.4[a]	14.3b	13.3[b,c]
PLT (10^9/L)	199	230	188	394[d]	450	423[d]	329	361	333
PLT (10^9/U)	1.4	1.4	1	4.3	3.6[d]	3.1	4.8[a]	5.6[a]	4.6[b]
MPV (fl)	8.8	10.1	11.1	8.4	9.2	11.2	9.8[e]	10.4	11.3
CD62p%	9.3	12.7	18.7	12.4	9	16.9	7.7	14.5	16
Annexin A5%	8.9	36.9	48.6	7.1	17.2	42.6	5.2	10.9[b]	24[a]
pH	6.8	6.77	6.57	6.75	6.69	6.41	6.71	6.59	6.52
HCO_3^- (mmol/L)	1.3	1	0.6	1.8	1.1	0.6	1.8	1.3	1
pO2 (mmHg)	181	178	174	164	160	163	151[a]	139[a]	146[a]
pCO2 (mmHg)	8.1	7	6.8	12.7	9.4	9.2	14.6[a]	13.5[a]	12.4[b]
Glucose (mmol/L)	15.1	10.1	12	16.4	13	11.3	19.2	18.1[b]	16
Lactate (mmol/L)	3	5.7	8.9	2.6	6.4	11.5	2.5	5.5	8.2
Morphology	313	260	239	315	305[d]	258	325	300	275
JC1%	9.6	26.4	49.4	32.5	25.2	58.9	35.8	25.3	35.5
JC-1 ratio	3.1	2.4	1.2	1.9	1.9	1.1	1.8[a]	1.8	1.4

Abbreviations: MPV, mean platelet volume; PLT, platelet.
[a]$p < .05$ Method 1 versus Method 3.
[b]$p < .01$ Method 1 versus Method 3.
[c]$p < .05$ Method 2 versus Method 3.
[d]$p < .05$ Method 1 versus Method 2.
[e]$p < .01$ Method 2 versus Method 3.

platelets. A fixed amount of platelet is trapped inside the filter, and with low volumes, as we have with UCB (with an average starting volume of only 59 mL), this loss inside the filter is relevant for the overall recovery. Filtration seems to affect platelet recovery more in CBPCs than in adult-derived PCs, as demonstrated by the platelet count per unit and confirmed by a comparison between the three methods. A hypothesis could be that the filter removes the largest and newest platelets first, which are more represented in UCB.[43] This hypothesis might be supported by the tendency of MPV to be higher in UCB platelets.

The low platelet recovery in PRP with filtration is the reason why we decided to remove the filtration step. The recovery increased to 50% with Method 2 and 80% with Method 3. Still, residual WBCs are an issue that requires further optimization, possibly by combining Methods 1 and 3 and using filters with a small dead volume, which will need to be developed. Moreover, we never reached the same platelet concentration of adult standard 5BC-PCs.

The difference between CBPCs and controls concerning pH and bicarbonate can likely be attributed to the ratio of storage medium (PAS-E) and the acidic anticoagulant (CPD, pH ~5.5) in the collecting bags rather than due to the product itself, and similarly results about pH and pCO_2, which were significantly lower in CBPCs in comparison with standard 5BC-PCs (combined results of all three methods), and pO_2 and glucose, which were higher (all determinations), can be attributed to CPD as well.

The quality parameters of CBPCs during storage were encouraging, as they showed similar, or even better, features compared with their adult counterpart. Lactate concentration, an indirect measure of cellular metabolism, is similar among all the products we compared. Activation and apoptotic markers in CBPCs are comparable with or even lower than in adult-derived PC controls or standard PCs. This is a positive result as fewer activated and apoptotic platelets mean a more stable product over time.

When compared with standard 5BC-PCs, CBPCs show higher CD62P, Annexin A5, MPV, and lower MMP, especially on D2. Parameters sensitive to storage conditions, like lactate production rates, MMP, phosphatidylserine exposure, and MPV, show a strong increase over time, suggesting that storage up to day 7 needs improvement.

Some limitations of the study must be highlighted. The starting features of UCB, such as volume and platelet

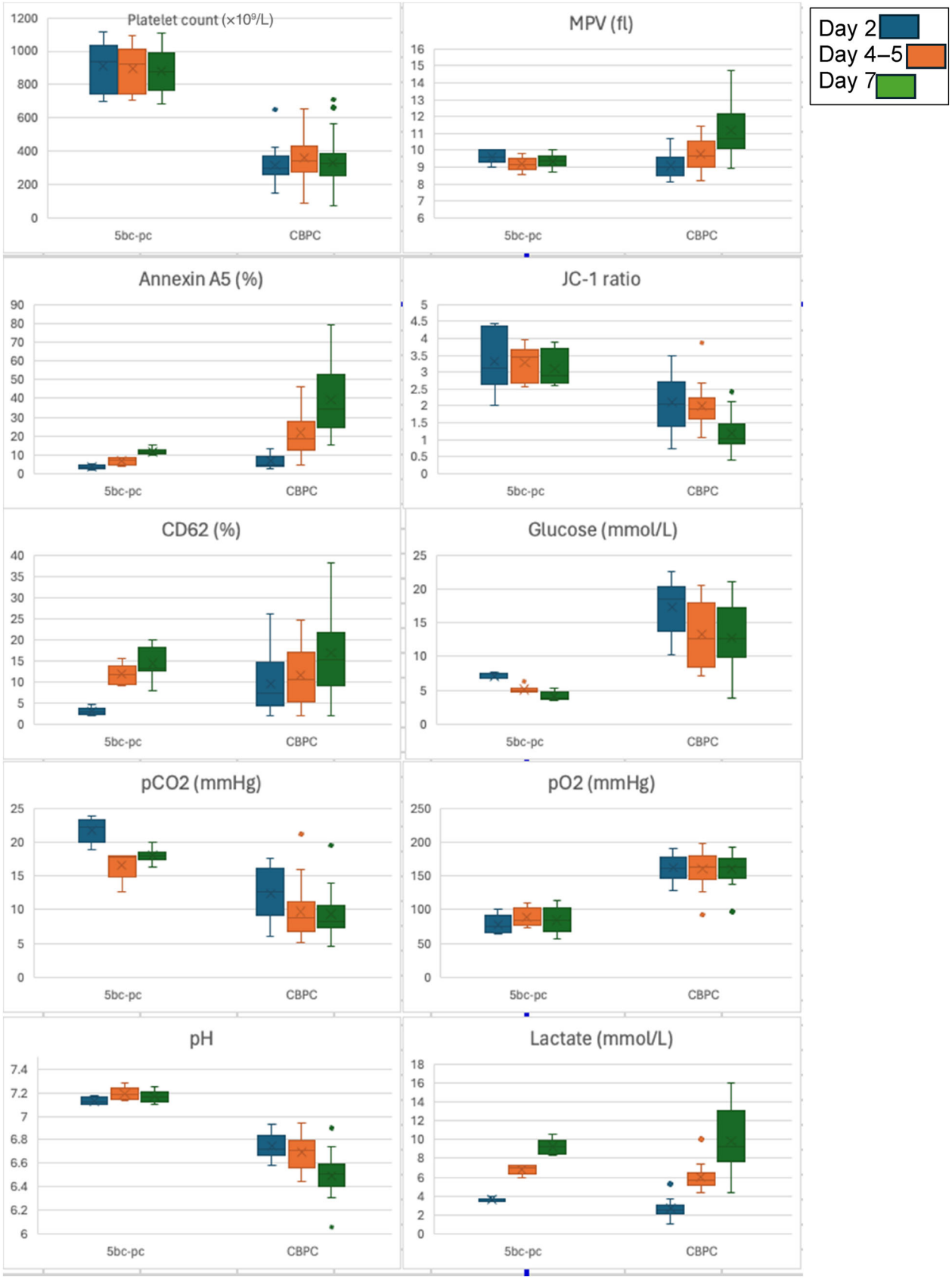

FIGURE 4 Comparison of in vitro platelet concentration parameters from five buffy coats versus cord blood-derived platelet concentrates (CBPCs). MPV, mean platelet volume. [Color figure can be viewed at wileyonlinelibrary.com]

count, are highly variable. This makes establishing a standardized protocol to process UCB difficult and can prevent obtaining a final product that meets specifications. We used small 150-mL bags to fit the low volumes of CBPCs. To what extent these storage bags, standardized for pediatric volumes of red blood cells, affected the storage properties of the platelets is unknown. However, we found they did not affect CBPCs more than adult-derived PCs stored in the same way. Even smaller 60-mL containers are available but need to be evaluated for storage of CBPCs.[44] We did not perform antimicrobial tests on our products. Moreover, this study has been conducted on a few CBPCs ($n = 23$), so further research must confirm these findings. Lastly, our study focused on in vitro characteristics. However, the clinical relevance of CBPCs still needs to be established in clinical trials.

We did not pool multiple UCBs together, but this option can be considered, as it should increase starting volume and platelet count. However, the units should be AB0-matched, which would be logistically challenging as AB0 determination is not routinely performed after the delivery. Moreover, this would demand a change in policy because single-donor apheresis platelets are now used for neonates needing a platelet transfusion. The number of residual white cells requires further optimization, and reducing filter dimensions or washing after filtration are options to be considered. Once the processing is optimized and a standard protocol is obtained, the clinical efficacy should be evaluated in a randomized controlled trial comparing CBPCs with adult standard PCs to assess the best product for newborns.

The methods described here can be used to obtain a CB-derived thrombocyte product of satisfactory quality. However, obtaining CE-certified bag systems and small filters will aid in the further optimization of processing CB-derived thrombocytes and meet predefined specifications.

AUTHOR CONTRIBUTIONS

Conceptualization: Valeria Cortesi, Thomas R. L. Klei, Enrico Lopriore, Giacomo Cavallaro, Stefano Ghirardello, and Genny Raffaeli, and Susanna Fustolo-Gunnink. *Methodology*: Thomas R. L. Klei. *Formal analysis*: Valeria Cortesi and Ido J. Bontekoe. *Investigation*: Valeria Cortesi, Ido J Bontekoe, and Thomas R. L. Klei. *Data curation*: Valeria Cortesi and Ido J Bontekoe. *Writing—original draft preparation*: Valeria Cortesi, Pieter F. van der Meer, Ido J Bontekoe, and Thomas R. L. Klei. *Writing—review and editing*: All authors. *Supervision*: Thomas R. L. Klei, Enrico Lopriore, and Giacomo Cavallaro. *Funding acquisition*: Valeria Cortesi, Giacomo Cavallaro, and Genny Raffaeli. All authors have read and agreed to the published version of the manuscript.

ACKNOWLEDGMENTS

We thank all the staff of the Department of Product and Process Development for technical help, especially Lara de Laleijne-Liefting, Joyce Bestebroer, Davina Ardanary, and Johan Lagerberg for their special support and contribution. We thank the "Griffini-Miglierina Foundation" for kindly supporting this study.

FUNDING INFORMATION

This study was (partially) funded by the Italian Ministry of Health – Current Research IRCCS. The study was partially funded by the "Griffini-Miglierina" Grant.

CONFLICT OF INTEREST STATEMENT

The authors have disclosed no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data will be provided under specific requests.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Cortesi V, Lopriore E, Cavallaro G, Bontekoe IJ, van der Meer PF, Fustolo-Gunnink S, et al. Storage properties of platelet concentrates from umbilical cord blood prepared using three different methods. Transfusion. 2024;64(10):1968–79. https://doi.org/10.1111/trf.18007