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Side effects after use of bedside thaw method in an umbilical cord blood stem cells for allogeneic transplantation in a children cohort: A single-center experience.

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Cover Page Footnote

The authors would like to thank the patients and their families, as well as the physicians, nurses, and staff members in the Pediatric Blood and Marrow Transplantation Program at The Hospital Pablo Tobon Uribe. We also want to thank Angelica Maria Llano who helped us in collecting some data.

ORIGINAL RESEARCH REPORT

Side Effects After Use of Bedside Thaw Method for Umbilical Cord Blood Stem Cell Allogeneic Transplantations in a Pediatric Cohort: A Single-center Experience

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Abstract

Background and objectives: **Several strategies and procedures have been described for thawing umbilical cord blood (UCB) products. The ideal method for each center depends on the resources, staff training, and access to each of these. We retrospectively evaluated the incidence of side effects using the bedside thaw method after unrelated UCB transplantation.**

Patients and methods: **For 34 children, patient, donor, graft characteristics, and side effects were identified. In addition, we attempted to identify the risk factors that could be associated with side effects.**

Results: **68% of patients experienced any adverse reaction. All the reactions were mild and transient events. The most frequent side effects were vomiting, hypertension, hemolytic reactions, and fever. There were more gastrointestinal events with a faster infusion rate.**

Conclusion: **The thawed at the bedside method is a practical, easy, and safe technique for cord blood transplantation in pediatric-patient settings.**

Keywords: Cord blood transplantation, Hematopoietic stem cell, Cellular therapy, Side effect

1. Introduction

Umbilical cord blood (UCB) has been adopted as a substitute source of hematopoietic stem cells in unrelated allergenic transplantations in children without a human leukocyte antigen (HLA)-matched related or unrelated donor [1]. In recent years, improvements within haploidentical transplantation have reduced the overall use of unrelated umbilical cord blood transplantation (UCBT) as an alternative stem cell source; however, promising clinical trials of adoptive therapies with UCB cells are under evaluation as potential novel strategies for viral infections, malignant diseases, and regenerative medicine [2]. Cell therapies must be simplified and made available in all regions to ensure their rapid expansion.

A cytoprotective agent named dimethyl sulfoxide (DMSO) is routinely added to UCB cells before they are frozen in liquid nitrogen and thawed for transplantation. Correct handling, thawing, and infusion of UCB products are essential at the transplant

Abbreviations: DMSO, Dimethyl sulfoxide; UCB, Umbilical cord blood; HLA, Human leukocyte antigen; UCBT, Unrelated umbilical cord blood transplantation; HSCT, Hematopoietic stem cell transplantation; ANC, Absolute neutrophil count; TNC, Total nucleated cells; PFS, Progression-free survival.

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center to maintain graft quality and limit the risk of delayed or no engraftment. To assure patient safety, several strategies and procedures have been described for thawing products [3].

Thawing procedures may be carried out in the laboratory or at the bedside and with or without washing for the removal of a cryoprotectant, cellular debris, and free hemoglobin before infusion. Washing procedures may negatively impact cell quality. These procedures have been associated with decreased cell count and viability, which have an impact on the transplant outcome [4].

Frozen blood products thawed at the bedside and administered immediately to the patient is characterized by minimal cell loss, and no additional trained staff is required since the pre-infusion procedure is similar to that performed with other frozen blood products (plasma, cryoprecipitate). Any delay in the infusion can cause DMSO toxicity in cells, as well as loss of viability and a variety of side effects, ranging from mild events like nausea/vomiting, hypotension or hypertension, abdominal cramps, diarrhea, flushing, and chills to more serious life-threatening events like cardiac arrhythmia, encephalopathy, acute renal failure, and respiratory depression [5]. Few studies have evaluated the main side effects following cord blood infusion in the pediatric population.

In this study, we retrospectively evaluated the use of a bedside thaw method for unmanipulated UCB transplantation in 34 children for a wide range of benign and malignant conditions.

2. Patients and methods

The study cohort comprised consecutive UCBT recipients undergoing HSCT at a large academic center for any indication between January 2014 and May 2021. Clinical records were identified and reviewed by the authors, who extracted the information to a predetermined database. All patients did not have a suitable HLA-compatible related or unrelated blood or bone marrow donor.

The hospital's Ethics Committee approved the study design.

2.1. Transplantation procedures

Patients received a full myeloablative or a non-myeloablative conditioning regimen according to individual clinical characteristics. Supportive therapy was given according to our standard operating procedures. Antimicrobial prophylaxis was administered with acyclovir, and either fluconazole or voriconazole. Cytomegalovirus infection was managed with a preemptive approach, based on weekly viral load monitoring up to day +100.

2.2. Cord blood processing

The sole graft source for the study was unmanipulated UCB units obtained from the EURO CORD REGISTRY (n: 27) and Cord Blood Bank, Instituto Distrital de Ciencia, Biotecnología e Innovación en Salud (IDCBIS), Bogotá, Colombia (n = 7). Eurocord is an international registry that works closely with Netcord banks, mainly European banks. Eurocord's UCB units came from: Barcelona (16, 59.2%), Malaga (5, 18.5%), Galicia (3, 11.1%), Valencia (2, 7.5%), and Madrid (1, 3.7%). All units were RBC-depleted according to the current requirement by accreditation bodies to wash RBCs. The Cord Blood Bank, Instituto Distrital de Ciencia, Biotecnología e Innovación en Salud (IDCBIS), performed volume reduction of the collected UCB units in a closed system (Biosafe S.A.) with hydroxyethyl starch (HESPAN 6%) [6]. However, there is no standardized practice across UCB banks regarding the use of DMSO concentration or any other manipulation prior to cryopreservation.

The units were thawed at the bedside and immediately infused. The UCB banks supplied data on the cell counts of UCB units before freezing. A cell viability test was performed on the samples at the time of infusion. A post-thaw CD34 count was done on a BD FACSLyric Flow Cytometer using a BD Stem Cell Eumeration Kit (Catalog N° 344563). An absolute CD34 count was obtained using BD Trucount tubes and a reagent containing CD45 FITC clone 2D1 and CD34 PE clone 8G12. Dye 7-AAD was used to assess the viability of the cells. Enumeration of the cell populations was performed using an automated method for gating and analysis.

2.3. Umbilical cord blood infusion

Diphenhydramine and hydrocortisone were administered to all patients 30 minutes before UCB infusion. At the time of infusion, bags were thawed in a 37 °C water bath and drawn into a syringe and infused, unfiltered, through a central intravenous catheter at a variable rate according to patient tolerance.

2.4. Patient monitoring

Vital signs were monitored and recorded every 5 minutes during infusion and thereafter every 30 minutes over 2 hours. The medical staff recorded the total volume, number of infused cells, and

symptoms occurring during the infusion and the following 24 hours. Hematopoietic recovery was followed with daily blood cell counts. Data on the appearance of side effects were collected retrospectively.

The side effects were registered as follows: chills, fever, nausea, vomiting, skin rash, cough, chest pain, and abdominal pain. The number of adverse reactions occurring at each infusion was recorded using a specifically designed worksheet. In all cases, the primary care physician and one of the authors performed observation and care of the patients during infusions. Also, we grouped side effects into three categories in order to identify risk factors. Gastrointestinal effects: vomiting, nausea, diarrhea, and abdominal pain. Circulatory side effects: hypertension, hypotension, bradycardia, or tachycardia and finally hemolysis, which included fever and hemolysis.

2.5. Definitions

Hypotension was defined as blood pressure in the 5th percentile or less for age, height, and sex [6]. Hypertension was defined as blood pressure in the 95th percentile or higher for age, height, and sex [7]. Neutrophil and platelet engraftment was defined as 3 consecutive days with an absolute neutrophil count of $>0.5 \times 10^9$/L and a platelet count of $>20 \times 10^9$/L (without transfusion support), respectively.

A patient who survived longer than 28 days after transplantation and who failed to achieve neutrophil engraftment was considered a primary graft failure [8].

2.6. Statistical analysis

A descriptive statistical analysis was performed for all the selected variables. Quantitative variables are presented as median with interquartile range (IQR). Qualitative variables are expressed as simple and relative frequencies. For survival analysis, we used the non-parametric method of Kaplan–Meier and reported median survival and 12-month survival; we reported 95% confidence intervals (CI) for all results. The data of patients alive at the end of the observation time were censored. Platelet and neutrophil engraftment rates were assessed using the cumulative incidence analysis. An exploratory analysis was carried out, comparing patients with or without infusion-related toxicities according to gender, patient's age, baseline diagnosis, sex mismatched, the number of cryopreserved total nuclear cell count infused, the volume and rate of infused UCB products, CD34+ cells cryopreserved, UCB banks, and ABO incompatibility with Fisher's exact test for discrete variables and Mann–Whitney U test for continuous data. The software used for statistical analysis was RStudio version 4.1.2.

3. Results

3.1. Patient and UCB graft characteristics

We included 34 consecutive patients who underwent unrelated UCBT between January 2014 and May 2021 in the analysis. The median age at the transplantation time was 3 years (IQR, 1–7 years), and 35% had a baseline diagnosis of Immunodeficiency. The median cryopreserved total nucleated cell count was 11.53×10^7 (range 3.7–44.3), the median CD34+ cell number cryopreserved were 4.68×10^5 (IQR 2.24 to 8.5), and the median viability pre-thaw was 97% (IQR 93.5%–99%). Characteristics of patients are described in Table 1.

3.2. Characteristics of UCB product infused

The median volume of UCB product infused was 26 mL (range 22–145). The median duration of UCB infusion was 13.5 minutes (range 5–45). The number of HLA disparities was defined as a low resolution for HLA-A and HLA-B and a high resolution for HLA-DRB1. Eight patients (23%) received 6/6, 20 (59%) received 5/6, and 6 (18%) received 4/6 matched UCB units; 16 donor–recipient pairs (47%) were ABO identical, 13 (38.2%) had a major mismatch, four (12%) had a minor mismatch, and one (3%) had a bidirectional ABO mismatch. The presence of sex mismatch between donor and recipient was documented in 12 patients (35%). The post-thaw median CD34+ cell number infused was 8.1×10^6/kg (IQR 5.3–22.8), and the median post-thaw viability was 88.4% (IQR 82.7%–92.1%). The main characteristics are summarized in Table 1.

3.3. Incidence and timing of side effects

Infusion-related toxicities associated with the CB infusions were documented in 23 (68%) of the patients. The main events observed were vomiting in 11 (32%), hypertension in 8 (24%), hemolysis in 8 (24%), and fever in 8 patients (24%). These reactions were mild and transient, no cases of fatal complications were observed, and no patient required intensive care management. In these patients, we did not identify dyspnea, hypoxia, or any serious cardiopulmonary complications (Table 2A). We assessed whether differences in UCB processing

Table 1. Patient, donor, and graft characteristics

Characteristics	
Number of cases	34
Age, years, median (IQR)	3 (1–7)
Sex, n (%)	Male 22 (65)
	Female 12 (35)
Sex mismatch, n (%)	12 (35)
Baseline diagnosis, n (%)	
Malignant diseases	11 (32)
Acute Leukemia	5 (15)
JMML	6 (18)
Non-Malignant diseases	23 (68)
Immunodeficiency	12 (35)
Metabolic disease	5 (15)
Bone marrow failure	5 (15)
Other non-malignant hematology diseases	1 (3)
Conditioning regimen, n (%)	
MAC	29 (85)
RIC	5 (15)
GvHD Prophylaxis [b], n (%)	
Cyclosporine/Methotrexate	21 (62)
Cyclosporine/micofenolato	12 (35)
Cyclosporine	1 (3)
ABO incompatibility n (%)	
Major incompatibility	13 (38%)
Minor incompatibility	4 (12%)
Bidirectional incompatibility	1 (3%)
None	16 (47%)
Degree of HLA matching n (%)	
4/6	6 (18%)
5/6	20 (59%)
6/6	8 (23%)
Mean infusion volume (mL), median (IQR)	26 (25–36.2)
Infusion rate mL (min), median (IQR)	13.5 (10–20)
Nucleated cells cryopreserved/kg (10^7), median (IQR)	11.5 (7–19)
CD34+ cells cryopreserved/kg (10^5), median (IQR)	4.6 (2.2–8.5)
CD34+ cells cryopreserved/kg (10^5) post-thaw, median (IQR)	8.1 (5.3–22.8)
Cell viability (%), median (IQR)	**n = 28**
Pre	97 (93.7–99)
Pos-thaw	88.4 (82.7–92.1)

IQR: interquartile range; JMML: juvenile myelomonocytic leukemia; MAC: myeloablative conditioning; RIC: reduce intense conditioning; GvHD: graft vs host disease.

steps had any correlation with side effects. We compared the units that came from the local bank and the Eurocord registry, but found no differences in the frequency of side effects related to the infusion. However, it is essential to emphasize that the Eurocord units came from different banks (Table 2B).

3.4. Factors potentially associated with side effects

Gender (p = 0.9), patient's age (p = 0.4), baseline diagnosis (p = 0.6), number of cryopreserved total nuclear cell count infused (p = 0.4), volume (p = 0.1), rate of infused UCB products (p = 0.4), CD34+ cells cryopreserved (p = 0.5), and ABO incompatibility (p = 0.3) had no influence on side effects (Table 3A). Grouping side effects shows that there are more gastrointestinal events with a faster infusion rate. We did not find any factors associated

Table 2A. Side effects associated with umbilical cord blood infusion

Infusion reaction[a]	N = 34 n (%)
Any reaction	23 (68)
Vomiting	11 (32)
Hypertension	8 (24)
Hemolysis	8 (24)
Fever	8 (24)
Nausea	6 (18)
Abdominal pain	3 (9)
Bradycardia	2 (6)
Cough	2 (6)
Diarrhea	2 (6)
Irritability	2 (6)
Hypotension	1 (3)
Headache	1 (3)
Tachycardia	1 (3)

[a] One patient could have more than one reaction.

Table 2B. Side effects according to UCB unit origin: Eurocord, Cord Blood Bank, Instituto Distrital de Ciencia, Biotecnología e Innovación en Salud (IDCBIS)

	Eurocord n = 27 n (%)	Hemocentro n = 7 n (%)
Side effects	19 (70)	5 (71)
Gastrointestinal side effects	12 (44)	3 (43)
Hemolysis	12 (44)	3 (43)
Respiratory side effects	2 (7)	0
Circulatory side effects	7 (26)	2 (27)
Engraftment	17 (63)	3 (43)

Table 3A. Results of univariate analysis of factors influencing side effects

	Side effects n = 23	No side effects n = 11	P value
Gender, n (%)			
Male	15 (44)	9 (26)	0.9[a]
Female	7 (21)	3 (9)	
Age (IQR)	3 (1–7.7)	1.5 (1–4.2)	0.4[b]
Baseline diagnosis, n (%)	7 (20)	4 (12)	0.6[a]
Malignant disease	17 (50)	6 (18)	
No- malignant disease			
ABO incompatibility, n (%)			
Yes	11 (32)	7 (21)	0.7[a]
No	13 (38)	3 (9)	
Infusion rate (min) (IQR)	12 (10–18.7)	18 (9.5–30)	0.3[b]
Infusion Volume (mL) (IQR)	26 (24.7–30)	38 (24.5–47.5)	0.1 [b]
CD34+ cells cryopreserved /kg (10^5) (IQR)	3.6 (2.2–8.7)	5.4 (3.2–8.3)	0.5 [b]
Nucleated cells cryopreserved/kg (10^7) (IQR)	11.5 (7.1–22.3)	12.1 (6.7–16.8)	0.4 [b]

[a] Fisher test, [b] Mann–Whitney U test.

Table 3B. Results of univariate analysis of factors influencing side effects according with groups side effects

	GI side effects n = 23	No GI side effects n = 11	P value*
Infusion rate (min) (IQR)	10 (10–15)	17 (10–25)	0.08
Infusion volume (mL) (IQR)	26 (25–30)	26 (24.7–40)	0.5
CD34+ cells cryopreserved/kg (10^5) (IQR)	3.6 (2.2–8.3)	5 (2.3–8.7)	0.5
Nucleated cells cryopreserved/kg (10^7) (IQR)	14.5 (10.2–22.8)	10.6 (6.4–17.3)	0.1
	Circulatory side effects	**No circulatory side effects**	
Infusion rate (min) (IQR)	13 (10–16.5)	15 (10–22.5)	0.4
Infusion volume (mL) (IQR)	26 (25–35.5)	26 (24.7–38)	0.6
CD34+ cells cryopreserved/kg (10^5) (IQR)	3.6 (1.6–8.7)	5 (2.5–8.3)	0.4
Nucleated cells cryopreserved/kg (10^7) (IQR)	14.5 (5.1–20.7)	10.7 (7.8–19.5)	0.8
	Hemolysis	**No Hemolysis**	
Infusion rate (min) (IQR)	10 (10–15)	17 (10–25)	0.1
Infusion volume (mL) (IQR)	26.6 (25.3–30)	26 (24.6–39)	0.6
CD34+ cells cryopreserved/kg (10^5) (IQR)	4.5 (1.8–8.8)	4.6 (2.2–8.3)	0.9
Nucleated cells cryopreserved/kg (10^7) (IQR)	17 (10.2–22.8)	10.2 (5.6–16.7)	0.1

Gastrointestinal effects: vomiting, nausea, diarrhea, and abdominal pain:.Circulatory side effects: hypertension, hypotension, bradycardia, and tachycardia.
Hemolysis: fever and hemolysis.
*Mann–Whitney U test.
Abbreviations: GI: Gastroinestinal, IQR: interquartile range.

with cardiovascular adverse effects or hemolysis. These results did not show any statistically significant differences due to sample size (Table 3B).

3.5. Hematopoietic recovery and survival

The median follow-up time was 273 days (range 61–692). The median overall survival (OS) was not reached (95% CI 8.23 months–NA), 12 months OS was 62.3% (95% CI 41.4%–78.8%), the median PFS was 52 months (95% CI 7.9–NA), and 12 months PFS was 64.3% (95% CI 49.3%–83.9%; Fig. 1).

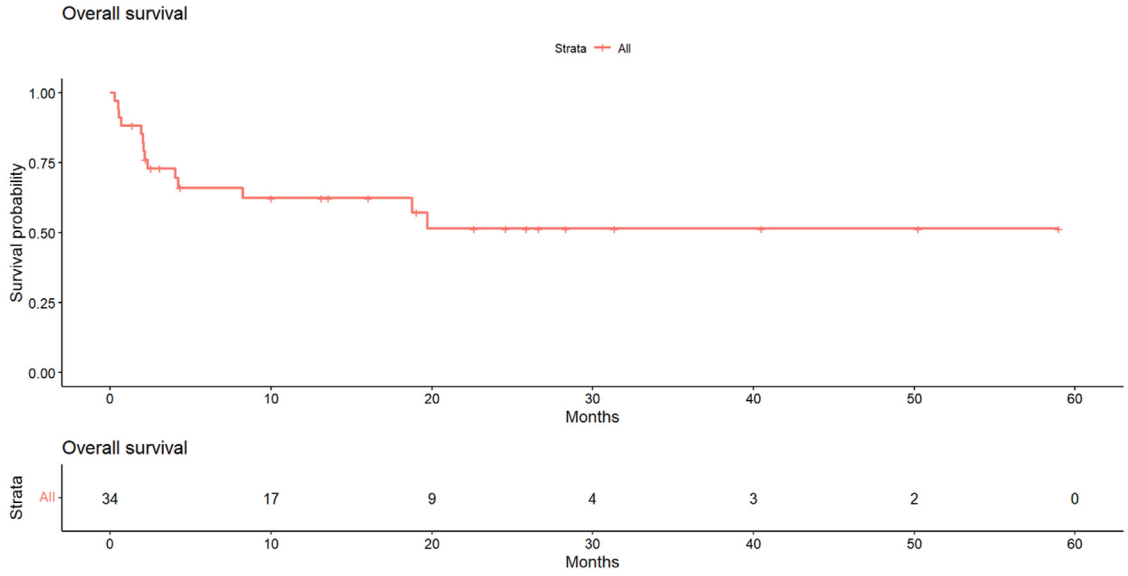
The median time for neutrophil and platelet engraftment was 18.4 days (IQR 17–21) and 24 days (IQR 19.7–34.7). The cumulative incidence of engraftment at 30 days was 59% and 53%, respectively (Fig. 2).

4. Discussion

In this study, we reported an incidence of 68% of infusion-related toxicities in pediatric patients who were transplanted with UCB products thawed at the bedside, and immediately administered without washing procedures. Despite being relatively common, the reactions were mild and transitory. The main events observed during UCB infusion were vomiting (32%), hypertension (24%), hemolysis (24%), and fever (24%). A faster infusion rate was associated with more gastrointestinal side effects. Despite the fact that the optimal thawing and infusion practice of cryopreserved cord blood has not yet been determined, our findings point to a simple and useful strategy that may be implemented in a range of clinical settings, including resource-limited scenarios.

Various factors might contribute to the development of side effects during UCB infusion. Early research suggested that cells preserved in DMSO are hypertonic and may undergo osmotic shock in circulation and possibly cause injury when infused directly. As a result, much progress on effective devices and methods for removal of DMSO from cryopreserved UCB grafts has been achieved in the last decade. However, it is still challenging to determine the optimal method. Nagamura-Inoue et al. [9] reported the influence of washing-out DMSO by dilution of the thawed CB unit with an equal volume of dextran and albumin solution to reduce the osmolarity produced by the cryoprotectant; 24 patients received units without washing (non-washed group), while 22 patients received washed units. Adverse reactions occurred in 1 of the 24 patients in the non-washed group and in 1 of the 22 patients in the washed group. Nausea, headache, hypertension, and dyspnea were reported. No life-threatening adverse effects at the time of transfusion were observed in either group. There was no difference in the number and severity of adverse effects [9]. Similarly, Hahn et al. [10] published a comparison of 18 unmanipulated and 8-volume reductions of umbilical cord blood units before infusion in 26 patients who underwent transplantation. They did not report serious toxicity from UCB, in both study groups [10]. Finally, Konuma et al. [11] prospectively evaluated the incidence and significance of infusion-related toxicities in 34 adult patients undergoing unrelated UCB transplantation.

A.Kaplan–Meier estimate of overall survival of the recipients of unmanipulated umbilical cord blood transplantation.



BKaplan–Meier estimate of progression free survival of the recipients of unmanipulated umbilical cord blood transplantation.

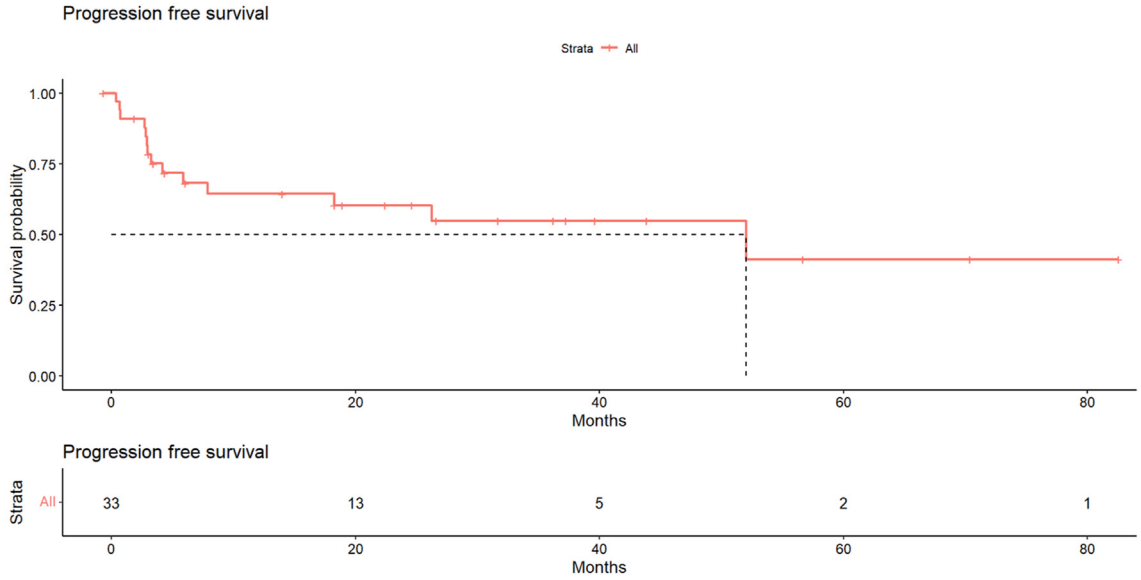
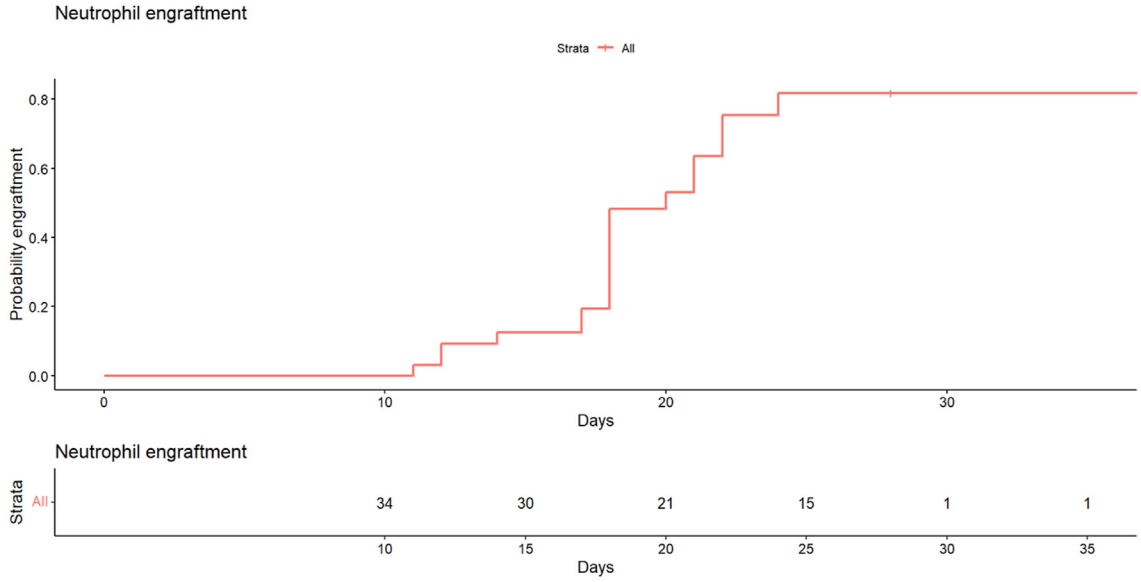


Fig. 1. A. Kaplan-Meier estimate of overall survival of the recipients of unmanipulated umbilical cord blood transplantation. B. Kaplan-Meier estimate of progression free survival of the recipients of unmanipulated umbilical cord blood transplantation.

Cryopreserved UCB units were thawed and immediately infused. A reaction was experienced by 79% of patients. Cardiovascular toxicities including systolic and diastolic hypertension, and bradycardia were frequently observed (58%, 64%, and 32%, respectively) [11]. The findings in adults are consistent with what we observed in children. Due to their very small volume, DMSO content is much lower in UCB compared to that in PBSC or BM products, which could explain the low incidence of adverse effects and raises the possibility that the washing-out of DMSO is not required in this setting.

A. Kaplan–Meier estimate of neutrophil engraftment following unmanipulated umbilical cord blood transplantation



B.. B. Kaplan–Meier estimate of platelet engraftment following unmanipulated umbilical cord blood transplantation.

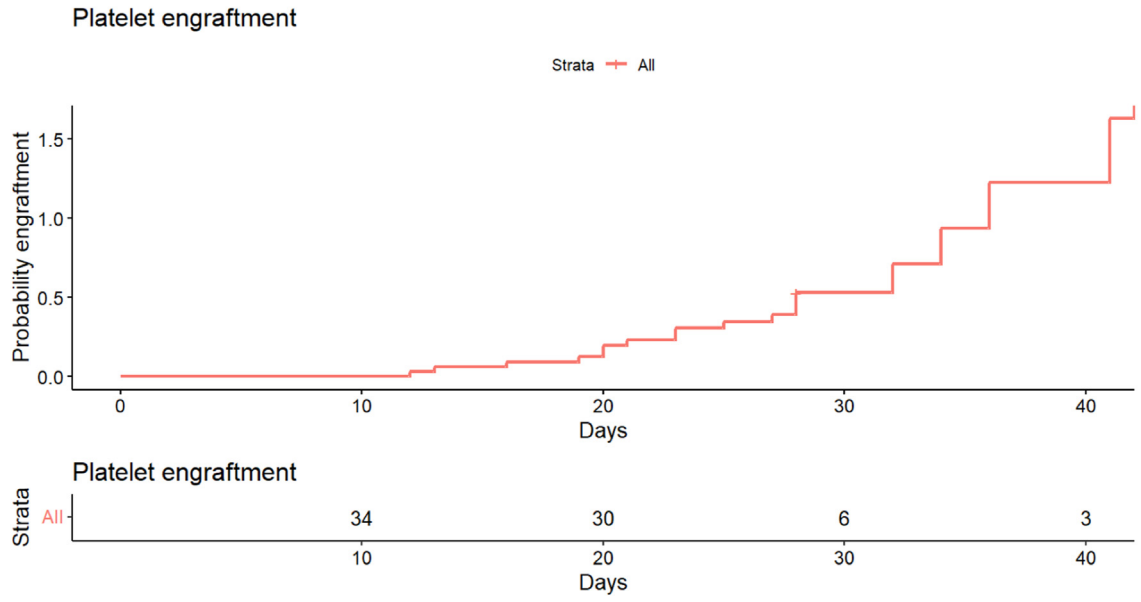


Fig. 2. . A. Kaplan-Meier estimate of neutrophil engraftment following unmanipulated umbilical cord blood transplantation. B. Kaplan-Meier estimate of platelet engraftment following unmanipulated umbilical cord blood transplantation.

Additional strategies reported to minimize infusion-related adverse effects include premedication given before transfusion, e.g., antiemetics, corticosteroids, and antihistamines, which are used to neutralize DMSO-induced histamine release; however, these kinds of medications could cause bradycardia [12]. We used antihistamine drugs before all infusions; interestingly, bradycardia was only present in 2% of the patients. Infusion-related cardiovascular effects have been widely reported in UCB infections in the adult population. However, the mechanisms of cardiovascular toxicity during

UCB infusion remained unknown. In addition to age, the low prevalence of bradycardia in our cohort could be attributed to the low volumes infused. Nevertheless, this should be investigated in larger pediatric populations in future prospective research.

Several studies have shown that infusing a high nucleated cell dose is a good prognostic factor for both engraftment and survival in UCBT [13]. Laroche et al. [14] reported a decrease in the number of total nucleated cells (TNC) using post-thaw processing including a wash step to remove DMSO, lysed red cells, and stroma. TNC recovery was 89% when UCB was not manipulated after thawing and 82% when the cells were washed to remove DMSO ($p < 0.01$), and the TNC recovery decreased from 90% to 82%, respectively ($p < 0.01$) [14]. Nevertheless, the UCB manipulation may cause qualitative changes in the product, including cell loss and viability changes, that may affect engraftment [13]. Our study showed a median time to neutrophil engraftment of 18.4 days and the median time to platelet engraftment was 24 d. Hahn et al. [10] presented data for transplantation of two types of products. Eight patients received volume-reduced washing units and 18 non-volume-reduced products thawed at the bedside. Of the 18 unmanipulated UCBT patients, 16 achieved ANC 4500/mm^3, corresponding to a median of 26 days (range 16–104) post-UCBT. Of the 18 unmanipulated UCBT patients, 10 achieved platelet recovery, corresponding to a median of 60.5 days (range 41–144) [10]. Nagamura-Inoue et al. [9] reported that the cumulative incidence of engraftment was not significantly different between the two groups. Median neutrophil recovery ($\geq 5 \times 10^9$/L) in the unwashed and washed groups was 26 and 25 d, respectively, and the median platelet recovery ($\geq 20 \times 10^9$/L) in patients with myeloid engraftment was 44 and 40 d, respectively. A dilution after thawing cord blood did not result in the improvement of myeloid engraftment speed.

This study has some limitations. The retrospective, descriptive and single-institution design might limit the statistical inference of the results for all pediatric populations who received UCB transplantations. Nonetheless, we believe that our findings can be useful because they could provide real-world evidence and could help different patients in the context of cord blood transplantation in low and middle-income countries. Safely using unmanipulated UCB is of great importance in certain global regions as it allows for expanded treatment capacity. The proposed method expands the possibilities of access, regardless of the economic conditions of the region, increasing human resources since specialized training is not required, and allows for cost reduction.

In summary, our findings could suggest that unmanipulated post-thaw infusion of cord blood units is a practical and safe technique for cord blood transplantation in pediatric-patient settings. This procedure enjoys various considerable advantages, the most notable of which is that it is a fast, simple, effective, and low-cost procedure, making it a very appropriate technique for the rapidly increasing field of cellular treatment in general.

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Authors' contributions

All authors contributed to the study's conception and design. Material preparation and data collection were performed by NB. Critical revision and analysis were performed by LN, JPC, and NB. The first draft of the manuscript was performed by NB. All authors commented on previous versions of the manuscript and read and approved the final manuscript version to be published. All authors agree to be accountable for all aspects of the work and to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

The authors declare no conflict of interest.

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