Predictors of high-quality cord blood units

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BACKGROUND: Analysis of umbilical cord blood (UCB) transplants shows a correlation between engraftment and total number of infused cells. Thus, it is worth evaluating what maternal and neonatal characteristics and collection techniques may affect the quality of UCB units.

STUDY DESIGN AND METHODS: A cross-sectional study was performed with 7897 donors sequentially selected in three health care institutions in Brazil from October 2004 to March 2012, in which both quantitative and qualitative approaches were applied. All donors were considered suitable for cord blood collection.

RESULTS: The maternal and neonatal characteristics and techniques of collection that influenced the total number of nucleated cells (TNCs; $p < 0.001$) were type of delivery, newborn weight and sex, and institution of UCB collection. The TNC count was associated with gestational age ($p = 0.008$), type of delivery ($p < 0.001$), newborn sex ($p < 0.001$), newborn weight ($p < 0.001$), and UCB collection technique ($p = 0.003$). Center B presented the largest number of nucleated cells in its results ($p < 0.001$), followed by Center A ($p = 0.001$). Other characteristics, such as maternal age, were analyzed but were not relevant for the nucleated cell number.

CONCLUSION: This study provides elements for a model that allows an efficient selection of UCB donors, prioritizing candidates who have a better chance to lead to an optimized use of cord blood cells units.

Umbilical cord blood (UCB) is a rich source for hematopoietic stem cells, which have been used for the treatment of various hematologic disorders in children and adults. Hematopoietic stem cells are found in the marrow, in the UCB, and after stimulus in peripheral blood. These cells are crucial for therapeutic procedures of long-term hematopoiesis reconstitution, even after myeloablative conditioning.

Using UCB for allogeneic transplants has made possible increasing numbers of these procedures, due to the feasibility of performing transplants with mismatched HLA. This property has benefited the Brazilian population, which is highly multiracial. It has also benefited patients carrying rare HLA haplotypes.

However, the volume and number of stem cells are usually low in UCB units, posing important limitations for transplantation. Thus, the use of a UCB unit that has adequate volume, cellularity, and viability is very important for the success of the transplant. A constant investigation of the best criteria for achieving high-quality UCB units is necessary.

Good results for transplantation of cord blood units are difficult to obtain, but some associated factors are predictable, such as the unit quality. One of the main criteria for considering a UCB unit for transplantation is the total number of nucleated cells (TNCs) collected. The minimum required TNCs in UCB for processing has increased over the years. Initially this number was between 5×10^8 and 8.5×10^8. Arrojo and colleagues[1] suggest the need for a higher TNCs (10×10^8), indicating that TNC count is an important factor affecting quality of UCB and placental units.

The optimal amount of volume and cells (dose) in a UCB unit has not been clearly defined, although usually high volume units are related to high cellularity. Previous studies strongly correlate hematopoietic recovery and graft rejection with TNCs and the recipient weight,[2,3] which leads the UCB and placental banks to give preference to providing units for children and adults of low body weight. The minimum number of cells required for a unit to be transplanted is not a consensus; it depends on factors such as HLA compatibility and the underlying disease being treated. Suggested variables have been at least 3×10^7 TNCs/kg or at least 1.5×10^5 CD34+/kg for a successful transplantation.[4,5] Some studies have shown that the quality of UCB units can be influenced by several obstetric and neonatal factors and by the collection technique.[6,7]

Thus, our study aimed to investigate the factors involved in UCB collection to obtain a better use and quality of the harvested material and increase the likelihood of transplantation. Our results may improve our current understanding[8,9] of the main factors affecting the quality of UCB units.

To this end, we evaluated maternal and gestational age; type of delivery and pregnancy; neonatal weight, sex, and race; and whether cell collection was intrauterine, extrauterine, or intra- and extrauterine, in three different health care institutions. The primary outcome used was the total number of cells ($\geq 12.5 \times 10^8$) and the cell volume of the UCB unit.

MATERIALS AND METHODS

This study was evaluated and approved by the Ethical Committee of the Albert Einstein Hospital in São Paulo, Brazil, under CAAE number 02623012.7.0000.5505. This is a cross-sectional, retrospective study in which both quantitative and qualitative approaches were applied. A survey was conducted in the Public Umbilical Cord Blood Bank (Department of Hematology) of the Albert Einstein Hospital in São Paulo, Brazil. This blood bank receives cord blood units from three institutions, here named as Center A, Center B, and Center C. The stem cell laboratory is located in Center A so it is where the units were evaluated for further processing, freezing, storage, and release for

transplantation of hematopoietic stem cells. We studied 8513 cord blood records from the public UCB bank. The data were collected for 8 years (from October 4, 2004, until March 31, 2012). A total of 96% of these records (7897) that met the inclusion criteria were included in this study.

Inclusion criteria

UCB reception forms, processing, and freezing samples containing complete records regarding newborn weight and race, maternal age, gestational age, type of delivery (vaginal or cesarean), type of pregnancy (single or double), cord blood collection technique (intrauterine, extrauterine, or combination of intra- and extrauterine), and collecting institution were considered.

Exclusion criteria

Reception forms containing incomplete or inadequate records regarding the variables selected for the study were excluded.

Independent variables

Newborn characteristics
Newborn characteristics included were weight (g), sex (male or female), and race/color (defined as the feature stated on the certificate of live birth): white and nonwhite (black, Asian, and mixed race).

Maternal characteristics
Maternal characteristics included age (years), gestational age (defined as the time measured in weeks and full days elapsed since the last menstrual period), delivery type (categorized into cesarean or vaginal), and pregnancy (categorized as single or twin).

Technique of collection
UCB collection techniques were categorized into 1) intrauterine, 2) extrauterine, or 3) intra- and extrauterine.

1. **Intrauterine collection** (before handling the placenta): This technique is used to collect the cord blood just after birth when the newborn is under the care of the neonatologist. After umbilical cord section, the professional responsible for the collection performs antisepsis of the vein to prevent contamination by microorganisms or maternal blood. The umbilical vein is punctured in the distal third of the umbilical cord with a needle coupled to a bag (a closed system containing anticoagulant) and the drainage of the whole blood is performed into the collection bag by gravity.
2. **Extrauterine collection** (after handling the placenta): A health care professional performs antisepsis of the umbilical cord and placenta vessels. Next, several punctures in the cord and placenta veins are made, gradually transferring the collected blood to the

collection bag device. At the end of extrauterine collection, the health care professional cleans and seals the collection bag.

3. **Intra- and extrauterine collection technique**: This is done whenever the two techniques can be combined to obtain a higher cell volume. The final volume is the sum of the volume obtained with each technique, which is then recorded on the collection form.

Institution of UCB collection

Three institutions named Center A, Center B, and Center C were included in this study. The UCB collection in the three centers followed the same operational procedure.

Dependent variable

The TNCs before being processed correspond to the number of white blood cells and red blood cells $\times 10^6$/L UCB times the total volume of umbilical cord and placental blood collected without anticoagulant.

Statistical analysis

To evaluate the relationship between the explanatory variables and TNC count of more than 12.5×10^8 we used a logistic regression model in multiple approaches. These analyses were performed with computer software (SPSS Statistics for Windows, Version 17.0, released 2008, SPSS, Inc.).

RESULTS

Descriptive analysis

The database contains records from 7897 UCB collections, of which 5157 (65.3%) samples were frozen and 2740 (34.7%) were discarded due to low volume and/or low TNC count. Table 1 shows the descriptive analysis of the variables observed in all samples.

Inferential analysis

For a better fit of the multiple regression models, the variable "twin/single pregnancy" was not included due to a strong association with newborn weight and gestational age.[10] Thus, for a multiple logistic regression model we considered the following variables: maternal age, gestational age, delivery type, sex, race, newborn weight, type of collection, and collecting institution. An association was investigated between these variables and the UCB quality, as defined by TNC count of more than 12.5×10^8. The results of this model are shown in Table 2; the model adjustment was verified by a residual plot (Fig. 1). The deviation component chart by percentile of the standard normal distribution shows adequacy of the model built for the outcome TNC count of more than 12.5×10^8, since

TABLE 1. Descriptive analysis of the variables in all samples (n = 7897)*	
Variable	
Maternal age (years)	
Mean (SD)	31.0 (4.2)
Median (IIQ)	32 (29-34)
Range	18-50
Gestational age (weeks)	
Mean (SD)	3.9 (1.1)
Median (IIQ)	39.0 (38.3-39.7)
Range	35-42
Twin/single baby pregnancy	
Twin	134 (1.7)
Single	7763 (98.3)
Delivery type	
Cesarean	6157 (78.0)
Vaginal	1740 (22.0)
Newborn race	
Asian	95 (1.2)
White	7388 (93.6)
Black	145 (1.8)
Mixed race	269 (3.4)
Newborn sex	
Female	3844 (48.7)
Male	4053 (51.3)
Newborn weight (g)	
Mean (SD)	3244,3 (405.2)
Median (IIQ)	3235 (2980–3500)
Range	1940-5200
Cord blood collection technique	
Extrauterine	52 (0.7)
Mixed†	7741 (98.0)
Intrauterine	104 (1.3)
Institution of UCB collection	
Center A	6459 (81.8)
Center B	1107 (14.0)
Center C	331 (4.2)
TNC	
Mean (SD)	12,6 (5.6)
Median (IIQ)	11.7 (8.6-15.4)
Range	1.2-49.7

* Data are reported as number (%) unless otherwise reported.
† Combination of intrauterine and extrauterine.
IIQ = first and third quartiles.

the points are close enough to the reference curve and within the 95% confidence range.

There was no association between maternal age and product quality. Regarding gestational age, we observed that collections performed between 39 and 40 weeks of pregnancy led to products with 46% higher chances of better quality than collections performed during Weeks 35 and 36. We also found that 43% more UCB collections were from cesarean sections (C-sections) than from vaginal deliveries.

Concerning newborn weight, we observed that UCB collections of higher-weight newborns are more likely to present a quality product (odds ratio [OR], 2.6 in the category 2501-3000 g; 5.6 in the category 3001-3500 g; 11.7 in category 3501-4000 g; and 24 in category > 4000 g) compared to lower-weight newborns (category ≤ 2500 g).

We also observed that the intra- and extrauterine combined UCB collection technique showed products with 2.6 times better chances of quality than UCB

TABLE 2. Association between product quality defined by TNC count of more than 12.5 × 10⁸ and all variables of interest in all samples

| Variables	Categories	OR (95% CI)	p value
Newborn weight	≤2500	1.00	
	2501-3000	2.62 (1.75-3.94)	<0.001
	3001-3500	5.64 (3.77-8.45)	<0.001
	3501-4000	11.71 (7.75-17.70)	<0.001
	>4000	24.00 (14.66-39.29)	<0.001
Newborn sex	Female	1.57 (1.43-1.73)	<0.001
	Male	1.00	
Newborn race	White	1.23 (0.99-1.53)	0.067
	Not white	1.00	
Gestational age	35-36	1.00	
	37-38	1.30 (0.99-1.71)	0.062
	39-40	1.46 (1.10-1.93)	0.008
	>40	1.41 (0.98-2.05)	0.068
Delivery type	Cesarean	1.43 (1.26-1.62)	<0.001
	Vaginal	1.00	
Cord blood collection technique	Extrauterine or intrauterine	1.00	
	Extrauterine and intrauterine	2.62 (1.76-3.90)	0.003
Institution of UCB collection	Center C	1.00	
	Center A	1.51 (1.17-1.94)	0.001
	Center B	1.59 (1.20-2.10)	<0.001
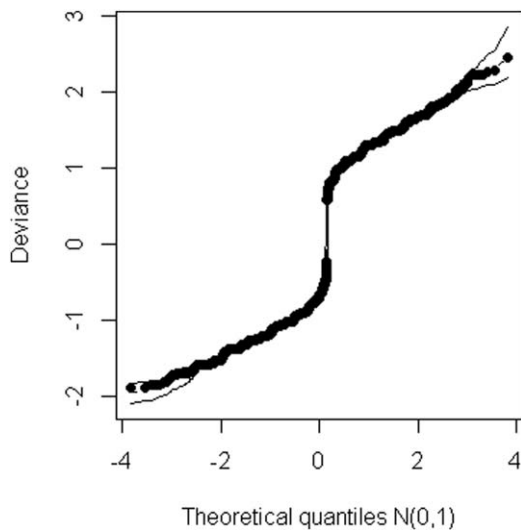
Fig. 1. Residual plot. This plot contains the ordered deviance residuals of the multivariate logistic regression model fitted for our data versus the standard normal quantiles, with simulated confidence bands. We did not identify observations with deviance residual outside the bands, which means that we had an indication of goodness of the final model fit. This analysis follows the recommendations of Pregibon.[11]

collections using only intra- or only extrauterine technique. Center A and Center B showed higher chances of adequate units (51 and 59%, respectively) than Center C.

DISCUSSION

Several analyses were carried out to determine the main dependent variable associated with high-quality UCB units, which are represented by higher TNC cells in the unit. All variables analyzed are discussed individually as follows.

Maternal age

There is an increasing number of pregnant women at an advanced age (older than 37 years)[12,13] and UCB might be collected from these women as well, hence the need to investigate whether advanced age affects the quality or number of collected cells.[12,13] Lampinen and colleagues,[14] in a review about maternal age in women over 35 years, concluded that we need to carry out observational studies involving pregnant women with advanced age, to increase understanding and knowledge in relation to maternal age and risks to pregnant women and their fetuses. Thus, in this study we investigated whether the older age groups would be associated with higher rates of low-quality UCB units. However, multiple logistic regression analysis found no significant association between maternal age and the TNCs, indicating that maternal age is not a variable affecting UCB quality, and thus pregnant women with advanced age are also suitable as UCB donors.

Gestational age

Since 2004, Brazilian legislation has called for the public cord blood banks to conduct their collections in pregnant women with gestational age equal to or over 35 weeks. This is justified by the increased TNCs that occurs between 32 and 41 weeks' gestational age, probably due to greater development of the fetus.[15]

We noted that the greater the gestational age the higher the TNCs, a finding that agrees with the results of Keersmaekers and coworkers.[16] In addition, Kurtzberg and

coworkers[2] find that larger term babies of any ethnicity are more likely to produce cord blood units with higher volumes and nucleated and CD34+ cell contents. This may be a critical factor for donor selection, since the chance of successful quality units between 39 and 40 weeks is 46% higher.

Delivery type

There are several hypotheses to explain the better UCB quality results obtained with C-section delivery compared to vaginal birth. One of them is that UCB collection is facilitated during cesarean delivery, since elective C-sections are always scheduled. Also, higher TNCs in C-sections may be explained by the faster UCB clamping, which favors the maintenance of blood flow, allowing collection of greater volume of blood, as described by Rodrigues and colleagues.[17] Higher TNC counts in C-sections is also shown in a study by Kurtzberg and colleagues.[2]

Another important determinant of UCB quality is physiologic placenta delivery, which is more frequent in vaginal than cesarean deliveries. During the C-section, manual handling of the placenta is recurrent and reduces the possibility of blood clots in the collected UCB. This hypothesis was suggested by Aufderhaar and coworkers[18] who found that manual placenta removal increases the viable cell numbers and leads to higher-quality UCB storage units.

Although several studies show higher cell numbers in UCB units obtained in C-sections than in vaginal delivery, we cannot forget that vaginal delivery is more beneficial to the mother and newborn.[19] Thus, optimizing UCB collection will include units from vaginal delivery.

Newborn sex

No difference between sex of the infant donors of the UCB unit has been associated with the quality of the unit. However, when we analyzed the results for the TNCs, we observed significant differences between sexes. TNC was higher in units collected from female newborns ($p < 0.001$) than those from male newborns. The smaller TNC counts in UCB collected from male newborns has been described by Solves and coworkers,[20] although, from the clinical point of view, this difference is considered small and of uncertain meaning. Our findings were comparable to those reported by Kurtzberg and colleagues who showed equivalent volumes from cord blood units collected from female and male infants, but higher cell counts were obtained from female infants than from male infants.[2]

Newborn race

The reason to consider race as a variable was suggested in a previous work,[21] which evaluated several institutions with varied racial composition of newborns. In addition, it is necessary to improve the racial diversity currently found in Brazilian blood banks. There is great difficulty in finding matching donors, while in other countries the chances are much higher (30 times higher). According to a study conducted by the National Register of Bone Marrow Donors (REDOME), the difficulty in finding a donor results from the small representation of racial minorities in cord blood banks and the low proportion of donation rates among individuals of these groups within the demographic areas.

Another problem, besides the low rate of finding matching donors, relates to the high costs in performing international bank searches. According to Samuel and coworkers,[22] a cord blood unit from an international donor costs between $20,000 and $30,000 while the cost of the same cord blood unit in the country would be threefold lower. A strategy adopted by the health ministry, through BrasilCord network, was to contemplate the racial diversity of our population by expanding collection to institutions that did not participate in previous collections.

Therefore, in this study race was categorized as white and nonwhite (mixed race, Asian, and black).[23] We did not observe any significant association between race and TNC counts when adopting the logistic regression model (Table 2). This result was in contrast to the study by Kurtzberg and coworkers, which found differences in TNC counts between African Americans and all the other ethnicities for the same volume of cells.[2] The differences observed between these studies are probably due to differences in the analysis applied in each of them. Because we separated the population between white and nonwhite individuals (black, Asian, and mixed race), we may have underestimated the differences between the two groups. In the other study, the population was separated into five groups. Another difference between the studies is the fact that the population in North America has characteristics different from those of the Brazilian population.[24]

Newborn weight

Previous studies[2,25,26] highlighted the relationship of newborn weight with the quality of the UCB unit, corroborating our findings of an association between newborn weight and TNCs (Table 2). George and colleagues[27] consider the ideal newborn weight as more than 3000 g. In this study, we used the cutoff proposed by Bart and coworkers[28] (12.5×10^8 TNCs) to determine the optimum UCB unit. Our findings show that collections from newborns with heavier weight (>3000 g) have an OR of 5.6 in the category 3001 to 3500 g and 24 in the category more than 4000 g. Consequently, newborn weight is an easy and reliable screening criterion for high-quality UCBs.

Cord blood collection technique

The blood collection technique is one of the predictors for obtaining a high-quality UCB unit. The intrauterine technique concerns collection while the placenta is still in the uterus; collection is interrupted only when the umbilical vein flow ceases. The good volume obtained by this technique is attributed to the natural blood flow from the umbilical cord and uterine contractions. As for the extrauterine technique, it is performed immediately after handling the placenta.[29] Coagulation may result in disposal of the UCB unit due to low volume of cells and consequently low TNCs. The mixed UCB collection technique (which combines both intra- and extrauterine techniques) is the best option to obtain nucleated cells (Table 2). Although the UCB volume represents a minor indicator of quality,[21] the higher the volume the greater the cell number and the chances of UCB use, ensuring greater probability of success in transplantation.[21] Keersmaekers and coworkers[16] found that each 10-mL increase in the unit volume corresponds to more than twice the likelihood of reaching the minimum unit of nucleated cells required for storage.

Institution of UCB collection

The choice of the institution for UCB collection has to be well planned, and several factors should be considered before an institution is officially designated for UCB collection. For instance, the number of deliveries per month, positive serology rates, and high-risk pregnancy rates are all considered. The knowledge and acceptance of professionals and their adherence to the UCB donation process also need to be verified. It is essential to invest in training and awareness of health professionals involved with the collection process, including nurses, technicians, pediatricians, anesthetists, and obstetricians.[30]

Center A is the collection center in which the operating period was longest (October 2004 to March 2012), which may explain the good results. The first center for external collection, Center C, represented a challenge for our study because it needed several adaptations to take part in our study, including staff training and development of a sense of commitment to the procedure. It is possible that the lack of expertise in external collection impacted the results obtained with this institution. Center B was included in the study after undergoing the same adaptations already done for Center C in regard to external collection of UCB. The team commitment to standard procedures, the need for training, and constant supervision have been highlighted by Roh and coworkers,[30] who discussed the role of obstetricians in guiding donors as well in the collection procedures and showed that lack of knowledge about the collection procedure can reduce donor numbers.

Statistics limitations

A multivariate statistical analysis determined the factors that mostly affect the cord blood unit collected for storage and eventual transplantation. Our analysis has some limitations; for instance, the training of health professionals was not included.

Another statistical limitation is related to the categorized variables. Our findings do not exclude a good unit that does not follow these variables; however, following the variables will highly increase the probability of obtaining better units.

In conclusion, a significant cost is involved in collection and storage of cord blood units, and thus knowing which births may produce good quality UCB could optimize costs and help avoid collection of samples that most likely will not result in good quality UCB. This study provides elements for a model that may optimize selection of cord blood donors, prioritizing candidates whose UCB has high chances of being of good quality. The variables that most positively influenced the cord blood unit quality were gestational age (39-40 weeks), C-section delivery, use of mixed collection technique, and newborn weight of more than 4000 g. While the birth method and collection method should be determined according to the best care for mothers and newborns, the gestational age and newborn weight are variables that have no effect on the mother's or newborn's well-being and represent information that is readily available. Thus, these variables are the most suitable to be used when choosing donors with the best chances of yielding good-quality UCBs.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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