ISSN: 2536-7153 SJMLS

Sokoto Journal of Medical Laboratory Science 2024; 9(1): 17 - 31

SJMLS - 9(1) - 002

# Umbilical Cord Blood Collection Protocol and the Impact on the Nucleated and Progenitor Cell Quantity and Quality

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**Summary**

The number of cells available in a single cord blood unit (CBU), in particular, the CD34+ and total nucleated cell (TNC) content influences the transplantation clinical outcome. By optimizing the CB collection, the quantity and quality of umbilical cord blood (UCB) for storage can be improved and increase the likelihood of its use for transplantation. Cord blood collection is the first step in cord blood banking and impacts significantly on the volume and quality of the collected blood. The Standard Operating Procedure (SOP) on cord blood banking recommends that education should be provided to a potential mother/donor of an umbilical cord blood unit so that she can make an informed choice on donation of her infant's cord blood. Parents need to be aware of the options that exist for their infant's cord blood and have access to the relevant information to inform their choice. Informed consent has been identified as one of the ethical issues confronting umbilical cord blood donation and banking. Some workers have opined that informed consent could be optimized by (1) having those personnel who obtain consent emphasize that banking involves research and to explain the true benefits of donation, (2) ensuring that parents know how and when to contact the umbilical cord blood bank after donation, and (3) using phone surveys to continue assessments and to monitor changes in the process. The degree to which the donated cord blood stem cells are molecularly similar to the recipient cells is measured by human leukocyte antigen. The current consensus is that CB should be at least 4/6 HLA matching for HLA-A, -B at the antigen level, and HLA-DRB1 at the allelic level. The collection could be in utero or ex utero usually by either a syringe or bag method. The interval between placenta delivery and CB collection has significantly influenced the volume of cord blood units and it has been shown that collection within not greater than 5 minutes of placental delivery produced higher volume and TNC count. Concerns have been raised about reduced red cell mass in the neonate resulting from early clamping of the umbilical cord that is necessary to maximize volume of UCB collection. Delayed cord clamping has been formally endorsed by a number of medical societies; however, it has not yet been universally adopted by obstetricians and neonatologists. Umbilical cord blood is always collected in sterile bags containing anticoagulant-based citrate, such as citrate phosphate dextrose (CPD) or CPD-adenine 1 (CPD-A1) to prevent coagulation and to maintain viability during transport to the processing facility. The TNC yield and viability of samples collected in lyophilized heparin (LH) compared to CPD suggest that UCB quality was impacted by anticoagulant selection. Some workers have done some analyses to determine the correlation between cell number, cell type, volume, and time between collection and processing. They reported significant losses of nucleated and CD34+ cells after storage at room temperature for up to 24 hours. Another group of workers studies the possible effect of time between collecting and processing umbilical cord blood samples on the quality of the sample. Their findings showed that an increase in the time interval between collection and processing negatively affects the quality of the UCB sample.

The effect of storage temperature before processing on the quantity of recovered cells has been studied and results show the optimum temperature to be between 2°C to 8°C. In all cases the loss of cells increased with the number of days of storage before processing.

***Keywords***: *Umbilical cord blood, CD34+ cell, Total nucleated cell, Human leukocyte antigen matching, Placenta delivery, Anticoagulant, Cell quantity and quality*

## Introduction

The primary functions of cord blood banks are the collection, processing and storage of cord blood. The collection is the first step and impacts significantly on the volume and quality of the collected blood. The collection protocol involves education of the donor on the possible uses of the blood, consent to donate, screening and human leukocyte antigen (HLA) typing, decision to collect in utero or ex utero, collection technique, anticoagulant, time and temperature of storage before transportation to processing centre among other factors. The number of cells available in a single cord blood unit (CBU), in particular, the Cd34+ and total nucleated cell (TNC) content influences the transplantation clinical outcome. By optimizing the CB collection, the quantity and quality of UCB for storage can be improved and increase the likelihood of its use for transplantation.

## 1. EDUCATION AND CONSENT TO DONATE

### *Education*

The Standard Operating Procedure (SOP) on cord blood banking recommends that education should be provided to a potential mother/donor of an umbilical cord blood unit so that she can make an informed choice on donation of her infant's cord blood. At the very least, information will be given at the time informed consent is requested. Parents' knowledge and understanding of cord blood banking and donation has been reported to be low and little is known about their source of information on this topic and the quality of the information provided (Perlow 2006, Fox *et al*., 2007, Manegold *et al*., 2011). Parents need to be aware of the options that exist for their infant's cord blood and have access to the relevant information to allow them to make an informed decision concerning donation. Parents can decide if they would like to privately store their infant's cord blood for later use if needed, publicly donate it, defer cord clamping to allow their infant to receive optimal volumes of cord blood at birth or to discard the remaining cord blood with the placenta after birth (Peberdy *et al*., 2018).

### *Consent to Donate*

Informed consent has been identified as one of the ethical issues confronting umbilical cord blood donation and banking (Petrini, 2010). Stavropoulos-Giokas *et al*. (2012) listed informed consent as one of the items in the first phase of cord blood banking. Prior to collection, UCB donors are required to sign an informed consent form (Sugarman *et al*., 2002; Vawter *et al., 2002;* Meyer *et al*., 2005; Kidane *et al., 2007;* Lubin and Shearer, 2007; Harris, 2008; Norris, 2014; Roura *et al*., 2015; Armitage 2016; Olayanju *et al*., 2017; Gerdfaramarzi *et al.,* 2022). In most cases, a mother will register with a bank prior to giving birth. Upon adequate completion of the informed consent, the mother's obstetrician is informed of her wish to be a donor, and arrangements are made to collect the cord blood. This is either by providing the mother with a kit or, if the delivery hospital is affiliated with a bank, by noting it in the mother's chart (Meyer *et al*., 2005).

The issue of obtaining consent for collection of cord blood has been controversial in the field of cord blood transplantation (Sugarman *et al*., 2002; Vawter *et al*., 2002; Gerdfaramarzi *et al.,* 2022). Historically, cord blood was considered to be the property of the hospital in which the baby was born, to be used, if desired, without patients' express consent. This practice, however, neglected the fact that for some women the placenta would not necessarily be considered a medical waste product, perhaps for some very important cultural reasons (Jenkins and Sugarman, 2004).

Informed consent is a process that begins with information, encompasses a dialogue, and culminates with a written, signed document. The informed consent process must begin prior to the start of active labor and be obtained from every mother/donor. Consent will not be

obtained during active labor or while the mother is under the influence of sedation or mood-altering medications (Lubin and Shearer, 2007). Very little is known about the perspectives of mothers agreeing to the collection of umbilical cord blood for public cord banks, whether for medicine or for research. The question of the views of fathers is largely absent, as are the views of 'donor children' (Busby, 2010). Although it is usual practice in the United Kingdom (UK) to treat this biological material as belonging to the mother, there is also a claim that it 'belongs' to the child. Depending on which view is accepted, the mother would be consenting to donate, or agreeing to the collection of the child's cord blood (Gunning, 2007). Danzer *et al.* (2003) explored the views of women who had donated cord blood and great majority of the respondents reported that they would donate again.

Fernandez *et al.* (2003) conducted a survey of knowledge and attitudes about cord banking among women attending an antenatal clinic in Halifax, Canada. A high proportion of those questioned supported the idea of public cord banking. However, some wanted more information on cord banking and about a quarter indicated that the cord blood bank should not be used to investigate the health of the newborn. It appears from these studies that some of the practices that are considered usual and necessary by cord banks are viewed with some ambivalence by those women whose views have been sought (Fernandez *et al., 2003)*.

Sugarman *et al*. (2002) opined that informed consent could be optimized by (1) having those personnel who obtain consent emphasize that banking involves research and to explain the true benefits of donation, (2) ensuring that parents know how and when to contact the umbilical cord blood bank after donation, and (3) using phone surveys to continue assessments and to monitor changes in the process.

In 2005 the United States (U.S.) Committee on Establishing a National Cord Blood Stem Cell Bank Program highlighted some ethical and legal key issues in informed consent for CB collection and storage. Some of the recommendations from the Committee included the need for clear policies about consent from the father. According to their definition if the blood is removed while the placenta is still in the uterus, generally the mother's consent is sufficient because it is an extension of her body. If the cord blood is removed after the placenta has been taken from the mother's uterus the father's wishes are also relevant (Petrini and Farisco, 2011). Funk *et al*. (2021) reiterated that the efforts to obtain consent of all eligible donors are high and optimization of the selection is needed.

Vawter *et al.* (2002) described a phased consent process-a process that permits consent during early labour to the ex-utero collection of cord blood followed by after-consent collection to donation. The phased consent policy attends to the unique characteristics of cord blood collection and donation, respects donors and their families, maximizes the number and diversity of cord blood units collected, preserves the relationship between providers and patients, and preserves public trust in cord blood and other types of tissue banking. Turcan *et al.* (2021) suggest that the informed consent offered to the future parents prior to the procedure should include the history of corona virus disease (COVID)-19 during pregnancy, the vaccination status of the mother and the gestational age at the time when this event occurred.

It has been observed that informed consents forms are not uniform but differ among umbilical cord blood banks (Petrini and Farisco, 2011). Broder *et al.* (2013) reported that of the 34 U.S public cord blood banks identified, 15 banks offered donor registration at the time of hospital admission for labor and delivery, 7 obtained full informed consent and medical history during early labor and 8 conducted some form of phased consent and/or phased medical screening and history. There has however, been some consensus that the best time to obtain written consent should be before the onset of active labor (Petrini and Farisco, 2011).

In Taiwan the Model Contract for Cord Blood Storage has been added to widen the scope of informed consent and protect parents' right to informed consent (Rei, 2009). Norris (2014) stressing the importance of informed consent stated that in the event umbilical cord blood

banking contracts conflict with informed consent, the contract should be subordinated to a person's understanding, acquired through procedures intended to achieve the patient or parent's, informed consent. Folger (2009) opined that the legislations in Ohio, United States does not have the potential to significantly increase the number of cord blood donations and it will be necessary to enact "required request" donation laws, which mandate health professionals to ask the family to consent to donation.

Details of the informed consent for different scenarios are given in different international standards (NetCord-FACT International Standards 2016 and FACT-JACIE International Standards 2021). NetCord-FACT International Standards (2016) presents an elaborate condition of informed consent in different scenarios.

i. Informed consent from the mother or an agreement between the mother and the CBB shall be obtained and/or verified and documented by a trained individual in accordance with Applicable Law.
ii. Informed consent or an agreement between the mother and the CBB shall be obtained and documented while the mother is able to concentrate on the information and is not distracted by aspects of labor.
iii. In cases of a surrogate mother, informed consent or an agreement shall be obtained and documented from both the surrogate mother and the genetic mother.
iv. All aspects of participation in CB donation shall be discussed with the mother in a language and with terms that she understands.

NetCord-FACT Standards (2016) requires that regardless of whether the unit is collected for unrelated or related use, if this unit may potentially be used for reasons other than the initial clinical intent, not only should this be mentioned in the informed consent but also the donor should have given consent with documents and information related to the potential related or unrelated use of the unit. It is ethically important to obtain informed consent for the donation of any cord blood unit, regardless of the timing of collection or the potential use of the unit Informed consent procedures for the donation of cord blood should follow a consistent set of protocols that educate the donor about the various options for cord blood use (Olayanju *et al*., 2017).

According to FACT-JACIE International Standards (2021) the case of a donor who is a minor, informed consent shall be obtained from the donor's legally authorized representative in accordance with Applicable Law and shall be documented and a donor shall have the right to refuse to donate or withdraw consent.

## 2. SCREENING AND HUMAN LEUKOCYTE ANTIGEN (HLA) TYPING

The degree to which the donated cord blood stem cells are molecularly similar to, the recipient cells is measured by HLA typing (Sheila, 1997, Flomenberg *et al*., 2004, Crocchiolo *et al*., 2009, Liwski *et al*., 2022; Muluhngwi and Tumer, 2023; Zhou *et al*., 2023). Crocchiolo *et al*. (2009) demonstrated that the importance of donor-recipient HLA-DPB1 matching for the clinical outcome of unrelated hematopoietic stem cell transplantation (HSCT) was rather controversial.

Blood samples obtained from the mother/donor following consent are processed and stored for HLA typing at the time a match for a potential recipient is identified for the corresponding CBU. The current consensus is that CB should be at least 4/6 HLA matching for HLA-A, -B at the antigen level, and HLA-DRB1 at the allelic level (Stavropoulos-Giokas *et al*., 2012). At the time of signing informed consent or alternatively up to 7 days before or 7 days after birth of the child, donors are tested for infectious diseases and microbial sterility (Roura *et al*., 2015). Edwards *et al*. (2016) reviewed results of screening umbilical cord blood from a US public cord blood bank during 2007–2014. Nineteen maternal donors accounting for 0.04% of their population tested positive for *Trypanosoma cruzi* parasites. Because perinatal transmission of Chagas disease is associated with substantial illness, they suggested that targeted prenatal programs should screen for this disease in CB donation. Meissner-Roloff *et al*. (2018) proposed that all CB units considered for storage undergo rigorous and reliable screening for HIV due to the high prevalence of human immunode□ciency virus (HIV) amongst women

attending antenatal clinics in sub-Saharan Africa together with the risk of mother-to-child transmission which increases the risk of transplant transmissible infection.

## 3. CORD BLOOD COLLECTION STRATEGIES

Previous reports (Wagner *et al.*,1996; Svenja *et al*., 2016; Sanchez-Petitto *et al*., 2023) have stated that low haemopoietic cell content of CB donations may limit their use to smaller recipients. Results from over 500 CB transplants performed worldwide showed that low cell dose significantly decreased post-transplant survival (Gluckman *et al.*, 1997; Wagner *et al*., 1997). Gluckman *et al*. (1997) found that only 22% of patients who received $<3.7\times10^7$ nucleated cells per kilogram survived to 1 year, whereas those who received at least $3.7\times10^7$ nucleated cells per kilogram had a 41% chance of one (1) year survival. There are two main strategies for CB collecting: *in utero and ex utero*.

### *In- utero Collection*

*In- utero* CB collection is generally performed in the delivery room while the placenta is still in the uterus by cord blood bank expert or obstetrician or midwife. After the newborn is delivered and assessed, the cord is clamped and cut, and the collection is started immediately. Several workers have found this procedure a better option as it does not disturb the natural course of birth or the postpartum period and has lower macroscopic clots than *ex utero* CB collection (Reboredo *et al*., 2000; Wong *et al*., 2001; Solves *et al*., 2004). Solves *et al*., (2003) evaluated the benefits and disadvantages between two different CB collection strategies in order to improve CB bank methodology. They came to a conclusion that collection before placental delivery is the best approach to CB collection and allows optimizing CB bank but the procedure can however, interfere to normal delivery process.

Solves *et al*. (2003) similarly concluded that the mode of collection in□uences the haematopoietic content of CB donations and that collection before placental delivery is the best approach to CB collection and allows optimization of CB bank methodology. The close relation that the delivering physician has with the prospective donors facilitates the process of obtaining quality consent for the banking. Obstetricians can easily decide not to collect the CB if there are some maternal/infant problems. This strategy avoids the financial investment that generates the presence of CB banking personnel in the maternity ward.

Surbek *et al*. (2000) also compared both strategies in vaginal deliveries and concluded that *in utero* collection yielded a significant higher volume and total number of mononuclear cells. The results of the work of Mostert *et al*. (2018) indicated that the *ex-utero* collection model using dedicated Cord Blood Bank (CBB) staff performed better than the *in-utero* model. The *ex-utero* collection method resulted in more qualifying units stored, lower contamination rates, and fewer quality events compared with the *in-utero* model.

Currently there is no standardized method of collecting and transferring umbilical cord blood to laboratory vacuum tubes. Current methods require needles to draw the blood presenting risk of blood exposure and percutaneous injury to obstetrical personnel. Q-Cup technology has been proposed as a safer means for collecting cord blood (Sireesha *et al*., 2017).

### *Ex- utero Collections*

David *et al.* (2011) explained the general procedure for *ex- utero* collections. The placenta can be removed from the delivery suite and transported to a nearby clean room for the collection. The cord should be clamped within 3–5 s of the infant's delivery, and the placenta taken immediately by bank staff to a suitable site where it may be suspended in a device to allow collection of blood by gravity.

Several authors (Surbek *et al*., 2000; Solves *et al*.,2003; Tamburini *et al*., 2006; Yang *et al*., 2011; Chandra *et al*., 2011; Chitra *et al*., 2015) have studied the merits and demerits of *ex- utero* collection. They all agree that that *in-utero* CB collection had a greater volume, CD34+cell count, colony-forming units (CFUs), and viability of nucleoid cells and higher monocytes, granulocytes and TNC, than *ex utero* CB collection. Larry *et al*. (2002) postulated that

both methods produce comparable nucleated cell, MNC, CD34+, and CFU-GM numbers. While Solves *et al*. (2003) believe that *ex- utero* collection may increase bacterial contamination, other workers (Larry *et al*. (2002). Chitra *et al*. (2015) are of the opinion that bacterial contamination was lower in the ex-utero collection as compared to the *in- utero* collection.

***Cord Blood Harvesting Techniques***

The blood in the umbilical cord can be collected in two ways, either by a syringe or bag method (Phuc *et al*., 2014). Primarily either large syringes (60 cc) or small bags (approximately 400 cc) are used in the collection of cord blood (Harris, 2008). The syringe collections provide visual feedback to the collector, allowing them to control not only the rate and volume of the collection, but also to restart collections that have stopped for any reason. Unattended bag collections, although somewhat simpler to perform, are not able to provide this option. Furthermore, first-time or inexperienced collectors routinely are able to collect larger volumes using the syringe method, with greater sterility of collection (Olayanju *et al*., 2017).

The blood from the umbilical cord can be collected using a syringe and cannula and collected into a bag containing antibiotics and other necessary elements for keeping the blood safe until it is correctly preserved. This is the closed technique of collection since the umbilical cord is not cut or disturbed in order to collect the blood (Hussain, 2012).

Standard blood bag systems for the collection and processing of peripheral blood consist of at least one collection bag and a collection needle, connected via a tube. The collection bag can contain an anticoagulant such as a citrate-phosphate-dextrose solution (CPD), citrate-phosphate-dextrose with adenine (CPDA), sodium citrate solution or an anticoagulant citrate-dextrose solution (ACD) or heparin (Hussain, 2012).

Armitage *et al*. (1999) described the Optipress II Automated Blood Component Extractor (Opti II) from Baxter Healthcare Corporation, to reduce the volume of the CB collection, preserving the quantity and quality of the progenitor cells, in a closed system. The CB collection is transferred to a triple bag system, centrifuged to produce a buffy coat layer and processed using a standard Opti II protocol to separate the whole blood into three components: plasma, buffy coat and buffy coat-depleted red cell concentrate.

According to Elchalal *et al.* (2000) *t*he syringe-assisted sodium chloride solution flush collection method with a blood bag has been found to be the most effective method for human umbilical cord blood collection. This method doubles the total white blood cells collected with respect to current yields, which may make cord blood transplantation applicable for adults.

Frans *et al*. (2005) developed a non-invasive needle-free device to ensure the safe, efficacious, and aseptic collection of UCB during vaginal childbirth or after cesarean section. The ease of use, speed of collection and UCB volumes collected compared favorably with traditional methods. The design of the device prevents medical personnel from being exposed to blood borne disease from blood splashing and accidental needle sticks. Because no careful placement of needles is required, semi-skilled personnel can perform the procedure in place of physicians, nurses, and highly trained technicians, improving the UCB collection procedure with minimal interference in the childbirth setting, potentially increasing the number of UCB units collected.

Hussain, (2012) compared the old and modern methods of extraction. In the old method the collected cells were cultured in a dish and then transplanted into mice, ex vivo expansion and then in vitro transplantation. Once the cells were grown, they were spun in a centrifuge in order to spin them down to separate and extract them. A major limitation observed in this method was that too much plasma content was collected with not enough mono nucleated cells and no reliable way to concentrate and isolate stem cells.

The modern methods are derived by doing the similar steps in an automated way. The cord blood is first separated into several layers such as a layer of red blood cells, a layer of plasma and an

in- between layer which is known as the buffy layer. Buffy layer is known to be rich in white blood cells and most essential stem cells. Then a suitable processing method is used, to help better separation of cord blood into these multiple layers, allowing for easier extraction of more stem cells (Hussain, 2012).

Cord Blood 2.0 banking concept is a new concept in cord blood collection. Cord Blood 2.0® is an entirely proprietary system developed by Americord, a leading American blood bank founded in 2008. Compared to traditional cord blood stem cell collections systems, the Cord Blood 2.0® can obtain substantially greater quantities of stem cells for preservation. The main advantage that results is that the cord blood units can be used for hematopoietic stem cell transplant in patients who are larger in size. Historically, the volume of stem cells preserved during traditional processing of a cord blood unit has only been sufficient to allow for the treatment of patients up to 60-70 pounds (John and Wagner, 2013).

Samareh *et al*. (2020) conducted an experiment on the use of cord blood serum (CBS) harvesting by hydroxyethyl starch (CBS-HES) as an alternative to fetal bovine serum (FBS) in expansion of umbilical cord derived mesenchymal stem cells (MSCs). They evaluated the impact of CBS-HES, as an enriched source of growth factors, on the basic MSCs characteristics. CBS-HES as an available and affordable additive, seems to be an optimal, relatively safe, and promising FBS alternative for cultivation, propagation, and subsequent clinical applications of MSCs.

Umbilical cord blood-derived cell collection adequate for cryopreservation and subsequent autologous reinfusion has been achieved in 70% of extremely preterm infants (Zhou *et al.,* 2023).

## 4. FACTORS AFFECTING THE QUANTITY AND QUALITY OF COLLECTED UMBILICALCORD BLOOD

The number of cells available in a single cord blood unit, in particular, the Cd34+ and total nucleated cell content influences the transplantation clinical outcome (Stefania *et al.,* 2022). By optimizing the CB collection, the quantity and quality of UCB for storage can be improved and increase the likelihood of its use for transplantation (Seyed *et al*., 2019). Craig *et al*. (1999) investigated the influence of obstetric factors on the volume and TNC of CB donations and identified favourable obstetric factors on the volume and TNC of CB donations to include long gestation, long labour, high infant and placenta weight and a short interval between delivery of the infant and cord clamping. Many factors influence the quantity and quality of UCB units that are collected after delivery. Such factors include mode of collection, interval between delivery and collection and the type and amount of anticoagulant among others (Craig *et al*., 1999; Turcan *et al.,* 2021).

### *Cell Separation*

Campos *et al*. (1995) carried out a work on the definition of optimal conditions for collection and cryopreservation of umbilical cord hematopoietic cells. They compared the influence of cell separation and of delay between collection and cryopreservation on the numbers of nucleated cells and of hematopoietic progenitors recovered before and after cryopreservation. The results of their work demonstrated that Ficoll separation resulted in the loss of more than 50% of nucleated cells, but also of a significant number of progenitors before freezing. Unseparated cells could be kept at 25°C as long as 24 h before freezing with minimal loss of progenitors before and after freezing and thawing. In contrast, there was a significant decrease in the number of viable cells and progenitors when cells were maintained at 4°C before freezing.

### *Time of UCB Collection after Delivery*

Time of clamping and extracting are important because the alteration in placental hemodynamics could cause hypervolemia in newborn. The umbilical vessels are also known to tend to collapse, according to Burton's theory (Yao *et al.,* 1977). The interval between placenta delivery and CB collection has significant influence on CBU's volume (Jones *et al*., 2003; Barini *et al*., 2011). Askari *et al*. (2005) showed that collection within not greater than 5 minutes of placental delivery produced higher volume

and TNC count. The proposal by the American College of Obstetricians and Gynecologists to recommend delayed cord clamping for term and preterm infants could therefore reduce the proportion of units with an acceptable TNC.

***Time of Clamping***

Concerns have been raised about reduced red cell mass in the neonate resulting from early clamping of the umbilical cord that is necessary to maximize volume of UCB collection. In one study, where cords were clamped within 30 seconds, haemoglobin values were 1.2 g/ dL lower than those in infants whose cords were clamped later (Deshpande, 2014). As early as 1969 a correlation between the time of cord clamping and infant blood volume had been demonstrated (Yao *et al*., 1969).

Delayed umbilical cord clamping has been reported to increase haemoglobin levels at birth and improve iron stores in the first few months of life, which improves the developmental outcomes. There is growing evidence that delayed cord clamping is beneficial and can improve the infant's iron status for up to 6 months after birth (Ola *et al*., 2011, McDonald *et al*., 2013, Busarira *et al*., 2019). The World Health Organization (WHO) recommends delayed cord clamping in order to prevent anemia in newborns (Otoo 1973, van Rheenen and Brabin 2006). Delayed cord clamping has been formally endorsed by a number of medical societies; however, it has not yet been universally adopted by obstetricians and neonatologists (Petrini and Christensen, 2015).

Bhandari *et al*. (2017) studied the awareness of cord blood collection and the impact on banking and reported, however, that a respondent cited delayed cord clamping as a reason for not donating.

***Anticoagulants***

Umbilical cord blood is always collected in sterile bags containing anticoagulant-based citrate, such as citrate phosphate dextrose (CPD) or CPD-adenine 1 (CPD-A1) to prevent coagulation and to maintain viability during transport to the processing facility (Seyed *et al*., 2019). Although CPD has been widely used based on the commercial availability of pre-filled collection bags, heparin is also accepted as an anticoagulant for processing hematopoietic stem cells (Harris *et al*., 2011; Seyed *et al*., 2019). The TNC yield and viability of samples collected in lyophilized heparin (LH) compared to CPD suggest that UCB quality was impacted by anticoagulant selection. Lyophilized heparin has been found to be more biocompatible than CPD as measured by cell viability endpoints (Harris *et al*., 2011).

Kraus *et al. (2009)* compared the effect of CDP and dry heparin on CBU's parameters. They found significantly higher pre-processed TNC count, post-processed TNC count, percent CD34+ cell, and number of CD34+ cells in the CPD than heparinized units. Interestingly, viability was significantly higher in the post-processed heparin units than CPD cord blood units. The viability of the CD34+ cells decreased in CBUs that was collected in heparin than CDP anticoagulant. Citrate phosphate dextrose has a dual role as an anticoagulant and a preservative as it contains dextrose which provides a substrate for glycolysis and preserves the metabolism in the cells (Tse and Laughlin, 2005). Heparin, which does not have specifications of CPD and because it is broken down over long periods of time, could only be useful for blood that is to be transfused within 12 h of the collection. In addition, the use of dry heparin may adversely affect the osmolality of the CBU (Harris *et al*., 2011).

Salge-Bartels *et al*. (2009) showed that anticoagulant concentration had no impact on cell viability although cell viability reduces gradually after storage for 25–48 h and higher. Pope *et al*. (2012) suggested that the ratio of anticoagulant could cause decrease cell viability in CBUs with the volume lower than 60 ml. Further, it was suggested that lower WBC viability in low volume CBUs could be due to a higher ratio of anticoagulant. Cell diameter does not differ when using the different anticoagulants, except for the increase reported for monocyte in the presence of citrate (Danusso, 2023).

***Time Between Collection and Processing***

Rogers *et al*. (2001) analyzed about 4000 UCB samples to determine the correlation between cell number, cell type, volume, and time between

collection and processing. They reported significant losses of nucleated and CD34+ cells after storage at room temperature for up to 24 hours. Ricardo *et al*. (2011) studied the possible effect of time between collection and processing of umbilical cord blood samples on the quality of the sample. Their findings showed that an increase in the time interval between collection and processing negatively affects the quality of the UCB sample (Figure 1).

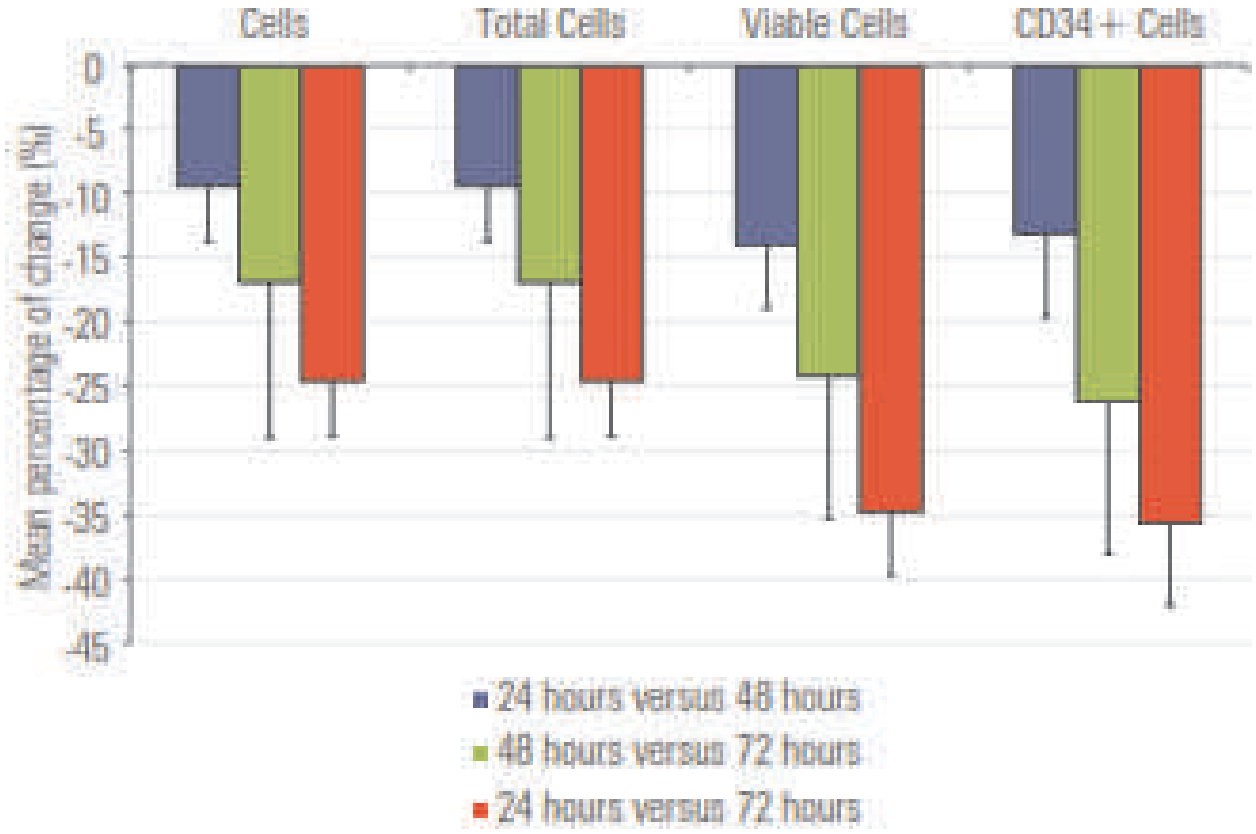


**Figure 1. Variation in the mean percentage of number of nucleated cells, viable cells and CD34+ cells in UCB bags between 24-, 48- and 72-time intervals**

In contrast, Isoyama *et al*. (1996) reported that CB nucleated cells maintained significant viability at room temperature for 24 hours or longer. Campos *et al*. (1995) also reported that unseparated cells could be kept at 25°C as long as 24 hours before freezing with minimal loss of progenitors before and after freezing and thawing. They also reported that in contrast, there is a significant decrease in the number of viable cells and progenitors when cells were maintained at 4°C before freezing.

***Temperature of Storage before Transportation to Processing Unit***

Hubel *et al*. (2003) reported recoveries of CB mononuclear cells stored at 4°C of 95 and 81 percent, compared to recoveries of 88 and 56 percent after storage at room temperature, at 24 and 72 hours, respectively. Mononuclear cell counts and the frequency of CFU-GM are reduced at 72 hours when compared with 24 hours (Hubel *et al*., 2003).

Antonenas *et al*. (2006) in their study of the effects of different storage temperatures on the viability of cells in Peripheral Blood Stem Cells (PBSC) and Bone Marrow Hematopoietic Progenitor Cells (BM HPC) products observed that the mean loss of viable CD34+ cells in HPC products at refrigerated temperature of 2°C to 8°C was 9.4%, 19.4% and 28% at 24, 48 and 72 hours, respectively in contrast to the mean loss of viable CD34+ cells loss of 21.9%, 30.7% and 43.3% at 24, 48 and 72 hours respectively at room temperature. No viable CD34+ cells remained after storage at 37°C for 24 h. Only

PBSC products and not BM showed temperature-related loss of CD34 viability. Antonenas *et al*. (2006) concluded that the optimum temperature for maintaining the viability of freshly harvested hematopoietic stem cells (HSCs) is 2° to 8°C. In all cases the loss increased with the number of days of storage before processing.

**Conclusion**

The number of cells available in a single cord blood unit is very important for the transplantation clinical outcome. By optimizing the CB collection, the quantity and quality of UCB for storage can be improved and increase the likelihood of its use for transplantation. Parents need to be aware of the options that exist for their infant's cord blood and have access to the relevant information to inform their choice. Parents can decide if they would like to privately store their infant's cord blood for later use if needed, publicly donate it, defer cord clamping to allow their infant to receive optimal volumes of cord blood at birth or to discard the remaining cord blood with the placenta after birth.

Prior to collection, UCB donors are required to sign an informed consent form. Consent will not be obtained during active labor or while the mother is under the influence of sedation or mood-altering medications. If the cord blood is removed after the placenta has been taken from the mother's uterus the father's wishes are also relevant.

The current consensus is that CB should be at least 4/6 HLA matching for HLA-A, -B at the antigen level, and HLA-DRB1 at the allelic level. All CB units considered for storage should undergo rigorous and reliable screening for human immunodeficiency virus (HIV) due to the high prevalence of HIV amongst women attending antenatal clinics in sub-Saharan Africa together with the risk of mother-to-child transmission which increases the risk of transplant transmissible infection.

*In-utero* CB collection has been found a better option as it does not disturb the natural course of birth or the postpartum period and has lower macroscopic clots than *ex-utero* CBUs collection. *In-utero* collection also yields a significant higher volume and total number of mononuclear cells.

Cord blood collection within not greater than 5 minutes of placental delivery produces higher volume and TNC count. Delayed cord clamping is beneficial and can improve the infant's iron status for up to 6 months after birth. Delayed cord clamping has been formally endorsed by a number of medical societies; however, it has not yet been universally adopted by obstetricians and neonatologists.

There have been suggestions from empirical studies that lower WBC viability in low volume CBUs could be due to a high ratio of anticoagulant. Similarly, increase in the time interval between collection and processing negatively affects the quality of the UCB sample. The optimum temperature for maintaining the viability of freshly harvested hematopoietic stem cells is 2° to 8°C while the loss of cell increased with the number of days of storage before processing.

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**Citation:** Eze Evelyn Mgbeoma, Jacob Ransom Baribefii, Lenox-Prince Tamunonengiye-Ofori and Okoye, Nelyn Akunna. Umbilical Cord Blood Collection Protocol and the Impact on the Nucleated and Progenitor Cell Quantity and Quality. ***Sokoto Journal of Medical Laboratory Science*; 9(1): 17-31**. DOI: 10.4314/sokjmls.v9i1.2