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Factors Affecting the Quality of Umbilical Cord Blood: A Systematic Review from Collection to Storage

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Abstract

Background: *Hematopoietic stem cell transplantation (HSCT) has transformed the treatment of blood disorders and autoimmune diseases. Umbilical cord blood (UCB) is a valuable source of stem cells but maintaining UCB quality is crucial for optimizing transplant success.*

Objective/Rationale: *This review systematically examines factors influencing UCB quality, focusing on collection, processing, and storage practices, with strategies to improve cord blood banking protocols.*

Methods: *We performed a comprehensive search of studies from databases such as PubMed, Scopus, and Web of Science, synthesizing data on key factors affecting UCB quality.*

Results: *Critical factors include collection methods, phlebotomy expertise, anticoagulants used, and storage conditions. Optimal UCB collection and advanced cryopreservation techniques enhance UCB integrity.*

Conclusion: *Improved UCB collection, processing, and storage protocols can significantly enhance transplant outcomes, despite some uncontrollable factors.*

Keywords: Stem-cell transplantation, umbilical cord blood, UCB quality, collection practices, processing methods, cryopreservation.

Introduction

Umbilical cord blood (UCB) is the residual blood in the umbilical cord and placenta after birth and has been utilized as a source of hematopoietic stem cells (HSCs) since 1988. It is notably rich in various stem and progenitor cells, including unrestricted somatic stem cells, hematopoietic stem cells, and mesenchymal stem cells (MSCs) [1, 2]. Over the past three decades, the practice of umbilical cord blood banking has expanded significantly, driven by advances in understanding the characteristics of UCB that contribute to successful transplantation outcomes. Despite this progress, the factors that influence the quality of UCB remain poorly understood.

UCB offers unique advantages over other stem cell sources like peripheral blood and bone marrow. It provides greater flexibility in Human Leukocyte Antigen (HLA) matching, which is crucial for minimizing graft-versus-host disease (GVHD) and reducing the risk of graft failure [3, 4]. This flexibility is attributed to the relatively naïve lymphocytes and the abundance of immature progenitor cells with longer telomeres found in UCB compared to adult bone marrow [5-7]. As a result, UCB is a valuable alternative for patients who lack HLA-compatible donors, particularly for ethnic and racial minorities who might face challenges in finding suitable donors [8, 9].

Hematopoietic stem cell transplantation, which involves administering immature stem cells from either the patient's own body (autologous) or from a compatible donor (allogeneic), is a crucial therapy for a range of blood-related malignancies and severe autoimmune diseases, including leukemia, lymphoma, aplastic anemia, multiple sclerosis, and therapy-resistant rheumatoid arthritis [10-12]. Historically, adult bone marrow and mobilized peripheral blood have been the primary sources of HSCs, but these come with risks such as donor discomfort and complications like GVHD [13, 14].

The success of UCB transplantation hinges on several factors, notably the quality of the UCB collected. This quality is determined by the volume of blood, cell count, and the concentration of key cell types, including total nucleated cells (TNCs) and CD34+ cells [15, 16]. Other determinants of transplantation success include maternal, neonatal, and obstetric factors such as maternal age, weight, mode of delivery, and gestational age, which can all impact UCB quality [17]. Additionally, the methods used for UCB collection, processing, and storage play a critical role in preserving its quality.

This review aims to systematically evaluate these factors, focusing on controllable elements of UCB collection, processing, and storage to enhance transplantation outcomes. By addressing these factors, the review seeks to provide insights into optimizing UCB quality, thus improving the effectiveness and success of stem cell transplants.

Methodology

Search Strategy: A thorough search was conducted across three major databases: PubMed, Scopus, and Web of Science, covering publications from January 2000 to August 2024. The search strategy incorporated terms such as "umbilical cord blood," "stem cell transplantation," "quality factors," "cell count," "collection methods," "processing," and "cryopreservation." The search was limited to articles published in English to ensure relevance and accessibility. The inclusion criteria were as follows: studies that examined factors influencing the quality of umbilical cord blood, including volume, cell counts (e.g., total nucleated cells, CD34+ cells), collection and processing methods, and clinical outcomes related to stem cell transplantation. Articles considered for inclusion encompassed randomized controlled trials, observational studies, cohort studies, and reviews. Exclusion criteria included studies with insufficient data, those not subjected to peer review, and articles focusing exclusively on animal models or non-relevant topics.

Data Extraction and Analysis: Data extraction was performed to capture essential details such as study design, sample characteristics, factors affecting UCB quality (e.g., volume, cell count, collection techniques), and transplantation outcomes. Key variables of interest included maternal and neonatal factors, collection and processing methods, and cryopreservation techniques. Any discrepancies in data extraction were addressed through a rigorous re-evaluation process. The extracted data were then synthesized narratively, providing a cohesive overview of the factors influencing UCB quality and their implications for stem cell transplantation. This synthesis aimed to highlight trends, gaps in research, and areas for future investigation, ensuring a comprehensive understanding of how different factors impact the efficacy of UCB as a source of stem cells.

Results

The initial search yielded a total of 1,023 articles. After conducting a preliminary screening based on titles and abstracts, 134 studies were selected for full-text review. Following a comprehensive evaluation of these articles against the inclusion and exclusion criteria, 109 studies met the criteria for inclusion in the review (Figure1). These selected studies encompass a variety of topics related to umbilical cord blood quality, including collection techniques, processing methods, storage practices, and their impact on stem cell transplantation outcomes.

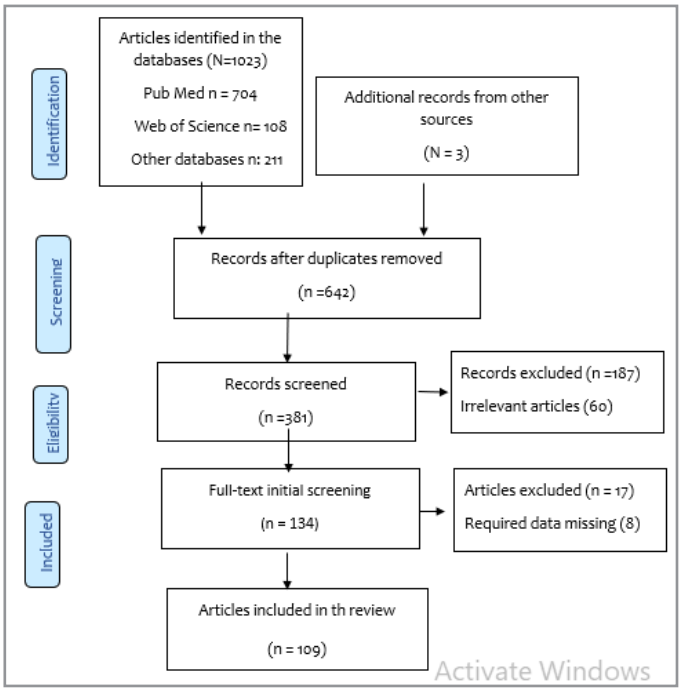


Figure 1: PRISMA flow Diagram Illustrating the Process of Article Selection for Inclusion in the Review.

Technological Parameters

The method of umbilical cord blood (UCB) collection significantly impacts the quality of the blood obtained. Two primary techniques are commonly employed by UCB banks: in utero and ex utero collection. The in-utero method involves drawing blood from the umbilical vein while the placenta remains in the uterus, which minimizes contamination risks [18]. In contrast, the ex-utero method collects blood after the placenta is expelled, relying on gravity to drain the blood. This approach, while simpler, generally results in lower blood volumes, decreased total nucleated cell (TNC) counts, and increased contamination risks due to delays in collection [19, 20]. Studies consistently indicate that the in-utero collection method results in superior UCB quality, as reflected by higher TNC and CD34+ cell counts in both vaginal and caesarean deliveries [21-23].

Phlebotomy Practices and Obstetric Predictors

Phlebotomy practices and obstetric factors also significantly influence UCB quality. Delayed cord clamping (DCC), although beneficial for newborns—especially preterm infants—can negatively affect UCB quality. Delays of over 60 seconds significantly reduce both the volume and TNC count of the collected blood, and delays beyond 120 seconds dramatically reduce suitable TNC counts from 39% to just 6.2% [24]. Furthermore, the interval between placental delivery and UCB collection is inversely related to blood volume, with delays exceeding 10 minutes critically compromising blood quality [25]. UCB can also be collected using either open or closed systems, with open systems associated with significantly higher bacterial contamination rates compared to closed systems [26, 27]. Caesarean sections using open systems demonstrate particularly high contamination rates, as shown in Table 1.

Delivery type	Sample volume (cc)	Bacterial Contamination rate(%)
Caesarean – closed system	61	5
Caesarean – Open system	65	15
Vaginal – closed system	71	3
Vaginal – Open system	78	11

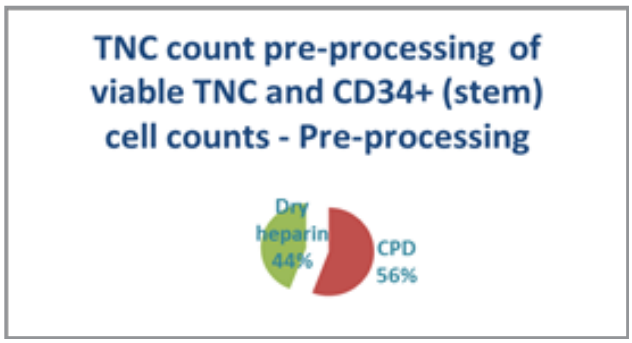
Note: χ^2-test statistic score = 9.51, df=3; p=.02 (Bertolini et al., 1995)

Collection Methods

Cord blood collection can be performed using either blood bags (standard clinical practice) or syringe-assisted methods. Blood bags allow free flow collection, while milking maneuvers may enhance the flow before sealing the bag. The syringe-assisted method, often performed with a heparinized syringe, can yield greater volumes and higher white blood cell (WBC) counts—sometimes double those collected with blood bags. However, the syringe method presents a higher risk of microbial contamination [29, 30].

Anticoagulant Types and Amounts

The choice of anticoagulant during UCB collection has a profound impact on blood quality. Heparin, while effective at maintaining larger blood volumes, has a limited shelf life and carries risks related to contamination and antigen matching [31]. Citrate Phosphate Dextrose (CPD), on the other hand, is preferred due to its non-toxic properties and longer shelf life, supporting better cellular metabolism during preservation [32]. Studies show that UCB collected with CPD contains higher TNC and CD34+ cell counts compared to heparin-preserved samples (Figures 2 & 3) [33].



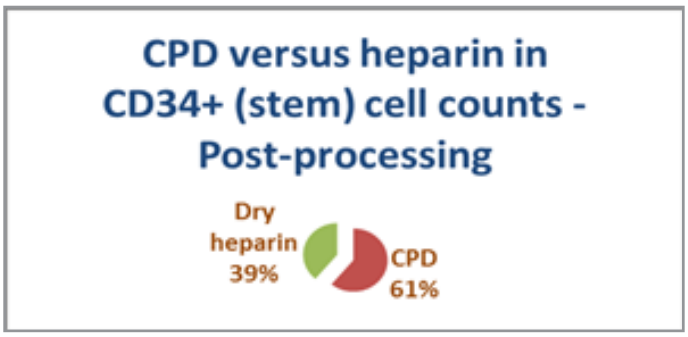


Figure 2 & 3: A Comparison of Viable TNC and CD34+ Cell Counts in Cord Blood Preserved with CPD vs. Dry Heparin
Source: Kraus M et al. (2009). DOI: 10.1182/blood.v114.22.4227.4227.

Processing Techniques and Stem Cell Isolation

Once received at the blood bank, UCB undergoes testing for microbial contamination and genetic diseases to ensure sterility and quality. The blood is then processed to preserve hematopoietic stem cells, essential for its therapeutic potential [34]. Processing methods like fractionation, which reduces blood volume

and removes red blood cells (RBCs), are commonly used to optimize storage and treatment outcomes by minimizing dimethyl sulfoxide (DMSO) cytotoxicity during cryopreservation [35 37].

Historically, UCB banks used whole blood cryopreservation (zero-generation processing), but this method was found inefficient [39]. More recent methods, such as rouleaux formation with hydroxyethyl starch (HES) and differential centrifugation, have improved cell recovery rates and storage efficiency [40, 41]. Table 2, adapted from Nagler et al. (1993), compares nucleated cell recovery from various RBC removal methods, demonstrating the superior efficiency of gelatin sedimentation.

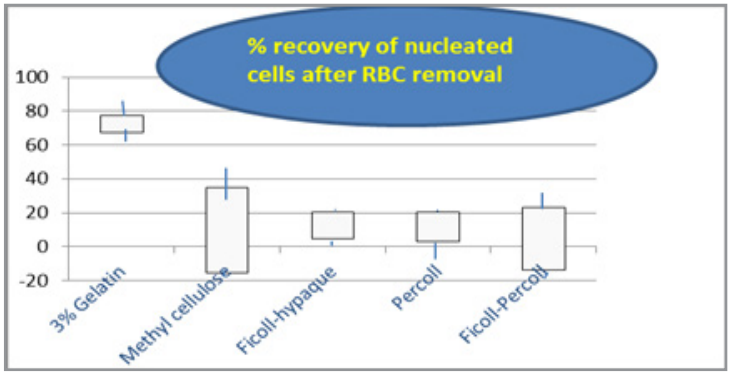


Figure: 4

First-generation processing methods, while simple and widely adopted, are associated with significant cell loss (up to 25%) [42-44]. To improve this, second-generation methods, which remove plasma while preserving nucleated and progenitor cells, have shown recovery rates as high as 99.9% [45]. Third-generation techniques, such as density gradient separation with Percoll or Ficoll, further optimize cell recovery by effectively depleting RBCs while maintaining essential stem cells [46-48].

Cryopreservation Techniques and Storage

Cryopreservation of UCB involves the use of cryoprotectants like DMSO, followed by controlled-rate freezing to maintain cell viability [49]. Optimal cooling rates of 1 to 2.5°C per minute are crucial for preserving stem cell function. Both liquid and vapor phases of nitrogen are used for long-term storage, each with unique risks and benefits for contamination [50].

Discussion

Our systematic review underscores the critical factors affecting UCB quality for hematopoietic stem cell transplantation (HSCT). The review highlights the superior outcomes associated with in-utero collection methods, which consistently yield higher total nucleated cell (TNC) and CD34+ cell counts. Standardizing this method across UCB banks could significantly enhance HSCT success rates.

The balance between delayed cord clamping (DCC) for neonatal benefits and UCB quality presents a dilemma for clinicians, as prolonged clamping reduces blood volume and cell counts critical for transplantation. Similarly, the choice of anticoagulant and collection method also influences the final UCB product, with CPD being preferable to heparin and syringe-assisted collection posing higher contamination risks despite higher yields.

Processing innovations, such as advanced fractionation methods, have improved both the efficiency of UCB storage and the safety of transplantation. Cryopreservation techniques, particularly controlled-rate freezing with DMSO, are vital for maintaining cell viability during long-term storage. Continued research is necessary to refine these processes and optimize both neonatal care and UCB quality for transplantation.

Conclusion

Optimizing umbilical cord blood (UCB) collection, processing, and storage to improve outcomes in hematopoietic stem cell transplantation (HSCT) is crucial. In-utero collection methods, the use of CPD as an anticoagulant, and advanced cryopreservation techniques have emerged as key factors in enhancing stem cell yield and viability. However, the ongoing challenge of balancing neonatal health benefits with UCB quality requires further research and innovation. Standardizing best practices across UCB banks will be essential to maximize the therapeutic potential of UCB for transplantation

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