



Cord Blood: A Review

Sunitha Dontha^{1*}, Hemalatha Kamurthy¹ and Nandakishora Chary Madipoju¹

¹Department of Pharmaceutical Chemistry, Malla Reddy College of Pharmacy, Maisammaguda, Secunderabad-14, Telangana, India.

Authors' contributions

This work was carried out in collaboration between all authors. Author SD designed the study, wrote the protocol and wrote the first draft of the manuscript. Author HK managed the literature searches, analyses of the study performed and author NCM helped in matter collection. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

The blood collected from a new born baby umbilical cord is known as Cord blood. It is a rich source of hematopoietic stem cells, used in the treatment of over 80 diseases like various cancers and blood, immune and metabolic disorders. Cord blood is collected from umbilical cord vein attached to the placenta after umbilical cord has been detached from new born. The cord blood is composed of all elements, found in whole blood like red blood cells, white blood cells, plasma, platelets and hematopoietic stem cells. Cord blood which is collected is cryopreserved and is stored in cord blood bank for future transplantation.

Keywords: Cord blood; diseases; stem cells; leukemia; autologous.

1. INTRODUCTION

Umbilical cord blood is blood that remains in the placenta and in the attached umbilical cord after childbirth. Cord blood is collected because it

contains stem cells, used to treat hematopoietic and genetic disorders.

Cord blood is a rich source of hematopoietic stem cells (HSC), used to treat certain diseases

*Corresponding author: E-mail: basasunitha@gmail.com;

of the blood and immune system. HSC are the stem cells that give rise to all the other blood cells through the process of haematopoiesis. They are derived from mesoderm and located in the red bone marrow. Patients with lymphoma, myelodysplasia and severe aplastic anemia are successfully transplanted with cord blood. Cord blood is collected from the umbilical cord vein attached to the placenta after the umbilical cord has been detached from the newborn. The umbilical vein supplies the fetus with oxygenated, nutrient-rich blood from the placenta. Whereas the fetal heart pumps deoxygenated, nutrient-depleted blood through the umbilical arteries back to the placenta. One unit of cord blood generally lacks stem cells in a quantity sufficient to treat an adult patient. The placenta is a much better source of stem cells since it contains ten times more than cord blood [1]. Some placental blood may be returned to the neonatal circulation if the umbilical cord is not prematurely clamped. According to Eileen and Eman, cord clamping should be delayed a minimum of two minutes to prevent anemia over the first three months of life and enriching iron stores and ferritin levels for as long as 6 months [2]. If the umbilical cord is not delayed clamping, a physiological postnatal occlusion occurs upon interaction with cold air, when the internal gelatinous substance, called Wharton's jelly, swells around the umbilical artery and veins. Cord blood stem cells are blood cell progenitors which forms red blood cells, white blood cells, and platelets, hence cord blood cells are currently used to treat blood and immune system related genetic diseases, cancers, and blood disorders.

There are several methods for collecting cord blood. The method most commonly used in clinical practice is the "closed technique", which is similar to standard blood collection techniques. In this method, the technician cannulates the vein of the severed umbilical cord using a needle that is connected to a blood bag, and cord blood flows through the needle into the bag. The umbilical vein catheter is another source for percutaneous peripheral or central venous catheters or intraosseous canulas and employed in resuscitation or intensive care of the newborn. On an average, by closed technique about 75 ml of cord blood [3] can be collected and cryopreserved, then stored in a cord blood bank for future transplantation.

Cryopreservation or cryoconservation is a process where cells, whole tissues, or any other substances susceptible to damage caused by

chemical reactivity or time are preserved by cooling to sub-zero temperatures. At low enough temperatures, any enzymatic or chemical activity which might cause damage to the material is effectively stopped.

Stem cells are immature cells that can both reproduce themselves and have the potential to turn into other types of cells. There are several types such as embryonic (Embryos formed during the blastocyst phase of embryological development stem cell) and Adult tissue (adult stem cells). The umbilical cord blood and bone marrow cells are called hematopoietic progenitor cells (HPCs).

1.1 Storage

Cord blood is stored by both public and private cord blood banks.

- 1) Public cord blood banks store cord blood for the benefit of the general public, and most U.S. banks coordinate matching cord blood to patients through the National Marrow Donor Program (NMDP). Public cord blood is stored and made available for use by unrelated donors and this banking is widely supported. One important obstacle facing public banks is the high cost required to maintain them, this lead to less number of banks. Because public banks do not charge storage fees, medical centers do not always have the funds required to establish and maintain them. There is a general support in the medical community for public cord blood banking.
- 2) Private cord blood banks are usually for-profit organizations that store cord blood for the exclusive use of the donor or donor's relatives. Banking is generally not recommended unless there is a family history of specific genetic diseases. Private cord blood is stored for and the costs paid by donor families and is controversial in both the medical and parenting community. Private cord blood banks typically charge around \$2,000 for the collection and around \$200 a year for storage. For private banking objections raised from many governments and nonprofit organizations.

Although umbilical cord blood is well-recognized to be useful for treating hematopoietic and genetic disorders, some controversy surrounds the collection and storage of umbilical cord blood

by private banks for the baby's use. Only a small percentage of babies (estimated between 1 in 1,000 to 1 in 200,000) ever use the umbilical cord blood that is stored. The American Academy of Pediatrics 2007 Policy Statement on Cord Blood Banking states that: "Physicians should be aware of the unsubstantiated claims of private cord blood banks made to future parents that promise to insure infants or family members against serious illnesses in the future by use of the stem cells contained in cord blood".

R. Morgan Griffin reported Umbilical cord blood banking as a procedure in which takes blood from the umbilical cord at birth and stores it for a fee in a blood bank. Because this blood is rich in stem cells -- cells that have the ability to transform into just about any human cell -- it could someday be used as treatment if your child ever became ill with certain diseases. It might also be useful for a sick sibling or relative. Banking cord blood is a way of preserving potentially life-saving cells that usually get thrown away after birth. New parents have the option of storing their newborn's cord blood at a private cord blood bank or donating it to a public cord blood bank. The cost of private cord blood banking is approximately \$2000 for collection and approximately \$125 per year for storage, as of 2007. Donation to a public cord blood bank is not possible everywhere, but availability is increasing. Several local cord blood banks across the United States are now accepting donations from within their own states. The cord blood bank will not charge the donor for the donation; the OB/GYN may still charge a collection fee, although many OB/GYNs choose to donate their time. After the first sibling-donor cord blood transplant was performed in 1988, the National Institute of Health (NIH) awarded a grant to Dr. Pablo Rubinstein to develop the world's first cord blood program at the New York Blood Center (NYBC), in order to establish the inventory of non embryonal stem cell units necessary to provide unrelated, matched grafts for patients.

1.2 Regulation

In the United States, the Food and Drug Administration regulates cord blood under the category of "Human Cells, Tissues, and Cellular and Tissue Based-Products." The Code of Federal Regulations under which the FDA regulates both public and private cord blood banks. Both the banks are also eligible for voluntary accreditation with either the American

Association of Blood Banks (AABB) or the Foundation for the Accreditation of Cellular Therapy (FACT). Potential clients can check the current accreditation status of laboratories from the AABB list of accredited cord blood laboratories.

1.3 Research

The uses of cord blood are beyond blood and immunological disorders, hence some research has been done in other areas [4]. Its uses is limited because cord cells are hematopoietic stem cells (which can differentiate only into blood cells), and not pluripotent stem cells (such as embryonic stem cells, which can differentiate into any type of tissue). Cord Blood for Neonatal Hypoxic-Ischemic Encephalopathy [5] is being studied in humans, and earlier stage research is being conducted for treatments of stroke, [6-8]. However, apart from blood disorders, the cord blood is also used for other diseases in clinical modality and remains a major challenge for the stem cell community [4,9,10]. An alternative approach, Stem Cell Educator therapy induces immune balance by using cord blood-derived multipotent stem cells [11]. A closed-loop system that circulates a patient's blood through a blood cell separator, briefly co-cultures the patient's lymphocytes with adherent CB-SCs *in vitro*, and returns the educated lymphocytes [12-15] to the patient's circulation. From the clinical trial, it was known that a single treatment with the Stem Cell Educator provides lasting reversal of autoimmunity which allows the regeneration of islet β cells. An investigation was also conducted to determine whether cord blood cells have any potential use in repairing damages cardiovascular tissue.

Training programs are also adopted for clinicians and researchers throughout the world, in order to coordinate the research efforts. In 2004 Eurocord,[16] an international platform specialized in clinical research on UCB stem cells, was founded by Pr. Gregory Katz and Eliane Gluckman. Eurocord centralizes and analyzes clinical data from 511 transplant centers in 56 countries. Eurocord funded by the European Union, works closely with the European School of Haematology. In 2007, the association was recognized by the *Medicen* network of cell therapy clusters. Eurocord also develops training programs for clinicians and researchers specialized in blood cancer and cell therapy.

The International Society of Cellular Therapy (ISCT) has established criteria for defining Mesenchymal stem cells MSC [17], differentiate to build bone, cartilage and connective tissue, and they can also mediate the body's inflammatory response to damaged or injured cells [18-21]. Clinical trials are not reported in humans using MSCs derived from cord tissue, but some reports are available, as used in treating certain diseases in animals [22-26].

There is no particular standard procedure or accrediting criteria for the storage of MSC from umbilical cord tissue. Many cord blood banks are storing the cord tissue by freezing a segment of the umbilical cord. This procedure has the advantage of waiting for the technology of cell separation to mature, but has the disadvantage of no guarantee to efficiently retrieve viable stem cells from a previously frozen cord. In few cord blood banks stem cells are extracted from the cord tissue before cryogenic storage. This method has the disadvantage of using current separation method, but the advantage is that it yields minimally manipulated cells which are ready for treatment and complies with FDA regulations on cell therapy products.

1.4 Controversy

The policy of the American Academy of Pediatrics states that "private storage of cord blood as 'biological insurance' is unwise" unless there is a family member with a current or potential need to undergo a stem cell transplantation. The American Academy of Pediatrics also notes that the odds of using one's own cord blood is 1 in 200,000.

Banking is not worth for most people. The banks opinion is that, it is a form of "insurance" in case their children ever get sick. But, many medical associations -- like the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists -- do not support the practice for most people. They say that possible benefits are too remote to justify the costs.

Stephen Feig, Professor of pediatrics, says that the use of stored cord blood is very less and it is a very expensive insurance policy and he also says that he will not object any one to not to store the cord blood. So the important thing is to make an informed choice. The patients should know the benefits and costs of cord blood banking before to make any decisions. Saving a

baby's cord blood for a family member who gets - or already is -- sick? Siblings are more likely to be a genetic match, which is crucial. The use of child's blood siblings is only about 25% and there is a 75% chance that he or she needs a donation from another donor's cells in a bank instead.

Cord blood is used in treating diseases in children. Only 3 to 5 ounces are taken from the cord, and since cord blood has a limited number of stem cells, which is not enough to treat most adults.

The parents also need to understand that cord blood is not the only possible treatment for these diseases. Most of the people who need a transplant of stem cells, can also get them from donated bone marrow, either from a family member or a bone marrow bank.

The current uses of the CB are limited. But many experts hope that stem cells will be a crucial part of future treatments for diabetes, Alzheimer's, spinal cord injuries, heart failure, stroke, etc. If it is really possible to make stem cells develop into any kind of cell, the uses are endless. But this is only theoretical, it is important to distinguish between what doctors can do now with cord blood stem cells and what they *will* be able to do in the future. Some people do not realize the distinction. They have exaggerated ideas of what is possible today.

Caplan says that people think the stem cell therapy is like its alchemy as a stem cell can be turned into anything, just like alchemists hoped to turn base metals into gold. But it is not true.

Even if researchers do have future successes with stem cells, they may not come from cord blood.

The science is moving fast right now, According to Caplan using stem cells from cord blood will be the new approach to take into the future. Caplan is more optimistic about techniques using embryonic stem cells or stem cells derived from adult tissue.

The controversy centers on varying assessments of the current and future likelihood of successful uses of the stored blood [27].

CB stem cells can be used for other purposes, like for regenerative medicine, says the World Marrow Donor Association (WMDA) and European Group on Ethics in Science and New Technologies. Therefore it is highly hypothetical

that CB cells kept for autologous use will be of more value in the future. WMDA, says that there are pediatric cancers (ex: neuroblastoma) and acquired conditions (ex: aplastic anemia) which can be treated by autologous transplant example leukemia.

WMDA Policy Statement for the Utility of Autologous or Family Cord Blood Unit Storage [28] stated that:

1. The use of autologous cord blood cells for the treatment of childhood leukemia is contra-indicated because pre-leukemic cells are present at birth. Autologous cord blood carries the same genetic defects as the donor and should not be used to treat genetic diseases.
2. There is at present no known protocol where autologous cord blood stem cells are used in therapy.
3. If autologous stem cell therapies should become reality in the future, these protocols will probably rely on easily accessible stem cells.

There were several known instances where autologous use of cord blood was possible, though other areas of research are more speculative [29,30].

2. VARIOUS REPORTS ON CORD BLOOD

2.1 Umbilical Cord Blood as a Source of Stem Cells [31]

Umbilical cord blood (UCB) is a source of the hematopoietic stem cells (HSC) and progenitor cells that can reconstitute the hematopoietic system in patients with malignant and nonmalignant disorders treated with myeloablative therapy. UCB cells possess an enhanced capacity for progenitor cell proliferation and self-renewal *in vitro*. The blood remaining in the delivered placenta is safely and easily collected and stored. Currently practiced collection procedure is a simple venipuncture, followed by gravity drainage into a standard sterile anti-coagulant-filled blood bag, using a closed system (similar to the one used for whole blood collection). After aliquots are removed for routine testing, the units are cryopreserved and stored in liquid nitrogen.

Children with both malignant and non-malignant hematologic disorders were transplanted with

UCB from a sibling donor, demonstrated comparable or superior survival to children who received BM transplantation. But the use of UCB transplantation in adult patients is less, since the limited number of HSC that harvested from umbilical cord and resulted in a slower time to engraftment and higher transplant related mortality. This is due to the long aplasia period after transplantation and susceptibility to viral and fungal infections. Despite prolonged periods of aplasia, the apparent reduction in the incidence and severity of graft versus host disease (GVHD). UCB lymphocytes has the lower incidence and severity of GVHD encountered in UCB transplantation compared to the allogeneic BM transplant setting. UCB transplantation is not associated with increased rates of disease relapse. From this data, suggested that nucleated cell dose in UK unit should be the primary criterion for donor selection. In 1991, the UCB transplantation program was established at the Zagreb University Hospital Center for related transplants, and until now only four UCB transplantations were performed successfully. To speed up the engraftment rate, several strategies (such as multiple UCB transplants and *ex vivo* expansion of HSC) have been assayed. The current strategies are focused on the development of much more efficient technologies for *ex vivo* production of progenitor cells. UCB is known to contain extremely immature stem cells (such as pluripotent or multipotent) and these are used for cellular therapy and regenerative medicine. Up to date there is no regarding these possibilities but preliminary *in vitro* and animal studies in the field of tissue regeneration suggest some degree of plasticity and/or trans differentiation. UCB cells are showing unique qualities and potential, and consequently UCB banks are dramatically increasing the scope of their clinical application.

2.2 Hematopoietic Stem-cell Transplantation Using Umbilical-cord Blood [32]

UCB is as an alternative source of hematopoietic progenitors (CD34+) for allogeneic stem cell transplantation, mainly who lack an HLA-matched marrow donor. From 1998, only about 2500 patients have received UCB transplants for a variety of malignant and non-malignant diseases. The vast majority of recipients were children with an average weight of 20 kg, however, more than 500 UCB transplantations (UCBT) have already been performed in adults. The "naive" nature of UCB lymphocytes explains

the lower incidence and severity of graft vs. host disease (GvHD) encountered in UCBT. UCB is rich in primitive CD16-CD56++ NK cells, which possess significant proliferative and cytotoxic capacities and used for IL-12 or IL-15, so as to mount a substantial graft vs. leukemia (GvL) effect. The major disadvantage of UCB is the low yield of stem cells, resulting in higher rates of engraftment failure. A rational approach thus involves *ex vivo* expansion of UCB derived hematopoietic precursors.

2.3 Cord Blood for Brain Injury [33]

CB is as an effective therapy for patients with brain injuries since cord blood (CB) cells induces repair through mechanisms like trophic or cell-based paracrine effects or cellular integration and differentiation. Recovery from neurological injuries is typically incomplete and often results in significant and permanent disabilities. Currently, most of the available therapies are limited to supportive or palliative measures. Because restorative therapies targeting the underlying cause of most neurological diseases are not existing. Cell therapies targeting anti-inflammatory, neuroprotective and regenerative potential holds great promise. Both are operative CB therapies for neurologic conditions, and there are numerous potential applications of CB-based regenerative therapies in neurological diseases, including genetic diseases of childhood, ischemic events such as stroke and neurodegenerative diseases of adulthood. This Review, mainly describes the state of science and clinical applications of CB therapy for brain injury.

For neonatal brain injury, UCB transplantation is emerging as a promising therapeutic method for treating hypoxic-ischemic brain injury and ischemic stroke. Number of the human clinical trials were conducted to examine the potential therapeutic benefits of undifferentiated CB cells for the treatment of established ischemic brain injury and established cerebral palsy. It is imperative that the timing of the administration of the UCB with respect to the time of the injury (if known) is defined, as well as the optimal dose of UCB for transplantation. Further, the contribution and beneficial effects of the different cell populations in UCB are to be elucidated in order to determine adequate therapies that leads to further improvement in neurological outcome, based on the clinical scenario.

2.4 Umbilical Cord Blood-derived Cellular Products for Cancer Immunotherapy [34]

Although the vast majority of experience with umbilical cord blood (CB) centers on hematopoietic reconstitution, a recent surge in the knowledge of CB cell subpopulations as well as advances in *ex vivo* culture technology have expanded the potential of this rich resource. Because CB has the capacity to generate the entire hematopoietic system, now a new source for natural killer, dendritic and T cells for therapeutic use against malignancies. This Review mainly focuses on the cellular immunotherapies derived from CB. Expansion techniques, ongoing clinical trials and future directions of CB application are also discussed.

2.5 Stem Cell Comparison: What Can We Learn Clinically from Unrelated Cord Blood Transplantation as an Alternative Stem Cell Source? [35]

Allogeneic hematopoietic cell transplantation (HCT) is an important therapeutic option for a variety of malignant and non-malignant disorders (NMD). The use of umbilical cord blood transplantation (UCBT) has made HCT available to many more patients. The increased level of human leukocyte antigen disparity that can be tolerated makes UCBT a very attractive alternative source of hematopoietic stem cells; however, the increased risk of early death observed after UCBT remains an obstacle. Novel strategies such as *ex vivo* stem cell expansion is now becoming a part of the standard clinical approach, and preliminary results are extremely encouraging with suggestion of reduction of early transplant-related mortality. Although there are no randomized studies that compare the risks and benefits of UCBT relative to those observed with related and unrelated donors both for malignant and NMD, several retrospective studies have compared outcomes between UCBT and other stem cell sources. This review, is aimed to describe and summarize the findings of the principal studies in this field. They hoped that what we can learn from these studies and how we can use this information will improve the outcomes of HCT for patients with malignant and NMD.

2.6 Topping it up: Methods to Improve Cord Blood Transplantation Outcomes by Increasing the Number of CD34+ Cells [36]

CB is increasingly recognized for its excellent stem cell potential, lenient matching criteria, instant availability and clinical behavior in transplant. With 1-2 kg fewer total (stem cell) numbers in the graft compared with other cell sources, the infused cell dose per kilogram is critical for engraftment and outcome, which leads to the development of stem cell support platforms. The co-transplant platforms of haplo cord and double unit cord blood (DUCB) transplantation are aimed toward increasing stem cell dose. Together with the optimization of reduced-intensity protocols, long-term sustained engraftment using CB is available to most patients, including elderly patients. Haplo cord has a low incidence of both acute and chronic GvHD but requires anti-thymocyte globulin ATG for effective neutrophil recovery. DUCB is performed without anti-thymocyte globulin with excellent immune reconstitution and disease-free survival, but engraftment is considerably slower, and GvHD incidence significant. Both haplo-cord and DUCB transplantation appears to be valid alternatives to matched unrelated donors in adults.

2.7 Improving the Outcome of Umbilical Cord Blood Transplantation Through *ex vivo* Expansion or Graft Manipulation [37]

UCBT for adult patients with hematologic malignancies now used for matched unrelated donor transplantation. Multiple strategies are studied to overcome the limitations of low lymphocyte and hematopoietic stem and progenitor cell dose, a source of significant morbidity and mortality. One strategy is *ex vivo* expansion of the UCB unit before transplantation, which increases the number of lymphocytes, committed progenitors and long-term repopulating hematopoietic stem cells. Increasing the numbers of lymphocytes and committed progenitor cells leads to delayed hematopoietic recovery after UCBT. Increasing the hematopoietic stem cell content will improve the availability of adequately sized and matched cord blood units for transplantation. The second strategy is exposure of the UCB graft to compounds for improving the homing and engraftment following transplantation. Such a strategy addresses the problem of slow

hematopoietic recovery and the increased risk of graft failure. Many of these strategies are tested in late-phase multi-center clinical trials.

2.8 Umbilical Cord Blood Banking for Transplantation in Morocco: Problems and Opportunities [38]

In 1989, the success of the first UCB transplantation in a child (with Fanconi anaemia), lead to the source of stem cells. UCB provides an unlimited source of diverse stem cells and is an alternative for bone marrow (BM) and peripheral blood (PB) HSCT. Thus, UCB and manipulated stem cells are collected and banked according to international accreditation standards. This work was aimed to identify the problems limiting the creation of a Moroccan cord blood bank and to highlight opportunities and issues of a new legislation promoting additional applications of cell therapy.

2.9 Concise Review: Cord Blood Banking, Transplantation and Induced Pluripotent Stem Cell: Success and Opportunities [39]

HCT became a standard practice to treat a number of malignant and nonmalignant hematologic diseases. Bone marrow, mobilized peripheral blood, and UCB served as primary sources of cells for HCT. Currently a large number of CB units are stored, although it represents only a fraction of potential collections. Since much of the collection is sequestered in private banks only for autologous use. In coming years, the demand for public banks increases by using for the treatment of patients with diseases like leukemia and lymphoma. A possible solution for the private banks is to encourage and share their valuable units and to apply recent methodologies to generate induced pluripotent stem cells from cord cells and to optimize techniques to generate hematopoietic lineages from them. This strategy has an advantage of the units already collected under appropriate regulatory guidelines, to access a pristine cell that can be converted to a pluripotent cell at a much higher efficiency in a shorter time period. The cord blood unit with new cells, for additional therapeutic applications, allows banks to develop an appropriate business model for both private and public cord blood banks.

The cord blood stem cell field is progressing rapidly, with extensive developments and accomplishments in recent years.

2.10 Umbilical Cord Blood-derived Cellular Products for Cancer Immunotherapy [40]

Although a majority of UCB centers on hematopoietic reconstitution, a recent surge in the knowledge of CB cell subpopulations as well as advances in *ex vivo* culture technology have expanded the potential of this rich resource. Because CB has the capacity to generate the entire hematopoietic system, we have a new source for natural killer, dendritic and T cells for therapeutic use against malignancies. This Review was focussed on the cellular immunotherapies derived from CB, expansion techniques, ongoing clinical trials and future directions of CB application are also discussed.

2.11 Therapeutic Potential of Umbilical Cord Blood Cells for Type 1 Diabetes Mellitus [41]

UCB is a rich source of regulatory T cells (Tregs) and multiple types of stem cells, with immunomodulating potential. It has the ability to restore peripheral tolerance toward pancreatic islet β cells by remodeling of the immune responses and suppressing the autoreactive T cells. Type 1 diabetes mellitus (T1DM) which is a chronic disorder results from autoimmune-mediated destruction of pancreatic islet β cells. The optimal therapeutic method for T1DM is to control the autoimmunity, restore immune homeostasis, preserve the residual β cells, reverse β -cell destruction, and protecting the regenerated insulin-producing cells against the re-attacking. Reinfusion of autologous UCB or immune cells from CB is a novel therapy for T1DM. The main advantages are no risk to the donors, minimal ethical concerns, low incidence of graft-versus-host disease (GVHD) and easy accessibility. This review, gives a report on the role of autologous UCB or immune cells from cord blood applications for the treatment of T1DM.

2.12 Fetal Endothelial and Mesenchymal Progenitors from the Human Term Placenta: Potency and Clinical Potential [42]

The phenomenon of fetal micro chimerism (FMC) which occurs during pregnancy, through the transfer of fetal stem/progenitor cells to maternal blood and tissues. Microchimeric mesenchymal stem cells and endothelial progenitors of fetal

origin have the capacity for tissue repair in the maternal host. The isolation of fetal stem cell populations from perinatal tissues, such as UCB and placenta, interest has been growing in understanding their greater plasticity compared with adult stem cells and exploring their potential in regenerative medicine. The use of similar fetal stem cells in therapy is significantly hampered by the availability of clinically relevant cell numbers and/or contamination with cells of maternal origin, using the chorionic and decidual placenta. In this review, the researchers highlighted the importance of FMC to the field of fetal stem cell biology and issues of maternal contamination from perinatal tissues and discussed specific isolation strategies to overcome these translational obstacles.

2.13 Allogeneic Haematopoietic Stem Cell Transplantation for Primary Myelofibrosis and Myelofibrosis Evolved from Other Myeloproliferative Neoplasms [43]

Allogeneic haematopoietic stem cell transplantation (allo-HSCT) is the only curative treatment for myelofibrosis. Major improvements in this field are the introduction of reduced intensity conditioning regimens, which made transplant a better tolerated treatment that can be offered to older patients and those with comorbidities. The treatment-related toxicities, GvHD, infectious complications and relapse remains the major problems of post transplant. The authors reviewed here the recent published data and outlined the criteria to select patients with myelofibrosis who can benefit the most from this curative treatment.

2.13.1 Recent findings

Data regarding mutations in myelofibrosis have been useful to better define the prognosis of patients and have provided a tool to monitor minimal residual disease after transplantation. New data regarding the use of age and comorbidities has allowed a better selection of patients who can benefit from transplantation. Janus-activated kinase signal (JAK) 1/2 inhibitors pretransplant can improve patient's performance status and potentially improve transplant outcomes.

2.13.2 Summary

Improvements in the field of allo-HSCT, the ability to improve patient's performance status prior to transplant with JAK1/2 inhibitors and a

more accurate disease risk stratification based on molecular mutations to select patients who can benefit from allo-HSCT should result in better transplant outcomes. Efforts should be made to transplant patients with myelofibrosis on prospective studies to answer some unresolved questions.

2.14 Adoptive Immunotherapy with the Use of Regulatory T Cells and Virus-specific T Cells Derived from Cord Blood [44]

Cord blood units are a valuable donor source for the development of cellular therapeutics. Virus-specific T cells and regulatory T cells are two cord blood-derived products that have shown promise in early-phase clinical trials to prevent and/or treat viral infections and GVHD, respectively. CBT is an alternative to traditional stem cell transplants (bone marrow or peripheral blood stem cell transplantation) and an attractive option for patients lacking suitable stem cell transplant donors. The researchers described the current strategies and uses of CB-derived regulatory T cells and virus-specific T cells developed to improve the outcomes for CB transplant recipients.

2.15 Transcription Factor -mediated Reprogramming toward Hematopoietic Stem Cells [45]

HSCs from renewable cell types are used in regenerative medicine. Paralleling efforts was made recently to use pluripotent stem cells substantial progress was made recently towards HSC generation via combinatorial transcription factor (TF)-mediated fate conversion, a paradigm established by Yamanaka's induction of pluripotency in somatic cells by mere four TFs. This review integrated the recently reported strategies to directly convert a variety of starting cell types toward HSCs in the context of hematopoietic transcriptional regulation and discussed how these findings will be further developed toward the ultimate generation of therapeutic human HSCs.

2.16 Characteristics of Hematopoietic Stem Cells of Umbilical Cord Blood [46]

UCB collected from the postpartum placenta is a rich source of HSCs and is an alternative to BMT. The differences (in phenotype, cytokine

production, quantity and quality of cells) between stem cells from UCB, bone marrow and peripheral blood were described. HSCs present in cord blood are more primitive than their counterparts in bone marrow or peripheral blood, and have several advantages including high proliferation. With using proper cytokine combination, HSCs can be effectively developed into different cell lines. This process is used in medicine, especially in hematology.

2.17 Concise Review: Umbilical Cord Blood Transplantation: Past, Present, and Future [47]

UCB is an effective alternate source of hematopoietic stem cell support. Transplantation with CB allows for faster availability of frozen sample and avoids invasive procedures for donors. Allogeneic HSCT is an important treatment option for fit patients with poor-risk hematological malignancies. The lack of available fully matched donors limits its use. In addition, this procedure has demonstrated reduced relapse rates and similar overall survival when compared with unrelated allogeneic HSCT. The limited dose of CD34+ stem cells available with single-unit cord transplantation has been addressed by the development of double-unit cord transplantation. In combination with improved conditioning regimens, double-unit cord transplantation has allowed for the treatment of larger children, as well as adult patients with hematological malignancies. The development of safer techniques to improve homing, engraftment, and immune reconstitution is current development after cord blood transplantation. Here the authors reviewed the past, present, and future of cord transplantation.

2.18 Umbilical Cord Blood Transplantation: A Maturing Technology [48]

CB is used increasingly as a source of allogeneic hematopoietic support for patients who need HCT and do not have access to an HLA-matched donor. To overcome the limitation of low cell doses in single CB units, dCBT has been adopted for many patients and is associated with outcomes comparable to those with other donor sources. There are new strategies under development to improve engraftment with *ex vivo* expansion or homing and to enhance immune reconstitution with the infusion of CB-derived NK cells and cytotoxic T lymphocytes with antiviral

and antileukemic specificities. Tregs are being evaluated to reduce the incidence of GVHD. Prospective, multicenter clinical trials are needed to determine the efficacy of these promising technologies that are likely to improve outcome for CBT patients.

2.19 Stem Cell Therapy to Protect and Repair the Developing Brain: A Review of Mechanisms of Action of Cord Blood and Amnion Epithelial Derived Cells [49]

Stem cell therapy is used to protect and repair the developing brain. In the research, clinical, and wider community the use of stem cells, is of great interest- to reduce the progression, or indeed repair brain injury. Perinatal brain injury results from acute or chronic insults sustained during fetal development, during the process of birth, or in the newborn period. The clinical trials are taking place worldwide targeting cerebral

palsy with stem cell therapies. It takes many years for emerge of strong evidence-based results from these trials. With such trials, it is both appropriate and timely to address the physiological basis for the efficacy of stem-like cells in preventing damage and regenerating, the newborn brain. The experimental animal models are best example. Stem cells that are readily and economically obtained from the placenta and umbilical cord discarded at birth. These cells have the potential for transplantation to the newborn where brain injury is diagnosed or even suspected. The novel characteristics of hAECs and undifferentiated UCB cells are explored. The UCB-derived endothelial progenitor cells (EPCs) and mesenchymal stem cells (MSCs), and how immunomodulation and anti-inflammatory properties are principal mechanisms of action that are common to these cells, and ameliorate the cerebral hypoxia and inflammation that are final pathways in the pathogenesis of perinatal brain injury.

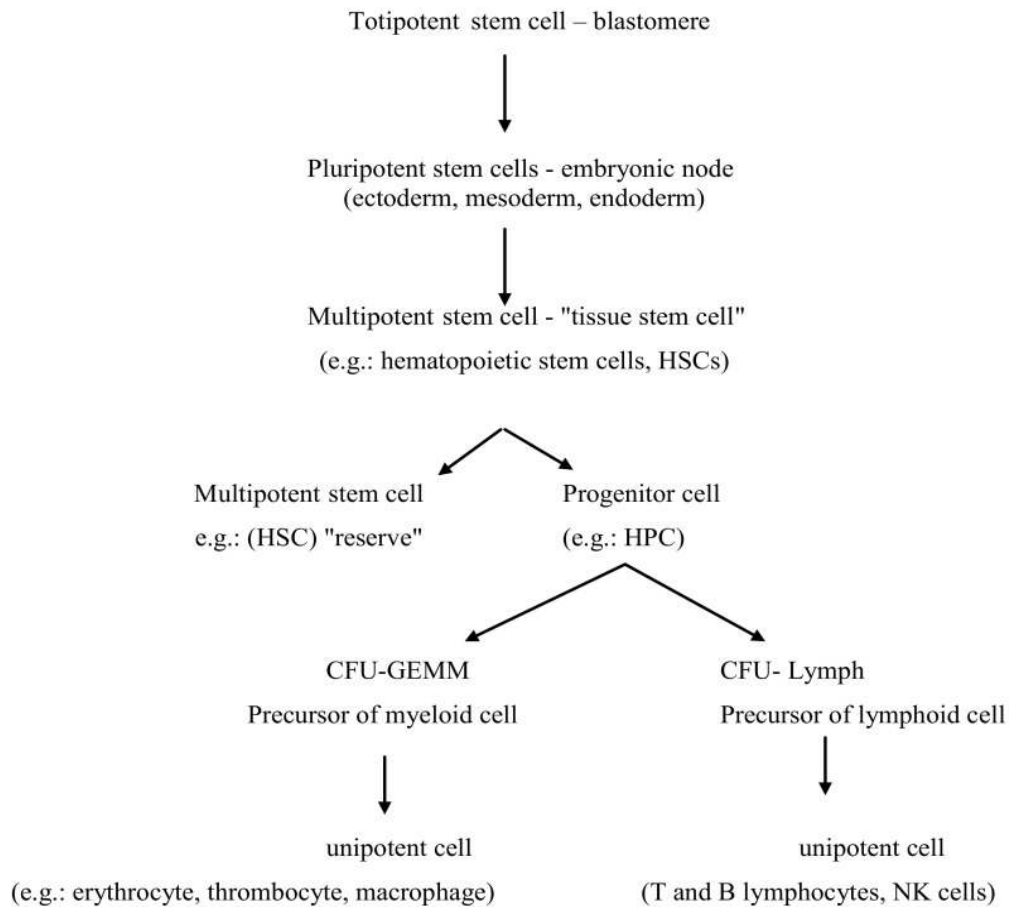


Fig. 1. Functions of stem cells

Table 1. Clinical trials being conducted around the world using umbilical cord blood in regenerative medicine therapies for the management of cerebral palsy and ischemic brain injury in the newborn

Study title	Main objective	Institution	Treatment	Current status	Trial identifier
A randomized study of autologous umbilical cord blood reinfusion in children with cerebral palsy	To determine the efficacy of a single intravenous infusion of autologous umbilical cord blood for the treatment of pediatric patients with spastic cerebral palsy.	Duke University, United States	Intravenous infusion. Autologous umbilical cord blood. Timing: not specified. (Children 12 months–6 years of age enrolled).	Currently recruiting	NCT01147653
Characterization of the cord blood stem cell in situation of neonatal asphyxia (NEOCORD)	To characterize cord blood stem cells of neonates with neonatal asphyxia and to compare them with those from healthy newborn.	Assistance publique Hopitaux de Marseille	<i>In vitro</i> characterization of the cord blood stem cell only.	Currently recruiting	NCT01284673
Allogenic umbilical cord blood and erythropoietin combination therapy for cerebral palsy	To determine efficacy of umbilical cord blood and erythropoietin combination therapy for children with cerebral palsy.	Sung Kwang Medical Foundation, Korea	Intravenous allogeneic umbilical cord blood infusion (Total nucleated cells $>3 \times 10^7/\text{kg}$) in combination with erythropoietin given twice a week for 4 weeks. Timing: up to 6 months after adverse event.	Completed	NCT01193660
Safety and effectiveness of cord blood stem cell infusion for the treatment of cerebral palsy in children	To test the safety and effectiveness of a cord blood infusion in children who have motor disability due to cerebral palsy. The subjects will be children whose parents have saved their infant's cord blood, who have non-progressive motor disability, and whose parents intend to have a cord blood infusion.	Georgia Health Sciences University, United States	Intravenous infusion of red-cell depleted, mononuclear cell enriched cord blood. Timing: not specified. (Children 1–12 years of age enrolled).	Currently recruiting	NCT01072370

Study title	Main objective	Institution	Treatment	Current status	Trial identifier
Autologous cord blood cells for brain injury in term newborns	To test feasibility and safety of collection, preparation and infusion of autologous umbilical cord blood during the first 3 days of age if the baby is born with signs of brain injury.	National University Hospital, Singapore	Intravenous infusion of autologous cord blood. Timing: 3 days post-birth.	Currently recruiting	NCT01649648
Cord blood for neonatal hypoxic-ischemic encephalopathy	To test feasibility of collection, preparation and infusion of a baby's own umbilical cord blood in the first 14 days after birth if the baby is born with signs of brain injury.	Duke University, United States	Intravenous infusions autologous volume reduced cord blood cells (up to 4 infusions). Timing: first 18 postnatal days.	Currently recruiting	NCT00593242



Fig. 2. Umbilical cord stem cells

2.20 Human Umbilical Cord Mesenchymal Stem Cells Transplantation Promotes Cutaneous Wound Healing of Severe Burned Rats [50]

MSC therapy contributes to facilitate wound healing for severe burns (highly lethal trauma) to promote the wound healing as early as possible. In this study, they investigated effect of human umbilical cord MSCs (hUC-MSCs) on wound healing in a rat model of severe burn and its potential mechanism. They concluded that hUC-MSCs transplantation can effectively improve wound healing in severe burned rat model.

3. DISCUSSION

UCB contains a rich and diverse mixture of stem and progenitor cells that have the potential to generate a variety of cell types with neuronal characteristics. It has also been shown that these stem cells have a positive impact on animal models of neural injuries and diseases. UCB stem cells are a potential candidate for clinical therapies for neural injuries and neural degenerative diseases for which current mode of therapy is inadequate [51]. In 1989, Broxmeyer, Gluckman, and colleagues demonstrated the UCB use in clinical settings for stem cell transplantation [52]. Since then, UCB has been used to treat nearly 80 diseases with over 25,000 transplants worldwide. UCB represents an abundant source of non-embryonic stem cells which are easily accessible with non-invasive collection of cells and no risk to the donor. Such cells are more immature than their bone marrow derived counterparts and displays an impressive proliferative potential [53] and have good viability after cells have been cryopreserved for later use.

UCB stem cells have high engraftment rates when used for replacement of haematopoietic stem cell populations, are relatively tolerant of HLA mismatches and thereby show low rates of GVHD, compared to bone marrow derived stem cells. They are rarely contaminated with latent viruses resulting in greater acceptance of UCB stem cells in comparison to bone marrow. UCB is used for the treatment of various hematopoietic disorders but, in the authors reported more recently induced regenerations in the central nervous system [54,55].

UCB is a rich source of hemopoietic stem/progenitor cells, regulatory T-lymphocytes (Tregs), monocytes, mesenchymal stem cells

(MSCs), endothelial progenitor cells (EPCs), and stromal precursor cells and, used for the treatment of neurological disorders. A recent pre-clinical study showed that UCB transplantation resulted in improved sensorimotor ability in a rat model of hypoxic ischemic brain injury. There are only a modest number of animal studies that are examined the effects of UCB transplantation following hypoxic-ischemic injury, predominantly in newborn rats. These experiments using the Rice-Vannuci animal model have reported positive brain results following UCB transplantation including decreased reactive gliosis, increased tissue repair, cognitive improvements amelioration of injury-related effects in the primary somatosensory cortex and enhancement of endogenous neural stem cell proliferation via Hedgehog signalin. These pre-clinical trials have not fully elucidated the mechanism underlying the beneficial effects of UCB transplantation. Nevertheless, autologous intravenous UCB transplantation is shown to be safe and feasible in young children with acquired neurological disorders. The evidence presented suggests that the UCB cells have a great deal of potential as a future treatment for stroke, both ischemic and hemorrhagic, in young and adult alike.

4. CONCLUSION

Collection of cord stem cells is painless and risk free to mother and baby. Cord blood stem cells have a greater ability to differentiate into other cell types. These cells have longer growth potential and have been shown to have a greater rate of engraftment. Cord blood stem cells are much more tolerant to HLA tissue mismatching than bone marrow therefore leading to lower rate of GVHD and are not exposed to the toxins and radiations. Cord blood stem cells are being used in the treatment of 40 medical conditions with over 72 potential disease targets. Research should be oriented towards prolonging their storage and enhancing their expansion.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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