Pool Banking: The Only Solution for Cord Blood Banking

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Abstract— There are at least 142 public and 25 private UCB banks world over, of which 4 public and 13 private banks located in India. In India, insufficient quantity of just about 5000 cord blood units is available in public banks. The chance of obtaining a matched donor for an Indian recipient from foreign registries is meagre due to ethnicity and exorbitant cost. In such cases, unrelated cord blood transplantation can be a lifesaving source of hematopoietic stem cells as cord blood is advantageous over bone marrow or peripheral blood in terms of rapid availability, human leukocyte antigen mismatch tolerance, and lower incidence of graft versus host diseases. The therapeutic utility of these cord blood stem cells led to development of storing the cord blood for future use in banks. Even though private cord blood banks store UCB for 21 years, the volume for transplantation purpose may not guarantee the effective weight per kilogram requirement of stem cells for diseased child's need. As HLA match is ethnically dependent, the required public bank size varies according to ethnicity of that area and HLA polymorphism. Cord blood pool banking advocates that all cord blood units stored as part of private banking be made available in a cord blood pool to find the best matched cord blood unit for stored persons suffering from haematological disorders. It make umbilical cord blood stem cell transplants a viable option, accessing unrelated cord blood (allogenic) as a solution, and having inventories of all the ethnic group will provide chance to get matched donor. The article emphasizes the new revolutionary concept for overcoming the hurdles of cord blood banking.

Key words: Cord Blood Banking, Cord Blood Transplantation, Inventory Size, Mycord-CelluGen, Pool Banking, Public Banking

I. INTRODUCTION

Hematopoietic stem cell transplants have come up as life-saving procedures to treat various hematologic malignancies, immune deficiencies, metabolic disorders and nonmalignant diseases like Thalassemia etc. Various sources of hematopoietic stem cells include bone marrow, peripheral blood, and umbilical cord blood. Peripheral blood and bone marrow stem cell transplants have an established track proof of success in treating hematologic disorders for a long time, but limited due to suitable donor availability and search process take several months. In spite of over 13 million bone marrow donor registries, many patients do not find HLA matched grafts. Hence the umbilical cord blood (UCB) transplant has established as a viable alternative transplant source for patients lacking appropriate donors.

Gratwoh et. al., reports 50417 HSCts done in 2006 across the globe with autologous cases being 28901 and 21,516 allogeneic cases. In Asian population 57 % transplantations were Allogeneic with matches found from family donor being 27.36 % and 29.64 % from Matched Unrelated Donor. It was noticed that contribution from India was very small compared to Japan and China contributing 48 % of MUD transplants. The reasons for India lacking behind these countries were majorly contributed by less numbers of donor's registries, and less number of donors registered in theses registries, number of health insurances and representation of Indian donor's registries amongst International registries also being very poor [1].

Bone Marrow worldwide annual report 2012 (BMDW) study shows Asia is lacking behind rest of the countries in finding the number of stem cells donors. Only 11 % of Asian populations are stem cell donors and only 0.3 % of them is registered as HSCs donor in International registries leaving the patients very difficult to source and find a matched unrelated donors in need [2].

It is highly evident that the stem cells transplantation is the only option for patients with Leukemia and Thalassemia. In order to address the issue of finding a matched unrelated donor with suitable HLA to patients without matched sibling donors, many countries across the globe has devised a database system to source HLA suitable Marrow Unrelated Donors (MUD) from the registries. As the international registries are required to create a pool for ease of accessing and sourcing, It is equally very important to have ethnic or racial groups pools amongst the international registries to find a matched unrelated donor. The greatest chance of finding a donor with the same ethnic background may lie from the same group [3]. However in Indian scenario, even though the Indian donors are also part of these International registries, finding a MUD is still being very difficult for Indian patients only because the Indian donor's registration in International registries is very less with only few thousands in 22 million being reported. Umbilical cord blood is the most recently identified stem cells source and is as effective as bone marrow when an human leukocyte antigen (HLA)-matched adult donor is not available [4-5]. UCB has many following advantages over the other sources of stem cells.

A. Less Restriction for Matching

With bone marrow or peripheral blood transplantation, a perfect match donor is needed, while with cord blood transplant perfect match is not required. Matching requirements for UCB are less stringent, as the naive immune system appears to cause less severe graft versus host diseases with cord blood.

B. Off-The-Shelf Available/ Ready To Use

UCB does not require extensive processing, unlike bone marrow transplantation. Importantly, UCB is HLA typed; banked and registered that allows rapid search and acquisition upon request.

C. Safe, Easy Collection Procedure

No risks are associated with mother and baby with a collection of cord blood. It is usually considered as a medical waste and discarded after delivery. The collection of cord blood during delivery takes less than 10 minutes.

D. Better Transplant Success

There are better chances of transplant success with cord blood in comparison to bone marrow as it has more hematopoietic progenitor cells. Reports are available in literature exhibits less Graft-versus-host disease (GvHD) occurrence with cord blood cells in comparison to bone marrow [6-7]. Takahashi Set. al., demonstrated that patients with hematologic malignancies had a lower risk of transplantation-related mortality (TRM), and a higher probability of disease-free survival (DFS) when received cord blood in comparison to bone marrow [8].

II. BANKING

The clinical therapeutic potential of UCB based cell therapy is increasing with positive outcomes of research with hematopoietic stem cell transplantation. Since the first transplant done in 1988 in a patient with Fanconi anemia [9], cord blood banking is getting spread all over the world with the potential success of cord blood transplantation in regenerative medicine [10-12]. Mainly two kinds of cord blood banks- private and public are available for storing the cord blood stem cells.

A. Public Cord Blood Banking

Storing the cord blood stem cells in a "Public bank" allows anyone in need to use stored stem cells if they find an appropriate match. Public cord blood bank receives cord blood unit with parental consent and cord unit can be used in future for any patient. The inventory is registered in the public database and searched for a suitable match when the request is received for stem cell transplant. Due to the involvement of huge establishment cost with public cord blood bank, it becomes mandatory to have financial support from funding agencies, government to operate them.

B. Private Cord Blood Banking

Storing the cord blood stem cells in a "Private bank" allows parents to store their own child's stem cells exclusively for them. The cord blood cells stored in the property of child under the parent's guidance and solely available in future for child and sibling only. Private Banks are not cost effective for the individuals to opt for banking. The numbers of private UCB banks are almost 4 times more than the number of public banks; however, unit released for therapy is 30 times higher with the public bank in comparison to private banks.

It is parent's personal choice to choose either public or private bank for storing baby's stem cells, however public banking should be promoted to have potential benefits of stem cells in future.

- The likelihood of requiring an autologous transplant in 21 years is very low.
- The volume of cord blood stored may not be sufficient as stem cells are needed according to body weight. In such cases, the public bank can provide double unit for transplantation.

III. TRANSPLANTATION - INDIAN CONTEXT

Nearly 70% of patients from Indian origin in need of bone marrow transplantation do not find a match within their family and finding a suitable marrow donor becomes more difficult for patients belonging to ethnic minorities. This led to the development of unrelated UCB as an accepted source of progenitors for hematopoietic stem cell transplantation. In India, umbilical cord blood transplantation is in infancy due to

a) Public banks in its infancy (Less number of banks)
b) Ethnicity of India
c) Inventory size (Limited number of UCB units)
d) Constraints of Private Banking
e) Limitation in cell dose and other factors

A. Public Banks in its Infancy

In India, currently, 14 approved private cord blood banks are operating in contrast to only 4 public banks. Private cord blood banking is based on the hope that it may be of therapeutic benefit to their child or family at some time point in future. No clear scientific data available for the efficacious use of these stem cells for personal use, though research is continuously going on to evaluate the therapeutic utility of stem cell transplantation in different diseases. It is a clear fact that child's own cord blood can rarely be used for transplant in blood-related disorders as they are present at the time of birth and not acquired. The cord cells of the child will have the same gene and if transplanted autologously, still will be no use, since the cells produced by these transplanted stem cells has same defect. The probabilities of requiring allogeneic stem cell transplants are higher than autologous stem cell transplant. The likelihood for a need of own cord blood as a transplant is estimated in between 0.04 and 0.0005% only; however, the likelihood of allogeneic stem cell transplant is estimated to be 0.04, 0.10 and 0.25 percent by age 20, 40 and 70 years respectively [13]. In most blood-related disorders, allogeneic cord blood transplant is recommended by transplant specialists. European countries like Italy and Fance also have banned cord blood storage in private cord blood banks due to their almost no autologous usage in therapeutic application.

B. Ethnicity of India

India is a rich diverse country having an amalgamation of various ethnic groups, culture, communities, and races that makes it different HLA typing from the other countries. Diverse ethnicity of India can be mainly categorized into four groups- Indo European, Dravidian, Austro Asiatic and Tibeto Burman. Indo European is mainly dispersed in northern, western and central India, Dravidian mainly confined to the southern region of India. Austroasiatic people are mainly present in central and eastern parts, while Tibeto Burman is concentrated in northeast India [14]. Each group has strong genetic affinity between its members, but different from another ethnic group. Different racial-ethnic groups possess diversity in HLA haplotype frequency. The high genetic diversity in India limits the probability of finding HLA match for Indian patients, as HLA match is ethnically dependent. The extreme diversity in HLA haplotype in the Indian subcontinent has arisen due to the racial mixture and geophysical and social-economic barriers [15]. The diversity of HLA allele frequency in Indian population poses challenges in finding a suitable transplant match; therefore India needs to develop its own pool of UCB units to find HLA matched UCBs for its patients.

C. Inventory Size

HLA typing is used as a tool to find a compatible match donor for HSC's transplantation including umbilical cord blood, bone marrow, and the polymorphism of HLA genes is the major reasons for difficulty in sourcing and finding a matched donor. This polymorphic nature of HLA genes is the major reasons for the reshuffling of expressions of gene coding and change in few amino acids sequences results in a difficulty to find a match. Currently A, B, C, DRB1 and DQB1 alleles are looked for 10/10 allele match thereby decreasing the chances of acute GVHD. Additionally, current family sizes in India majorly in tier-1 and tier-2 cities, resulting in increasing the difficulty of finding a 10/10 alleles match [16]. A.K. tewari et. al., study concludes number of patients in different age groups from 10-70 suffering with blood disorders found an allele match as only 0.00026% in a database of 22,55,0071 suggesting the difficulty in finding an allele matched donors even from big databases. To our knowledge this is the first study which signifying the probability of finding a MUD for an Indian patient from Multi-national Human leukocyte Antigen (HLA) registry. When we analyze why the allele match was only as 0.00026 % for Indian patients, the finding reveals more alarming issues with international registries being more suitable for Caucasian populations than Indian population. 90 % population of US or European Caucasian origin, Hispanics with 76 % 62 % of Black/ African American with least percentage of 33 % being Asians find matched unrelated donor from the database. These percentages reveal the polymorphism; halo type frequency distribution amongst various ethnic groups making Indian population finding an unrelated donor for patient with life threatening blood disorders is almost negligible. The study also revealed that greater the percentage of Indian populations in these databases, more the chances of patients finding a match along with allele unmatched donors finding a match from their own ethnic pool [6]. The key question in establishing a large pool of umbilical cord blood units is how big should be the inventory size to provide transplant match to maximum requests. No defined method is available to calculate accurate inventory size, however, inventory size required for pool banking varies depends on factors such as ethnic diversity, the degree of HLA matching, and HLA typing resolution. HLA are cell surface antigens that play an important role in activation of immune responses. HLA typing is used to find a compatible donor for blood stem cell transplant. The HLA frequency and number of nucleated cells in cord blood vary in the different ethnic group. Some HLA antigens are unique to the racial or ethnic background, so chances for finding a suitable donor are higher if searched in the same ethnic group. It is essential to include all ethnic groups in inventory to find a suitable match for a patient in need of a transplant. The ethnic groups that have more HLA polymorphism will require more cord units in the bank. In a study done by Beatty et. al., in the US, 10,000 donors provided a 4/6 HLA match to donor request using the conventional CB match criteria (low resolution for HLA-A,-B and high resolution for HLA-DRB1). For 5/6 match, 5000 units will provide a match to 50% of the request, and 15,000 and 50,000 units will provide a match to 65% and 80% of the request [17-18]. Querol et. al., estimated that a bank having 50,000 units will be able to provide 5/6 HLA match to 80% of requests and 4/6 match to 98% of patient requests in the United Kingdom [19].

In the Indian context, Maiers et. al., compiled HLA data from 10 collaborating centers and UCB registries data in India and predicted the likelihood of finding a suitable donor for Indian patients by applying the population-based genetic model. With a registry size of 50,000 units, 79.6 % patients would find a 5/6 match; however, only 25.8% will get a 6/6 match. Increasing the registry size up to 5,00,000 units, 92.9% patients will be able to find 5/6 match and 57% will get 6/6 match [20]. Chandra V et. al., also studied how many HLA match graft was they able to offer to 112 requests from their 1800 units. With this inventory size, 4/6 match could be offered to 99%, 5/6 and 6/6 match could be offered to 29% and 7% respectively. With probability analysis, they predicted to have inventory size of 55000 units to provide 6/6 match to each unit [21]. The high-resolution typing of HLA needs a large inventory size. In a Korean population study, 95% of patients could find 5/6 match in 50,000 units with low-resolution typing of HLA-A and B and high-resolution typing of DRB1; however with high-resolution typing of HLA-A, B, and DRB1, the inventory size need to be doubled i.e. 1,00,000 to provide 5/6 match to 94.6% requests [22]. The increase in the size of cord blood inventory with high-resolution HLA typing is due to higher heterogeneity of HLA alleles.

D. Constraints of Private Banking

While there are a few clear indications for private banking (eg, a sibling with cancer, marrow failure, a family history of hemoglobinopathy, congenital immunodeficiency syndrome, or inborn error of metabolism), the vast majority of families who store cord blood with private banks have to pay for access to stem cells in the future for use in treating degenerative diseases or problems related to injuries or aging. Currently, there is no evidence that this future use will be feasible or efficacious in such circumstances. Most private facilities provide an opportunity for donors to store their cord blood. This is in the hope that if in the future, a member of their family becomes sick with a stem cell treatable disease; there might be a perfectly matched unit available to them. Other private banks collect UCB in case that child develops a situation that could be treated with their personal cord blood. One general reason offered by several private banks for storing the autologous UCB is to have a source of stem cells for transplantation if the child were to develop leukemia [23]. Conversely, the majority of children with childhood leukemia can be cured with conventional chemotherapy alone and in those who do not count to this approach, allogeneic transplantation is the treatment of choice. Moreover, Stem cell autologous transplant cannot be used for genetic disorders such as Thalassemia and Sickle cell disease, since the genetic mutations which cause these disorders are present in the baby's cord blood also [24]. Thus, the possibility of privately banked cord blood being used by the child is exceptionally low.

IV. DISEASES TREATABLE BY UCBT

The first successful allogenic hematopoietic stem cell transplant was performed in 1968, establishing the field of

bone marrow transplantation (BMT) [25]. Twenty years later, in 1988, the first umbilical cord blood (UCB) transplantation (UCBT) was performed in France. In the past 28 years UCBT has gained popularity, as an efficacious treatment modality for various malignant and nonmalignant hematological disorders. Over 600,000 UCB units have been stored for transplantation worldwide and more than 30000 UCBTs performed [5].

India has a high birth rate of 26 million births per year with a genetically diverse population. This could possibly position our country as the largest pool of genetically diverse UCB units in the world. Yet, unfortunately so, UCBT are scarceowing to a lack of effective UCB depositories. Till date, approximately only 32 patients have received transplant using related or unrelated UCB [26]. It is an accepted fact that endorsed by the medical fraternity world over, that due to the nature of the disease; autologous use of the umbilical cord blood is not a preferred choice (Table 1). The factual information such as:

- In most blood related disorders Umbilical Cord Blood Transplant (UCBT) is recommended to be from another person and not from own
- The accepted probability of finding a partially matched UCB is higher in allogeneic use
- UCBT needs a 4/6 match as against a perfect 6/6 match in case of a Bone Marrow transplant (BMT)/Peripheral blood stem cell transplant (PBSCT)
- The nature of the diseases treatable is such that timely availability of stem cells for transplant is of utmost importance
- Unlike Bone Marrow/Peripheral blood transplant, dependence on donor for UCBT at the time of need is eliminated in allogeneic UCBT.

Diseases treatable by UCBT	Autologous UCBT	Allogenic UCBT
Leukemias[27-30]		
Acute Lymphoblastic Leukemia (ALL)	✗	✓
Acute Myelogenous Leukemia (AML)	✗	✓
Chronic Lymphocytic Leukemia (CLL)	✗	✓
Chronic Myelogenous Leukemia (CML)	✗	✓
Lymphomas[31-32]		
Non-Hodgkin's Lymphoma	✓	✓
Hodgkin's Disease	✓	✓
Myelodysplasias[33-34]		
Myelodysplastic Syndrome	✗	✓
Myelofibrosis	✗	✓
Bone marrow failure syndromes[35-36]		
Fanconi's Anemia	✗	✓
Severe Aplastic Anemia	✓	✓
Hemoglobinopathies[37-38]		
Sickle Cell Disease	✗	✓
Thalassemia	✗	✓
Immune-deficiencies [39-42]		
Severe combined Immune deficiency	✗	✓
Wiskott-Aldrich Syndrome	✗	✓
Neutrophil disorders		
Chediak-Higashi Syndrome	✗	✓
Chronic Granulomatous Disease (CGD)	✗	✓
Metabolic/storage diseases[43-47]		
Hurler disease	✗	✓
Krabbe disease	✗	✓
Auto Immune Disorders	✓	✓
Solid Tumours (Neuroblastoma, Brain Tumours)	✓	✓

Table: 1 Diseases Treatable by Autologous and Allogenic Cord Blood Transplantation

V. Unrelated UCBT Effectiveness & Outcomes

Cord blood transplantation has been particularly effective in the treatment of young infants and children with certain inborn errors of metabolism, for example, mucopolysaccharidoses such as Hurler syndrome and leukodystrophies such as Krabbe disease. In these patients, durably engrafted cord blood cells of donor origin provide the missing or defective enzyme. Most patients with untreated Hurler syndrome usually die between 5 to 10 years of age from progressive cardiac and pulmonary involvement. They also suffer from severe bony abnormalities, corneal clouding, massive hepatosplenomegaly, and severe neuroregression. Engrafted cord blood cells have the ability to cross the blood-brain barrier and have been shown to effectively prevent neurodevelopmental progression, a beneficial outcome that is not expected with the alternative approach of recombinant enzyme replacement therapy [48]. Unrelated cord blood transplantation, when performed before the age of 2 to 3 years, leads to correction of cardiac, pulmonary, liver, and neurologic damage and improves survival [45]. In fact, a recent risk factor analysis of 146 patients from the European Group for Blood and Marrow Transplantation (EBMT) suggests that cord blood could be the preferred stem cell source in this disease [49]. Similarly, in patients with leukodystrophies, cord blood transplantation in the presymptomatic phase of the disease can prevent demyelination in the central and, often, the peripheral nervous systems [47].

According to the report published by the New York blood center 2015, 35,000 cord blood transplants have been performed worldwide so far. On the report of United States, more than one-half of all stem cell transplants from unrelated donors in children now use cord blood. For Japan, this is actual for adults as well. The program has contributed over 5,300 cord blood units for transplantation, thus far (more than one-seventh of all units transplanted from unrelated donors). Most patients were affected by leukemia, lymphoma, and severe aplastic anemia [50]. However, the subject of umbilical cord blood transplantation has not been stable. Certainly, umbilical cord blood transplantation in children

has evolved much more rapidly in comparison to adults, mainly due to the limitations in cell dose. As expected, the adult cell dose available from a single umbilical cord blood unit is, on average, half that of what it would be for a child. This, in combination with age, the greater possibility of existing comorbidities, and disproportionate use of more HLA-mismatched units, may account for the poorer result noticed in adults transplanted with Umbilical cord blood in comparison to children [51]. Eventually, these studies demonstrate that the use of umbilical cord blood transplantation in children's with blood-related disorders is more prevalent than adults.

A. Umbilical Cord Blood Transplantation for Hematological Malignancies & Nonmalignant Diseases

Clinical studies reports that children with acute leukemia achieved long-term disease-free survival rates of 35–60%. Analyzed results in children undergoing umbilical cord blood transplantation specifically with acute myeloid leukemia (AML) and reported a 2-year leukemia-free survival of 42% and overall survival of 49%.In a subgroup of patients, with infant leukemia and leukemia in young children, survival was 47% at 2 years with a median follow-up of 28 months [52]. For this group (median age 1.6 years, range: 0.5–3.9 years), the 100-d transplant- related mortality (TRM) and 2-year relapse rates were 25% and 31% respectively. Comparatively outcomes in adult patients with acute leukemia are more confined and also the results have been strikingly variable in contrast to those in children. One group studied the leukemia-free survival of 77% and 56% in patients with AML and acute lymphoblastic leukemia (ALL) respectively. Another group studied a survival of 34% for patients with de novo AML and ALL, and 22% and 25% for those with secondary leukemia and myelodysplastic syndrome respectively [50, 52]. For example, previous study reported on partially HLA-mismatched unrelated donor umbilical cord blood used for patients receiving myeloablative chemotherapy and cyclosporinebased prophylaxis. They figure out the impact of patient characteristics, graft versus host disease, and clinical outcomes and followed the patients for a median time interval of 4.2 years. Unrelated cord blood units were selected from eight USA public banks for transplantation with at least three of six HLA loci in common in their survey. For the 159 children in their report, the top five metabolic diseases were: Hurler syndrome (n=45 patients); Krabbe disease (n=36); Sanfilippo syndrome (n=19); metachromatic leukodystrophy (n=15); and adrenoleukodystrophy (n=13). All grafted patients, except three, achieved donor chimerism of greater than 90% and all but four engrafted patients achieved and sustained normal enzyme levels relating to each specific metabolic disease when measurable in the blood. They one year probability of overall survival in Hurler syndrome was 77%, Krabbe disease (74%), Sanflippo syndrome (79%), metachromatic leukodystrophy (65%) and adrenoleukodystrophy (77%). As anticipated, the children who underwent transplantation as newborns had better functional outcomes than those with progressive symptoms of the disease [44].

B. UCBT Engraftment

Jaing T-H et. al., performed 45 unrelated cord blood transplants after myeloablative therapy in 38 pediatric patients with transfusion-dependent hemoglobinopathy (36 thalassemias and 2 sickle cell disease) at the authors institutions and 11 other centers using mostly non-red cell reduced plasma-depleted cord blood PDCB (non-red cell reduced plasma depleted cord blood) units that were not washed after thawing (6 double cords and 1 re-transplant). The median age of patients was 6 years old (range 0.3-20 yr) with a median weight of 19 kg (range 8-76 kg). No significant adverse events were observed after direct infusion despite Major ABO incompatibility in 9 cases. Neutrophil and platelet engraftment cumulative incidence with donor chimerism was achieved in 81 ± 7% and 79 ± 8% of the cases, and median times to neutrophil and platelet engraftment were 17 (range 11-33 days) and 37 (range 16-133 days) days after transplantation, respectively. Eight patients died with 3 deaths unrelated to cord blood transplantation (2 early deaths prior to day 20 and one accident). All remaining 30 patients are alive (5 with autologous recovery) with 25 thalassemias free with a mean and median follow up time of 392 and 257 days respectively (range 7-1,760 days) The median day to hospital discharge was day +58 (range 22-137 days) [34]. Prasad VK et. al., have reported on unrelated donor umbilical cord blood transplantation for inherited metabolic disorders in 159 pediatric patients from a single center who received UCB transplant. Engraftment occurred in 87.1 percent and one-year overall survival was 71.8 percent. Notably, those children with high-performance status had better overall survival of nearly 85 percent which emphasizes the importance of UCB transplant early in the course of the disease. As anticipated, the children who underwent transplantation as newborns had better functional outcomes than those with progressive symptoms of the disease [40, 44]. The overall outcome of the UCB transplantation and benefits of UCB include rapid and reliable recovery of immune function, low risk of GvHD, and low viral transmission rate.

VI. CORD BLOOD POOL BANKING

An impressive statistics shows that 4 million UCB units are stored across all private banking companies worldwide with inventory size being 6 times more than public banks. However, umbilical cord blood unit released by the public banks is 30 times more than private banks emphasizing the fact that majority of UCB units stored in private banks are not available for public use. Amy E et al. study reports that medical practitioners across worldwide support private banking only in conditions when the stored UCB unit are being a part of sibling or close relative donor program and for child's own usage for future indications. Interestingly, Public cord blood banking got a unanimous support from the medical practitioners across the globe since the units stored in the banks being useful for helping unrelated patients, limited chance of child benefitting from its own unit and limited chance of family members of the child utilizing the stored unit. The report also indicates that the usage of stored UCB units in private banks is extremely low with 0.04 % usage for 1in 2500 population to 0.0005 % usage for 1 in 20,0000 populations. With the introduction of pool banking,

umbilical cord blood units of the child's as well as from the donors sample stored in the pool are made available thereby making sure the demand for greater need for UCB units in allogeneic transplantation is addressed. The pool banking also allows the parents for a free access to stored UCB units specifically of Indian ethnicity. The very advantage of pool banking is that when a stored umbilical cord blood unit of a child is released to a recipient who is in need for an unit after HLA matching, not only the donor child but the family will continue to have an unlimited access to the pool [53].

Cord blood pool banking is a slightly different concept. The strategy of the pool banking concept offers each donor with an HLA matches stem cell sample. This ensures that each donor and their direct family members get right to use to their own stem cells for autologous treatments as well as HLA matched stem cell samples from a different donor for allogeneic treatments. The comparison of the pool banking concept with private and public UCB banking is tabulated in Table 2.

Benefits	UCB Pool Banking	UCB Private Banking	UCB Public Banking
Blood related diseases treatable (allogeneic)	More than 95% blood related diseases treatable by donor cord available in same ethnic pool	No access to other ethnically compatible cords. Cords stored for self use only	More than 95% blood related diseases treatable, but subjected to availability of UCB.
Blood related diseases treatable (autologous)	5% blood related diseases treatable by own cord in addition to the above 95%	Only 5% blood related diseases treatable by own cord	No access to use Autologous UCB.
HLA matching	Mandatory to conduct the HLA test at the time of storage to built a common data base	No HLA matching done	Mandatory to find an allogeneic matched cord is done before storage.
Accessibility	For every UCB that is stored a best matched cord provided from the pool	Only own cord blood available	Donor UCB that is stored a best matched cord provided from the inventory.
Availability	Instant to transplant use because of the ethnicity compatibility	Instant to transplant for 5% of own blood disorders	Depends on the UCB availability.
Blood Collection	Minimum 80 ml of blood is required for match successful transplantation criteria	No stringent limit adhered to for the volume of blood collected	Minimum 80 ml of blood is required for match successful transplantation criteria.
Dual Storage	Dual storage not recommended to obtain minimum volume of blood (80 ml) for successful transplant	Dual storage recommended	Depends on donor UCB availability.

Table 2:

VII. Current Status & Future Prospects of Cord Blood Pool Banking

The growing awareness of stem cell treatments and cord blood pool banking is influencing more and more expecting parents to choose for the future well-being of their new-born baby. In India, cord blood banking regulations are laid down by DCGI (Drug Controller General of India), under part "Biologicals" of the "Drugs and Cosmetics Act, 1940". In the ICMR (National Guidelines for Stem Cell Research, India, 2017), instructed their guidelines on stem cell banking and storage to keep all such service providers in check and protect their customers against fraudulent and unnecessary practices and encouraging public umbilical cord blood banking [54].

Since the first unrelated donor UCB transplant in 1993, UCB transplants have been performed worldwide. It has been found to produce outcome comparable to those from matched unrelated hematopoietic stem cell (HSC) in patients with hematologic malignancies [55]. It has been proven that cryopreserved unrelated UCB from 0 to 3 HLA-A, B, DRB1-mismatched donors contains sufficient HSC to engraft most pediatrics and some adult patients [56]. Unfortunately, utilize of UCB transplant is inadequate by the petite number of HSC in every of the cord blood units. This is predominantly a problem for adult patients. It is now achievable to pool UBC so that adequate cell numbers are obtainable for adult transplant [57]. UCB is rapidly accessible and has a very low rate of contamination with herpes group viruses. Umbilical cord blood transplant outcomes in a low incidence of both extensive chronic GVHD and severe acute GVHD, although the use of grafts with substantial donor-recipient HLA disparity [58-59]. However, the recent researches prove close matching may be needless. So, if cord blood from different donors can be pooled, larger numbers of stem cells can be offered for clinical use and pooling does not produce a negative effect [60].

Hematopoietic stem cell transplantation (HSCT), with a human HLA-matched sibling or peripheral blood stem cell donor or distinct bone marrow, has been used

successfully to treat patients with high-risk or relapsed hematologic malignancies. But, utilize of HSCs for the transplantation has been inadequate by the accessibility of fully HLA-matched donors, even with the increasing size of unrelated donor registries [61]. For individuals transplanted with unrelated donor bone marrow stem cells, increased HLA difference adversely affects survival due to increased risks of severe acute and chronic graft-versus-host disease (GVHD) and opportunistic infections [62]. Only young recipients are capable to accept a single HLA-A, B, DRB1 mismatch in this setting [63]. To potentially expand the donor pool, Umbilical cord blood has been used as an optional source of HSC from bone marrow. In addition, by combining multiple samples of human cord blood, sufficient numbers of stem cells could be pooled for use in children and adults to provide cells for transfusion [60].

Double unit cord blood transplantation (DUCBT) has emerged as a prosperous approach to develop engraftment and reduce transplant-related mortality in adults and large children undertaking cord transplantation [26]. Simultaneous transfusion of two UCB units obtained from different donors of HLA mismatched UCB units showed lower time of engraftment (12-28 days) than the median duration using single UCB unit without influencing GVHD [64]. In phase I clinical trial of 23 adults with high-risk hematologic malignancies, double unit UCB transplant with 1-2 HLA mismatch and total TNC dose of 3.6x 10^7/kg with CD34+ dose of 3.7x10^5/kg, led to neutrophil recovery at 24 days (median) for myeloablative conditioning and 13.5 days (median) for non-myeloablative conditioning. The overall survival in this high-risk patient was 33 percent at one year. The causes of death were graft failure, GVHD or progressive disease and infection/regimen-related toxicity. This observation clearly suggests that two different UCB units are not associated with crossed immunological rejection and suggests that immunological mechanisms may facilitate engraftment in donors receiving two unrelated UCB units [65].

VIII. The Advantages of Cord Blood Pool Banking

A. Availability

Stored Cord blood in a cord blood pool banking system has been prescreened, tested, frozen and instant to use; as compared to quite a few months it takes to get and substantiate a marrow or peripheral blood donor.

B. Human Leukocyte Antigen (HLA) Matching

A close match among the patient and the cord blood unit can progress a patient's result after transplantation. However, clinical research studies put forward that the match may not have to be as close as the match that is compulsory for bone marrow or peripheral blood transplants.

C. Graft-Versus-Host Disease (GVHD)

Studies have found that after a cord blood stem cell transplant, both the incidence and severity of GVHD is less as compared to Bone Marrow or Peripheral blood stem cell transplant.

D. Diversity

As a consequence of extending collection efforts to hospitals where births from diverse ethnic backgrounds are well represented, Pooled cord blood units have the potential to grant a source of stem cells that reflects racial diversity.

E. Double Unit Cord Blood Transplantation

Transplantation of two partially HLA-matched UCB units is safe, and may overcome the cell-dose barrier that confines the use of cord blood in many adults and young peoples.

F. Infectious Disease Transmission

Pooling of cord blood stem cell transplants hold take away the risk of transmission of blood-borne infectious diseases compared with stem cells from the peripheral blood or marrow of related or unrelated donors.

IX. Conclusion

The goal of cord blood bank should be ease of access of cord blood transplantation to patients belonging to all ethnic background and to achieve this goal, donor diversity should be present in cord blood bank. India has great potential for UCB banking due to a high birth rate and genetically diverse population. Considering the huge ethnic diversity of India, a large number of units at least 50,000 to 60,000 would be required to provide a match to a reasonable number of patients. Genetic diversity of India can make it probably the largest pool of genetically diverse UCB units in the world. It is important to establish cord bank having inventories of all ethnic populations as patients have better chance to get a suitable match from the same ethnic group. The awareness should be spread among citizen and doctors that transplant program can meet its demand only if a sufficient number of people make a wise decision to donate cord blood in public bank.

On the other hand, the pool banking concept offers each donor with an HLA matches stem cell sample. This ensures that each donor and their direct family members get right to use to their own stem cells for autologous treatments as well as HLA matched stem cell samples from a different donor for allogeneic treatments. Thus, Pool banking is not only offers increases the probability of procuring an HLA matched sample from different donors but also enhanced protection against terminal disorders.

X. Conflict of Interest

The authors would like to state that there is no conflict of interest whatsoever.

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