

Strategies to Make Cord Blood Banking More Meaningful

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Abstract— Umbilical cord blood (UCB), a rich source of hematopoietic stem cells and progenitor cells, has been used successfully to treat a variety of genetic and hematologic disorders. The demonstrated success of CBT (Cord Blood Transplantation) and the impressive scientific progress in the last two decades led to the establishment of several cord blood banks world over. Most banks offer storage services of cord blood for one's own future use (autologous) or solicit cord blood donations from birthing mothers to help develop a pool that can help people in need. The later falls under the public banking category, whereas those that are kept for self or family's use, in the distant future, is called family or private banking. The most appropriate indication and justification for private banking however is for those families with a history of hematological disorder. We are witnessing increasing arguments and controversies in scientific meetings and the questioning for the scientific basis for family banking, in view of its low probability of use. Service providers are caught between the need to be in business, place facts to the potential customers and the pressure to remain relevant. They are therefore forced to look at innovative ways to address this challenge. The objective at hand is therefore to find ways of helping families in need by a change in approach and demonstrate the good intent. The present review is a critical analysis and discussion on the current family cord blood banking practices, review the trend, and suggest strategies to address current gaps in the public banking programs. The interest of the public at large was given more weightage at all times. An account of challenges one faces in adopting a hybrid model is being discussed in details in this review.

Key words: Cord Blood Banking, Family Banking, Public Banking, CD34+ Cells, Mesenchymal Stem Cells

I. BACKGROUND

The success of the first related CBT (Cord Blood Transplantation) on a child with Fanconi's Anemia in 1988 [1] and the continued research thereafter on cord blood led to the utilization of UCB (Umbilical Cord Blood) as an alternate source of stem cells for transplantation. Hematopoietic stem cell transplantation (HSCT) is an accepted therapy for many hematological and non-malignant conditions affecting children and adults [2] [3]. It is quite evident from the fact that almost a million total number of stem cell transplants have been reported until 2013 by WBMT (Worldwide network for Blood and Marrow Transplantation) for a variety of hematological disorders according to press-release by WBMT [4]. However, umbilical cord blood transplants till date accounts for 35000 worldwide [5].

Where possible, stem cells for HSCT are provided by human leukocyte antigen (HLA)-matched, related donors [3]. Only 30% of patients have suitable matched donors; for other patients, donors are sourced from bone marrow registries or public umbilical cord blood (UCB) banks worldwide [6]. Thus, non-availability of matched relative

donors was the genesis of the public cord banks. These offered immense advantages to public, like ready availability of grafts, large HLA data base, ethnic diversity and more.

This further strengthened the establishment of cord blood banks and repositories for collection, separation, processing, testing of stem cells from the cord blood followed by cryopreservation for variable periods of time for hematopoietic reconstitution [7]. Public UCB banks are set up with the sole objective of supporting transplant programs locally and sometimes internationally, and are expected to be financially supported by the health department of the government or by the private sector. This is because this program has a huge public relevance and societal impact. As can be expected, its quality, functioning and success will depend on the importance and investment given to its furtherance.

In a private banking mode, there is little social or community benefit other than some reassurance to parents, knowing well of the very low likelihood of needing these UCB cells later in life. In fact, autologous cord blood is not recommended for treating leukemia and inherited genetic disorders [8] [9]. The attraction towards private banking is mainly on account of the benefits it might offer for tissue repair or replacement in the management of degenerative disorders, such as diabetes, Parkinson's and other life style diseases. There are several clinical trials ongoing and results are expected in several of them [10]. Time and trial results alone throw light on whether private banking will be beneficial at all.

According to the ASBMT (American Society for Blood and Marrow Transplantation) committee report, although the probability of use of autologous cord blood unit for one's own use is as low as 0.04%, it is believed that cord blood banking is still recommended for families having known history of disorders that could be potentially treated with cord blood transplantation [11].

In the Indian context, one probability analysis report showed that from an inventory size of 55500 units, at least one 6/6 HLA-matched cord blood unit was issued for an unrelated family looking for a match from a public bank [12]. This is the reason while counseling donors is relatively easy; altruistic and non-remunerated donation and the sense of duty plays a great role in the uninterrupted flow of units for this program. The plans and program strategy of a public bank is entirely based on the local demography, HLA types, ethnicities etc. As it is a regulated activity, there is a continuous quality improvement albeit, with the attendant expenditure, which the cord blood bank has to bear.

That said, currently, lack of funds has been a major challenge faced by many of them. This gave rise to the concept of hybrid banking.

II. NON-HEMATOPOIETIC COMPONENT OF CORD BLOOD

The widespread clinical entry of non-hematopoietic regeneration using cord blood stem cells is a subject of great interest. Cord blood has been shown to contain non-hematopoietic pluripotent stem cells as well, that have the potential to differentiate and grow into non-hematopoietic tissues such as cardiac, neurologic, pancreatic, endothelial and skin tissue in vitro [13]. It also contains unrestricted somatic stem cells (USSCs), and endothelial colony forming cells (ECFCs) that possess all qualities of endothelial progenitors with potential regeneration capabilities. Research has also demonstrated the possible role of these cells in hematopoietic stem cell expansion in vitro [13] [14] [15] [16]. Therefore, there seems to be a distinct non-hematopoietic hierarchy, which some have observed from fresh cord blood unit/s. Several research groups have been able to isolate Mesenchymal Stem Cells (MSCs) even from frozen cord blood but with a lesser frequency [14] [15]. These cells can be grown in plenty, can be banked, and unlike embryonic stem cells or induced pluripotent stem cells, pose no ethics issues [15]. The potential of the MSCs from various besides the perinatal tissue sources is being evaluated for treatment of degenerative disorders.

The above reason is attractive enough for parents who have the choice of storing their child's UCB stem cells in a private commercial UCB bank for personal or family's future use.

III. RESEARCH PROGRESS

A. Status of Research on Mesenchymal Stem Cells (MSCs) from Cord Blood for Non-Hematopoietic Applications

Cord blood stem cells have been tried in clinical trials as a vehicle for gene therapy in infants with severe combined immune deficiency with variable results. The search for scientific publications on Pubmed database using term 'mesenchymal stem cells' revealed 47000 publications [17][18]. Clinical trials registered till date as per the government website database searched using term 'mesenchymal stem cells' are only 727 in number [19]. Out of these 727 clinical trials, 250 clinical trials are reported to be completed at various phases while remaining trials are at various stages [19] [20].

Most of the above studies reportedly completed at phase II and few of them have completed phase III, however, results of these studies remains to be available on the website. The sponsors for these clinical trials include private and government sector, as increasing government organizations have started investing in stem cell research. The published literature describe various sources of stem cells, different combinations and permutations of cell types, methods of manipulation, quality assurance and control strategies, cryopreservation techniques, various disorders/disease and the ideal mode of administration, cell density etc. This is an encouraging trend, but we will need to keep a close watch for developments in this space.

B. MSCs from Other Sources

MSCs are isolated and from various other sources like mononuclear cell fraction of bone marrow and characterized as recommended by the ISCT (International Society for Cell Therapy) [21] [22] [23]. Other sources of MSCs include,

human umbilical cord tissue [24], adipose tissue [25], dental pulp [26], skeletal muscle [27], Wharton's Jelly [28], amniotic membrane and fluid [29], chorion [30] etc. Bone marrow and adipose tissue are good sources for deriving MSCs and the most researched and cited in literature [31]. However, they have their own limitations [32] [33].

C. MSCs from Perinatal Tissues

Perinatal tissues like placenta, amniotic sac and umbilical cord tissue for the derivation of MSCs are superior for various reasons. These MSCs are reported to be ontogenetically more primitive [33]. The functional and genetic variability is reflected by the difference in the quality and quantity of secreted growth factors and cytokines [34] [35]. It may be thus useful to investigate their suitability for clinical applications, especially for the non-hematopoietic indications, which is why we find a large body of literature on this subject.

D. Role of CD34+ Cells in Regenerative Medicine

CD34+ cells present in the cord blood have a potential role in regenerative medicine apart from its role in hematopoietic reconstitution. They have been reported to transdifferentiate into Neural Stem Cells (NSCs) mediated by OCT4 with satisfactory outcomes [36]. It has also been reported that peripheral blood derived CD34+ cells transplanted in animal models resulted into significant vasculogenesis in regenerating tissues and improved recovery in non-union fractures [37]. In an another study, an immunodeficient rat model was locally transplanted with circulating CD34+ cells along with atelocollagen at the injury site of the medial collateral ligament (MCL) which resulted in a conducive environment for healing of ligament through vasculogenesis & angiogenesis in which CD34+ cells played a significant role [38]. Traditionally, bone marrow mobilizing agents [39] were used for mobilizing CD34+ cells to other parts to induce vascularization and angiogenesis. It is reported that the total count and the functionality of CD34+ cells declines with the increasing age [40] [41]. In mobilization of granulocytes from bone marrow in Myocardial ischemia [42] and or peripheral ischemia [43] or through administration of granulocyte stimulating factors, a simultaneous increase in CD34+ cells migrate to the site and stimulate angiogenesis either by themselves getting recruited to form new blood vessels or through secretion of pro-angiogenic growth factors that initiate endothelial vascular development [44]. CD34+ cells have been shown to execute its function through the mechanism of neovascularization and neoangiogenesis in animal models of cerebral ischemia as [45], myocardial ischemia [46], and peripheral ischemia [47].

CD34+ cells isolated and tested by intramuscular injection into ischemic myocardium in patients with advanced coronary heart disease has been found to be efficacious as compared to placebo group, as shown by Losordo et al [48]. In patients with critical limb ischemia, purified CD34+ cells were used for the first time in a clinical trial in the year of 2009 [49]. Subsequently, various doses were injected intramuscularly, with significant clinical improvement [49]. Viswanathan et al reported healing of non-healing diabetic ulcers in patients with severe peripheral arterial disease using combination of mesenchymal stem cells and CD34+ cells when administered locally [50]. Given this dimension, CD34+ contained in the cord blood is another

molecule whose applications researchers are very keen to see. This gives an added importance of cord blood banking regardless of whether it is private or public.

IV. TYPES OF CORD BLOOD BANKING

Cord blood banking is a process of minimal manipulation and mononuclear cell enrichment followed by storage using validated methods in a bio-bank, for future use. Used in a way similar to stem cells from bone marrow, cord blood stem cells have the power to build a new blood and immune system.

There are three types of cord blood banking as indicated in Figure 1 below.

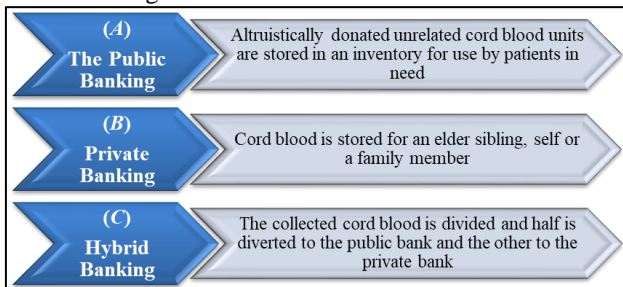


Fig. 1: Cord Blood Banking Models

A. Quality features of Public Cord Blood Banking Program

It is observed globally, that the size of the inventory of most public banks has for some reason either remained the same or has increased very marginally [51]. This perhaps is because it is very cost intensive and the quality requirements are very demanding. It is a well-known fact that the probability of getting HLA matched unit for transplantation is directly proportional to the size and the ethnic representation of the inventory. In 2011, C. Viswanathan et al published the need to plan the size of an inventory [52]. Also, a higher cell dose is needed for larger body weights, and this influences success of transplantation. Thus, larger patients may need two or more matched grafts to make it transplantation effective.

The Cord Blood foundation in their website reported that there are about 181 public cord blood banks spread across 45 countries and there are three times more, 432 private or family banks spread across 97 countries in the world and the count continues to increase [53][54]. Most private banks have been selling ‘hopes’ to all the families and coax them to consider this option. While there is a definite indication in families with high risk or when there is a sibling awaiting transplant, its justification applied to all family’s needs a thorough review.

Statistics on the use of autologous and allogeneic units gives us some food for thought. Gregory Katz-Benichou spoke about use of cord blood from various registries for hematopoietic transplants and he quoted specifically that ‘almost all patients can find at least one potential 4 by 6 HLA-matched cord blood unit through registries like NMDP, Netcord or other public banks and registries [55]. About 30,000 patients were treated from about 7, 31,000 units banked worldwide in various public cord blood banks [56]. The role of various cord blood registries and individual web sites has done a lot of good in disseminating the information regarding availability of cord blood grafts for families in need. Even if the usage from various registries is not a huge number, it has opened up a great new potential, and it is keeping us motivated to spread the reach to more in need. According to one report from the

World Marrow Donor Association there are approximately 7, 31,000 umbilical cord blood units banked in public cord & 4.03 million umbilical cord blood units banked in the private cord blood banks worldwide [56]. The inventory of family banking (4.03 million units) is almost six times greater than that of inventory by public banking (7, 31,000 units) with a far too low pick up rate [56].

The cord blood sample is considered ‘fit for banking’ if it qualifies certain stringent acceptance criteria. For example, for cord blood sample to be clinically useful only if it has a certain minimum preprocess cell numbers; that translates into a minimum of 50 to 65 ml of collected volume and a total nucleated cell count of at least 800 million if not more. Various cord blood banks define their ‘cut offs’ based on their demographics, maternal health and new born weight trends. In the author’s experience, only 50% of all public cord blood units collected meet the ‘inclusion criteria’ and the rejected units are diverted for research purposes.

The informed consent along with other necessary documents must be obtained well before donation of the cord blood unit so that it is not done under pressure. The family must be informed of the stringent inclusion criteria for volume and cell counts. By donating, the family waives all ownership rights and no longer legally owns the cord blood. The donor family is given a disclosure that the sample may not be available for retrieval and use by the family in the future, as donations to public storage facilities is meant to be used for transplantation by other patients in need. In the unlikely event of such a family needing a cord blood unit from this public bank, in the future, the bank can still check for its availability and if available, the bank can, at its discretion, support the family as per their policy. Donor confidentiality is maintained at all times [57] [58] [59]. The mothers who donate cord blood have a responsibility of informing the bank of any new genetic or other illnesses that may appear later in the child’s life. Thus, there are several checks and balances to assure quality of the graft.

B. Features of the Private Cord Blood Banking Program

Family banking finds its importance only if there is a family history of hemoglobinopathies, blood cancer, genetic and metabolic disorders. In such cases where the recipient is already identified from the family, it is referred to as directed cord blood banking [60]. While the quantum of research on the clinical application of non-hematopoietic components like MSCs from the cord tissue and the cord blood is increasing steadily [61] [62], there are no formal studies or research estimates of the likelihood of children needing their own stored cord blood stem cells in future.

Private cord blood banks are ‘for-profit entities’ that store cord blood for a certain fee for a specified period with a legal agreement with the family. Many of the operational procedures and quality policies for a comprehensive banking contrast sharply with those established for public banking. Although the decision to process and bank should be identical to those laid down for the public program, there are compulsions to relax these conditions when it is meant for a specific directed use. For example, lesser volumes and lesser counts will usually not be a disqualification. However, cord blood unit is usually not banked in cases where there is an evidence of presence of infectious disease agent in the maternal blood.

C. The Hybrid Cord Blood Banking

Hybrid banking is a slightly different concept. It is sometimes referred to as ‘community banking’. The strategy here is to divide the final enriched product into two portions; one for the family’s use and the other for community’s use. Let us see the four scenarios that emerge here.

- 1) The volume of the collected Cord Blood is excellent, therefore qualifies to get divided for cryopreservation under both private and public banking programs. The divided public and private portions will independently qualify as a CBU, fit for consideration to be transplanted. This is the most desirable scenario.
- 2) A certain consenting mom learns that her cord blood volumes and counts are far too low to be divided and shared; such a scenario will result, if at all, into two unsatisfactory units, not suitable as such for being considered for transplantation ever.
- 3) A certain family may seek higher and qualifying portion in the private banking (for them) and leave the rest to the public bank. Such a scenario, will always force the bank to divert such samples to yet another classification of low volumes, low counts public cord blood units.
- 4) In certain rare instances, the families can choose not to bank their units for further periods, and thus request the cord blood bank to move their entire cord blood unit to the public program. If the units meet the quality criteria, appropriate documentation for public banking is done

before the transfer. Non-qualifying units will go for research, or validation experiments.

Let us dive deeper into these scenarios and check its long term and short term implications on the working of the cord blood industry.

- Scenario ‘A’ is the best and most desirable; it meets all regulatory needs and both programs get qualifying units.
- Scenario ‘B’ is most undesirable as the volumes collected are so low that you can hardly divide the sample. In our own experience, almost 30% of units fall under this category. Our immediate imperative is to focus on getting higher volumes that will have some significance for either program.
- Scenario ‘C’ is where the collection volumes are better than scenario ‘B’, when the donor may insist that a major portion is stored for self. The good part is that his private unit will meet the norms and the remaining smaller amount can be stored as a supplemental unit, or for future expansion depending on the need.
- Scenario ‘D’ will need some policy changes as the complete shift from private to public happens after a few years. There are several legal and financial implications to be expected and handled.

In summary, using the hybrid model, some financial support is managed from family donors. This subtly instills confidence amongst the public and the fraternity that goes a long way in the development of this specialty.

Sr. No.	Banking Aspect	Banking Model		
		Public	Private	Proposed Hybrid banking
1	Family /Medical History	Clearance is mandatory	History needed; specific medical issues are recorded	History mandatory; Migrating units should qualify as per Public Cord Blood program
2	Informed Consent	Mandatory	Mandatory	Mandatory
3	CBU volume & starting counts	≥ 60 ml; upwards of 800 million absolute count	Defined by individual banks	Minimum 60 ml; upwards of 800 million absolute count desirable
4	Time-lapse between collection and processing	≤ 48 hours	No strict regulation	≤ 48 hours
5	Infectious Disease Testing	Must be free from TTD disease	Must be free from TTD disease	Must be free from TTD disease
6	HLA Typing	Mandatory for data base	On request, not mandatory	Mandatory only when it migrates
7	Birthing centers	Collection from approved centers	Can be performed at any birthing center with basic facilities	Flexible
8	Collection process, counseling & documentation	By a trained nurse	By a trained nurse/personnel	By a trained nurse

Table 1: Showing current practices of the three banking models

V. SHORT TERM & LONG TERM CHALLENGES OF HYBRID BANKING

In the short term, the challenge is to elevate the quality of the grafts such that the programs are sustainable and trustworthy. A concerted effort to educate and improve every step of the program will be the first and foremost requirement. It amounts to setting standards for family banking that is a ‘notch’ higher than the public banking, so that this division of units does not affect the public program adversely. This calls

for time, energy and motivation among all participants including all franchisees and collection hubs so that we can truthfully convince a family an opportunity to help the community at large while safeguarding their own interest. This alone can help classify maximum units under Category ‘A’.

In the intermediate term, we foresee a major change in documentation, numbering system, creation of new storage locations, additional storage containers, new labeling, software configuration changes, legally acceptable revised

informed consent and agreements with the families. The financial aspects, the ethics' aspects and reward programs for the donor families are some areas that need to be discussed with experts in the respective domain.

As and when these fall on track, the long term challenges would unfold. We expect serious changes from the regulatory angle, and we need to prepare for a host of questions from the public, especially when regenerative medicine based trials start showing favorable results.

As can be expected, cells stored will need a lot of additional processing before it can be made 'fit-for-use'. It is difficult to say at this juncture how the actual end to end processing can be made financially feasible. We will park these open ended questions for the present, and watch for developments in this space.

VI. REGULATIONS & ACCREDITATIONS

In India, cord blood banking regulations are laid down by DCGI (Drug Controller General of India), under Part 'Biologicals' of the 'Drugs & Cosmetics Act, 1940'. In the US, the Regulatory structure for cord blood banking activities has been finalized by the FDA under the category of "Human Cells, Tissues, Cellular and Tissue Based-Products." Both public and private cord blood banks are regulated under the CFR Title 21 Section 1271. Other countries may have their own regulations with regards to cord blood banking. Quality assurance and regulatory surveillance by agencies like AABB (American Association of Blood Banks) [63], FACT (Foundation for the Accreditation of Cellular Therapy), and the US-FDA (United States – Food & Drugs Administration) help maintain continuous quality maintenance, given the unique challenges in this industry.

VII. THE INDIAN SCENARIO

In the Indian context, The private sector took a lead in setting up the first public cord blood bank in 2001, and has listed over 3,500 fully tested CBUs for public use in 2008 [64][65]. Their quality plan has process controls, monitoring of production environment, standards for supplier's qualification, training of staff, training on SOPs and policies, document control, label control, data integrity, safety, software integrity, stability studies and proficiency testing that directly contribute to the success of the program.

It is learnt that three more public banks have been established in India, in the recent past. However, increasing budgetary requirements coupled with poor popularity of cord blood transplants among hematologists is forcing people to find ways to cross subsidize public banking and keep the program afloat.

Thus, the scope and need for hybrid banking is becoming more apparent as clinical progress in the field of regenerative medicine is emerging. Perhaps, on the top of our wish list is the need to have a comprehensive hybrid cord blood bank ably supported by a well-funded research on prospective clinical trials using cord blood for various applications.

VIII. TAKE HOME MESSAGE

- 1) Cord blood transplantation is curative in patients with a variety of hematologic disorders.

- 2) Research on cord blood stem cells, for treatment of degenerative and life style diseases are on the increase. Physicians should monitor the results of several ongoing trials [66] [67] [68].
- 3) Physicians should familiarize themselves with various types of cord blood banking, and the proposed hybrid model. That will help them counsel their patients as appropriate. Private banking should be considered when there exists a family predisposition to a condition in which umbilical cord stem cells are therapeutically indicated. However, because of its cost, limited likelihood of use, and inaccessibility to others, low-risk families should not be pressurized to opt for private banking.
- 4) The significance of hybrid banking must be understood and shared by way of continuous training programs.
- 5) Governments and health departments must invest in the furtherance of public cord blood banking and related research, so that the societal obligations can be met; hybrid cord blood banking models will help address some gaps.
- 6) Several challenges are expected, but they are not insurmountable; sound policies and a conducive regulatory environment will definitely contribute immensely to the success of this program.

IX. CONFLICT OF INTEREST

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

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