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Umbilical Cord and Placentary Blood Storage for the Treatment of Blood Diseases in Brazil: the Third Bone Marrow Donor Facing New Technologies

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ABSTRACT

Contemporary medicine has had several advances when it comes to treating diseases such as leukemia. One of these innovations was the use of human stem cells, through bone marrow transplantation, because these cells have the capacity to originate new cells when stimulated. Currently, the use of hematopoietic stem cells is performed in the treatment of more than 80 blood diseases and is the most efficient method, of which we have access, in the highlighted scenario. However, there are still several obstacles to the use of bone marrow cells, given the difficulty of compatibility between the donor and the recipient of the transplant. Due to such impediment, it was then observed that umbilical cord and placenta blood have transplantable cells, albeit in limited numbers, but are more likely to be compatible with the patient that will be receiving such cells. The present study aimed to analyze the Brazilian situation regarding the collection, processing, storage and use of this type of blood, as well as to investigate, from public access data about health, the difficulties for its greater use in the treatment of blood diseases.

Keywords: Cellularity, Umbilical Cord, Stem Cells, Placenta, Blood, Transplant

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INTRODUCTION

Around 80 related to blood diseases can be treated with bone marrow transplant, which has hematopoietic stem cells capable of differentiate themselves in blood tissue cells. Brazil has currently the third register of bone marrow donors in the world, staying only behind of United States of America and Germany, with 3.8 millions of the 26 million donors registered worldwide. However, there is a huge difficulty in find compatible cells for the patient that needs the transplant and, even when the compatibility is found, many times it is not possible to contact the registered donor for the lack of data update in the Bone Marrow Donors National Register platform. In this way, it is necessary to use alternative sources of this cell type for this matter (ABRALE, 2017)

For a long time, the bone marrow was the only used source in the medical clinic for hematopoietic stem cells collect, although other sources, as umbilical cord and placenta blood, has transplantable cells, even in limited numbers (NEVES, 2012)

The use of Umbilical Cord and Placentary Blood (SCUP) for transplant was proposed in 1982 in a private meeting between Hal Broxmeyer, Edward Boyse and Judith Bard. Boyse believed that discarting SCUP after labour was waste and that this blood should be used as source of mature cells for transplant. Broxmeyer, otherwise, found this blood a source of transplantable stem and progenitor cells. This meeting leaded to the foundation of *Biocyte Corporation*, which made studies about SCUP and improved its capacity of replacing the bone marrow (BALLEN et al., 2013). SCUP actuation is similar to embrionary stem cells, having as an advantage not to involve ethical and moral questions (SILVA, 2010).

In Brazil. Umbilical cord blood started being collected from 1990 intending to utilizate them in allogeneic akin transplants. In 1996 was accomplished the first transplant using SCUP, aiming to treat a case of juvenile chronic myeloid leukemia (SILVA, 2010).

Furthermore, the SCUP use shows to be a viable alternative for the treatment of blood related diseases, because, beyond the benefits occasioned by the use of these cells, another positive factor relating to its use is the absence of risk for mother and fetus, the low risk of graft versus host disease and transmission of infectocontrants pathologies (NUNES, 2014).

The SCUP storage can be made for autologous use (for the own donor) in Autologous Use Umbilical Cord and Plancentary Blood Banks (BSCUPA), which are private and regularized by tje Sanitary Vigilance National Agency (ANVISA), or for allogeneic not-akin use in public banks belonging to Rede BrasilCord (ANVISA, 2010).

From this, it became necessary to make a data collection about the process of collecting, analisys, storage and use of these cells for public or private institutions in Brazil.

METHODOLOGY

It was performed, for this text elaboration, a periodic revision by means of the following data bases:*Scientific Electronic Library Online – SciELO* (http://www.scielo.org), *Departamento de Informática do SUS - DataSUS* (http://datasus.saude.gov.br/), *Agência Nacional de Vigilância Sanitária - ANVISA* (http://portal.anvisa.gov.br/). Articles that did not have the full text available and the ones which did not frame in the propose of this research were discarded. In the data collection were utilized keywords such as “Cellularity”, “Umbilical Cord”, “Stem Cells”, “Placenta”, “Blood” and “Transplant”, according to the descriptions of the Descriptors in Health Sciences (DeCS).

RESULTS AND DISCUSSION

The hematopoietic stem cells are multipotent, that means they are capable of generating all the cellular types referring to the specific tissue where they are placed, in this case, the blood (ANVISA;2010). In this way, they generate white and blood cells and platelets. Its use is very eficiente in the replacement of the bone marrow damaged by the same tissue in healthy conditions. Allowing, in this form, the blood production with integral cells in patients with blood diseases, such as leucemia (ABRALE, 2017).

The clinical benefits and the simple logistics of the umbilical blood use include the possibility of finding donors and perform the transplant with 21 to 37 days of antecedence when compared to bone marrow since the cellularity and the leukocyte antigen were previously set. The unity of blood, collected without any risk for the mother or the newborn, can be stored for undetermined time without influences in the transplant results. Added to this, there is the viability of transplant between incompatible leukocyte antigens and lesser risk of graft versus host disease, since T lymphocytes are few and immature (RODRIGUES et al., 2010).

Regarding the operation of the transplantation of SCUP, it is observed that, when it is performed, the transplanted cells will come into contact with growth factors, which results in the formation of large colonies of hematopoietic progenitor cells. This is likely to be effective in assisting individuals who have undergone myeloablation, thus being a further advantage of the use of umbilical cord blood in medicine (BOUZAS, 2000).

ABRALE refers to Ottmar Saffier, physician and president of the Pró-Vita Association, presenting his data that only 25 % of patients find donors in the family, due to their compatibility. Another 75 % will find donors through the National Bone Marrow Donor Registry. Although Brazil has the third largest register of bone marrow donors in the world, with approximately 4 million registered donors, it is still very difficult to find donors compatible with patients due to several factors, the main being the genetic variety of Brazilian society (ABRALE, 2017).

Seeing this situation, the science investigates sources and methods of collection and transplantation of hematopoietic cells alternative to the bone marrow. One is the collection of blood present in the placenta and umbilical cord. Cells of this origin, although limited in number, present an alternative and promising method for the treatment of patients with blood-related diseases (NEVES, 2012).

In Brazil, the storage of these cells can occur in two ways. When the donation of blood is for non-related allogeneic use, the blood will be stored by one of the collecting establishments belonging to Rede BrasilCord, available for use by anyone, including the donor, if available. In this case, the costs of all processes are covered by the Sistema Único de Saúde (SUS), Brazil’s public health system. In the collections for autologous use, which is only for the donor’s own use, blood is stored in Bancos de Sangue de Cordão Umbilical e Placentário para Uso Autólogo (BSCUPA), and these institutions are private and regularized by the Agência Nacional de Vigilância Sanitária (ANVISA, 2010).

The collection procedure begins with anonymous donation of blood by the child's family, undergoing processing and, after analysis, can be stored or discarded. In units with more than 500 million cells post-processing and free of fungal or bacterial infections, storage occurs. Otherwise, the unit is discarded (ANVISA, 2010).

In order for the storage to be carried out, the unit to be stored must meet the technical-sanitary criteria defined by the Resolução da Diretoria Colegiada RDC / Anvisa n º 153 / 2004. In cases of donations for unrelated allogeneic use the criteria are: family history without narrative of hereditary diseases of the hematopoietic system, degenerative neurological diseases, metabolic diseases or other diseases of genetic origin. In addition, the absence of positive or reactive microbiological or serological tests is required. For autologous use, units with positive serological tests are accepted, but without reagent microbiological tests. In both cases the minimum number of cells (5 x 10^8) is required for storage (MENDES-TAKAO et al., 2010).

The following table, extracted from the ANVISA Report for 2017, sets forth the production data of the BrasilCord network BSCUP in 2016.

Bank	State/ Region		Hematopoietic Progenitor Cells from umbilical cord and placental blood quantitative							
			Collected	Processed	Stored	Desqualify	Destin			
							Transplant	Research	Discard	Others
Fundação Centro de Hemoterapia e Hematologia do Pará (HEMOPA)	PA	NO	130	109	91	34	0	0	52	0
Hemocentro do Ceará (HEMOCE)	CE	NE	156	156	81	75	0	0	0	0
Fundação de Hematologia e Hemoterapia de Pernambuco (HEMOPE)	PE		85	85	53	32	0	0	32	0
Hemocentro de Brasília	DF	CO	321	241	223	107	0	0	9	12
Centro de Tecidos Biológicos (Cetebio) Fundação Hemominas*	MG	SE	256	68	38	80	0	0	256	256
Instituto Nacional de Câncer (INCA)	RJ		315	307	97	210	0	0	194	0
Hemocentro de Ribeirão Preto	SP		201	110	87	108	0	0	0	3
Hospital Israelita Albert Einstein	SP		239	131	129	139	3	0	117	22
Hospital Sírio Libanês	SP		301	72	63	238	0	0	239	0
UNICAMP	SP		854	418	418	436	0	103	304	0
Hospital de Clínicas da UFPR	PR	S	0	0	0	0	0	0	0	0
Hemocentro de Santa Catarina (HEMOSC)	SC		79	75	73	9	0	0	6	10
Hospital de Clínicas de Porto Alegre	RS		138	138	84	55	0	0	0	0
National Amount			3.075	1.910	1.437	1.523	3	103	1.209	303

As can be seen from the data highlighted in the table, of the 1437 units stored in the year 2016, only 3 were destined for transplantation. This low number of transplants recommended from SCUP for allogenic use in patients may be related to the experimental conditions of this type of treatment. In addition, although it has several advantages over the use of bone marrow, transplantation of this type of cell has its limitations, as shown in the following table, taken from the publication of Mendes-Takao et al. (2010).

Advantages	Disadvantages
- Lower restriction of HLA compatibility and, consequently, lower rejection; - Possibility of using the cells of one or more donors with different HLA antigens; - CPH in a more primitive state of development, reflecting in greater proliferative potential; - Reduced incidence/severity of graft versus host disease; - Lower incidence of viral transmission; - Prompt availability and no refusal of donation; - Most easily collected material.	- Low volume of material available for collection and hence limited number of cells, generally insufficient to treat an adult or large child; - Increased risk of transmission of genetic diseases; - Delayed kinetics with regard to graft attachment; - Impossibility of additional collection of donor cells in case of graft failure or disease relapse; - High cost of storage.

Fonte: MENDES-TAKAO et al.; 2010

As for the low volume of material available, there is a minimum number of cells required for the unit to be stored, as previously mentioned. In addition, for transplantation to be effective, it is important that the number of transplanted cells is greater than 2 x 10^7 / kg in adults and 3.7 x 10^7 / kg in children receiving transplantation (IZU et al., 2013). According to studies conducted at the Federal University of Pernambuco, this number of cells is directly related to fetal weight, with no apparent relation to the sex of the child, number of gestations or deliveries (IZU et al., 2013).

However, even though SCUP has a smaller volume of available material than the bone marrow, umbilical cord blood cells proliferate and expand more easily than the alternative. Thus, in order to perform an effective transplant, about 10 times less SCUP cells are needed than the bone marrow to reconstitute a hematopoietic system that underwent myeloablation (CRUZ, 2009).

Regarding the delayed kinetics of the graft, umbilical cord transplantation presents a risk of graft failure, slow immune reconstitution and consequent increase in hospitalization time, in addition to a greater need for transfusion support. The amount of nucleated and CD4 positive cells - an antigen present on the surface of the hematopoietic progenitor cells - in each unit is fixed, which makes it impossible to adapt it to the weight of the receptor or to use it later for immunotherapy by lymphocyte infusion. Therefore, the original graft conditions must be preserved so that there is no impairment of cell number and in the function of the SCUP, since the processing and sample collection phases imply the loss of 10 % to 20 % of blood volume collected and, in thawing and handling, 20 % of the cells are lost. (RODRIGUES et al., 2010).

Among the advantages related to cardiovascular treatment, CD133 + cells present in the SCUP presented angiogenesis in a functional assay, through the tubular formation in Matrigel^{TM}. The formation of three-dimensional structures in vitro, due to cell migration, suggests that SCUP may contribute to the recovery of infarcted areas by an increase in blood perfusion in the myocardium (SENEGAGLIA et al., 2018).

Regarding a comparative analysis between the public banks of the different Brazilian states, São Paulo has a larger number of public cord blood banks and, consequently, it is the state that makes the most collections in Brazil (51.77 %). However, in some banks with an elevated collection rate in São Paulo, such as UNICAMP and Hospital Sírio Libanês, high levels of disqualification are also observed, being 51 % and 79.06 %, respectively. It should be taken into account that it may serve as an indicator of the bank's quality policy. In this way, it is notorious that even in the Southeast this level of disqualification is high in Rio de Janeiro, 66.7% in INCA, but falls in Minas Gerais, 31.25 %. When we compare the Southeast with the other Regions of Brazil we see that the North, more specifically the state of Pará, has less disqualification, 26.15 %, which allows the investigation of the low degree of selectivity in HEMOPA. In the South, according to data from Santa Catarina and Rio Grande do Sul, this disqualification increases to 29.49 % and in the Midwest, taking Brasília’s database, to 33.33 %. When this comparison refers to the Northeast, it can be seen that even though Ceará takes parte in only 5.1 % of the total collection, the state collected almost twice as much umbilical cord and placental blood when compared to Pernambuco, besides having a disqualification index of 48, 04 % while HEMOPE presented disqualification of 37.65 %.

In the case of private banks, there were 19 banks in Brazil in 2016 according to the ANVISA report of 2017. It can be seen that these banks have a discard rate lower than that of public banks, as can be seen in the table below.

This drop in the number of discards may have occured because some public banks, by storing blood for allogeneic use and following stricter storage criteria, disqualify units containing less than 750 million cells, while sanitary legislation states that the minimum storage should be 500 million cells. In another aspect, public banks must disqualify units with positive serology, while private banks are allowed to store units for autologous use with this condition (ANVISA, 2016).

When comparing the banks of the BrasilCord and the BSCUPA network taking into account the discard percentage of the collected units, we have that in the Brazilian public banks analyzed by ANVISA in the table above, on average 39.31 % of the collections were discarded, while that, in Brazilian private banks, the average number of units discarded in function of those collected was 8.26 %, which shows a significant difference between the two storage modes in Brazil. There is a great discrepancy between the number of units kept in public banks (1437) and private banks (8048) and, as can be seen in the table, of the 8048 units stored in private facilities, one (01) was used for transplantation. This is due to the fact that autotransplantation of SCUP has not yet proven effective and, in cases of genetic disease, the transplanted cells have the same donor dysfunction. In addition, most of the units stored in BSCUPA are from children with low risk of blood diseases, which means it is very likely that the units stored there will never be mobilized for use.

Bank	State/ Region		Hematopoietic Progenitor Cells from umbilical cord and placental blood quantitative							
			Collected	Processed	Stored	Desqualify	Destination			
							Transplant	Research	Discard	Others
Criocord	CE	NE	97	96	96	1	0	0	1	0
Hemocrio	RN		0	0	0	0	0	0	0	0
Cordcell Brasília	DF	CO	333	333	331	2	0	0	2	0
Hemovida	GO		62	55	55	8	0	7	6	0
Honcord	GO		102	102	102	24	0	0	24	0
Criobanco	ES	SE	288	287	282	6	0	0	6	0
Criovida - Hermes Pardini	MG		151	141	282	10	0	0	10	0
Núcleo de Hematologia e Oncologia	MG		0	0	0	0	0	0	0	0
Cellpreserve	RJ		690	690	699	141	0	0	1	141
Cryopraxis	RJ		1.731	1.635	1.701	465	0	0	344	0
BCU Brasil	SP		545	545	1.090	3	0	0	1	0
Widecells Brasil (Biocells)	SP		54	54	54	0	0	0	0	0
CCB	SP		1.088	1.088	2.212	2	1	0	0	0
Cordcell São Paulo	SP		1.208	1.208	1.125	13	0	0	13	0
Cordvida	SP		680	623	666	44	0	0	45	0
Criogênesis	SP		722	644	581	141	0	0	141	0
Cryogene	PR	S	101	101	101	3	0	0	3	0
Instituto Pasquini de Hemoterapia e Hematologia	PR		0	0	0	0	0	0	0	0
Hemocord	RS		448	446	594	90	0	0	89	0
National Amount			**8.300**	**8.048**	**9.971**	**953**	**1**	**7**	**686**	**141**

FINAL CONSIDERATIONS

The present work sought to show, from a survey of public data, the Brazilian scenario facing an alternative treatment for hematological diseases. This type of treatment may facilitate the care of patients who have not found compatibility in bone marrow donations. However, it is necessary to raise the amount of donations, since, according to ANVISA, the collection of units in banks of the BrasilCord Network in 2016 was 19.8 % lower than in 2015 and in the quadrennium (2013- 2016), this reduction was 30 %.

REFERENCES

1. ABRALE. Cerca de 80 Doenças Hematológicas Podem Ser Tratadas Com Transplante de Medula Óssea. 2017. Disponível em: <https://www.abrale.org.br/abrale-noticias/242-cerca-de-80-doencas-diferentes-relacionadas-ao-sangue-podem-ser-tratadas-com-o-transplante-de-medula-ossea>. Acesso em: 14 de dezembro de 2017.
2. ABRALE. REDOME lança portal no Dia Mundial do Doador de Medula Óssea. Disponível em: <http://redome.inca.gov.br/ola-mundo-6/>. Acesso em 16 de abril de 2018.
3. ANVISA. Relatório de Avaliação dos Dados de Produção dos Bancos de Sangue de Cordão Umbilical e Placentário. Anos: 2010, 2013, 2014 e 2016. Disponíveis em: <http://portal.anvisa.gov.br/sangue/publicacoes>. Acesso em: 14 de dezembro de 2017.
4. Ballen, K.K.; Gluckman, E.; Broxmeyer, H.E. Umbilical cord blood transplantations: the first 25 years and beyond. Blood, 2013, 122.4: 491-198.
5. Izu, M. et al. Influence of obstetric and neonatal factors in cellularity and volume of the umbilical cord. Journal of Nursing UFPE on line-ISSN: 1981-8963, v. 7, n. 7, p. 4621-4626, 2013.
6. Mendes-Takao, M. R. et al. Private umbilical cord blood banks for family use, in Brazil: technical, legal and ethical issues for an implementation analysis. Rev. Bras. Hematol. Hemoter., v. 32, n. 4, p. 317-328, 2010.
7. Neves, S.A. Banco de Sangue de Cordão Umbilical e Placentário: Proposta de Sistema

Híbrido Brasileiro. 2012. 105 f. Dissertação (Mestrado Acadêmico em Engenharia Biomédica) - Programa de Pós-Graduação em Engenharia Elétrica e Informática Industrial, Universidade Tecnológica Federal do Paraná, Curitiba, 2012.

8. Nunes, R.D.; Zandavalli, F.M. Association between maternal and fetal factors and quality of cord blood as a source of stem cells. Rev. Bras. Hematol. Hemoter., São Paulo, v. 37, n. 1, p. 38-42, fev. 2015.
9. Rodrigues, C.A. et al.Transplante de sangue de cordão umbilical - SCU. Rev. Bras. Hematol. Hemoter. [online]. v.32, p.08-12, 2010.
10. Bouzas, L.F.S. Transplante de medula óssea em pediatria e transplante de cordão umbilical. Medicina, Ribeirão Preto 241-263, julho/setembro 2000.
11. Cruz, L.E. et al. Sangue de cordão umbilical para uso autólogo ou grupo de pacientes especiais. Rev. Bras. Hematol. Hemoter., São Paulo, v. 31, p. 36-44, maio 2009.
12. Oliveira Silva, M., Tenório Leoi, L. (2010). Banco de sangue de cordão umbilical e placentário no Brasil. Ensaios e Ciência: Ciências Biológicas, Agrárias e da Saúde, 14 (2), 125-141.
13. Senegaglia, A.C. et al. Formação *in vitro* de túbulos capilares a partir de células de sangue de cordão umbilical humano com perspectivas para aplicação terapêutica. Rev Bras Cir Cardiovasc, São josé do Rio Preto, v. 23, n. 4. dez. 2008.