Umbilical Cord Blood Transfusion and Its Therapeutic Potentialities

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Abbreviations

DM	Diabetes mellitus
GVHD	Graft-versus-host disease
Hb	Hemoglobin
HbA	Adult hemoglobin
HbF	Fetal hemoglobin
Hct	Hematocrit
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
RBC	Red blood cell
UCB	Umbilical cord blood

Umbilical cord blood (UCB) is being used around the world for stem cell transplants. However, this source could be used in transfusions and its practical use should be encouraged, since the needs of transfusion are increasing considering the possibility of wars, terrorism, natural disasters, and epidemics around the world.

There have been several clinical trials with patients in reference to autologous and allogeneic umbilical cord blood transfusion. Despite the fact that autologous methods are more common throughout the world, the allogeneic use has been studied in order for this transfusion source to be applied to both children and adults.

It is important to consider the hematological particularities of UCB, such as higher levels of hemoglobin, hematocrit, mean corpuscular volume, leukocytes, and fetal hemoglobin, and low levels of coagulation factors. The advantages of using umbilical cord blood in transfusions include diminished expression of erythrocyte antigens, low levels of immunoglobulin, and also an absence of natural antibodies. On the other hand, UCB also has immature nucleated cells with engraftment capacity, which can provoke graft-versus-host disease (GVHD) without leukoreduction. However, blood irradiation before the use of UCB eliminates the risk of GVHD, making the use of allogeneic cord erythrocytes a therapeutically useful option, especially for preterm and lower weight newborns.

5.1 Introduction

Since 1988,[1] UCB has been routinely used in transplants as an alternative to bone marrow transplants, and UCB banks are being built around the world.

To cryopreserve the stem cells, among leukocytes, during the preparation of UCB, erythrocytes, platelets, and plasma are discarded. All attention on UCB use has been given to stem cell transplants only. However, stem cells constitute 0.01% of the nucleated cells of umbilical cord whole blood and the rest of the blood (99.99%) is apparently discarded.[2] Until now, this material has been underestimated as a source of other blood components for autologous and allogeneic transfusion.

Placental vessels contain anything from 75 to 125 mL of blood. Therefore, it has been considered that using this otherwise wasted resource could serve as a means of autologous[3] and, most recently, allogeneic transfusions.[4-6] Taking into consideration that about 100 mL of UCB from each delivery is discarded

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and multiplying that by the number of daily deliveries, it is easy to estimate the huge wasted volume, while blood banks are suffering from a lack of donors.

Since UCB volume collected is generally small, initially its use for adult transfusion will be limited. On the other hand, it is sufficient for newborns and low weight children, and it has been successfully used in individual cases around the world. Some estimates indicate that around 80% of infants with birth weights of less than 1,500 g receive at least one red cell transfusion.[7-10]

So, to verify the feasibility of using placental and UCB as a new source of transfusion, it is important to evaluate theoretical advantages and disadvantages, as well as consider published and known experience about the use of UCB in transfusions.

The aim of this chapter is to evaluate the safe application and the therapeutic viability of UCB components for transfusions, based on previous evidence.

5.2 Umbilical Cord Blood as a Source of Components in Transfusional Therapy

There is a rising interest in increasing the therapeutic use of UCB, besides using it as a source of hematopoietic stem cell transplants. One of the alternatives is its use for transfusion goals. This alternative is very interesting, as UCB is abundant and most of the time it is discarded and, consequently, underused.

Autologous blood is widely accepted as a preferred source of red blood cells when blood transfusion is clinically indicated in children and adults because it diminishes problems inherent to allogeneic transfusion, including infectious disease transmission and transfusion reactions. UCB obtained at delivery after cord clamping has been suggested as a source of autologous blood for transfusion in neonates,[11] mainly in preterm and low birth weight newborns, where blood transfusions are often necessary.[6-9,11]

In view of the usual blood volume transfused in neonates being approximately 10–20 mL/kg body weight,[11,12] sufficient UCB for at least one or two autologous transfusions even in extremely low birth weight neonates can therefore be expected to be available.[11,13] Thus, UCB is a feasible alternative source of erythrocytes, as most newborns of 24–27 weeks' gestation will require red blood cell transfusions.[12]

There have been several clinical trials in newborn, pediatric, and adult patients referring to not only autologous but also allogeneic UCB RBC transfusions.[4,6] Notwithstanding the fact that UCB has been considered a feasible alternative source of blood for transfusions, two limitations for its use are its small blood volume, compared to adult blood collected and the higher risk of bacterium contamination. To compensate for the small volume of cord blood collected, it is important to identify the advantage of cord blood as, for example, its immunological particularities.

Features of UCB from a transfusion practice point of view will be analyzed as follows. It is important to compare it to blood obtained from adult donors. The main components used are red blood cell concentrate (RBC), platelet concentrate, and plasma. The most potential and useful component is RBC. The small volume of cord blood probably does not contain enough platelets for transfusion.

The neonate plasma is poor in coagulation factors when compared to adult blood. On the other hand, other features show potential advantages, such as the weak expression of some erythrocyte antigens and the absence of anti-erythrocyte antibodies. The high concentration of progenitor cells brings a theoretical risk of higher implantation of nucleated cells in the patient, mainly in a immunosuppressed receptor leading to chimerism or, even, GVHD. However, this risk could be diminished significantly with a leukoreduction process.

5.3 Human Umbilical Cord Blood Features

5.3.1 Hematologic Parameters of Newborn Blood

Several hematologic parameters are different in neonate blood when compared to adult blood. Among these are the blood volume and erythrocyte mass per kilogram of body weight, as well as hemoglobin concentration, hematocrit, and mean corpuscular volume (MCV), which are higher in newborn than adult blood. Erythrocyte survival in neonate blood is about 60 days, reduced when compared to adult blood. The reduced

lifespan of newborn erythrocytes (60–80 days) is most likely explained by the increased osmotic fragility caused by the increased MCV.[14]

The leukocyte number is also higher in newborn blood, mainly mononuclear cells. On the other hand, there is no difference in platelet numbers between newborn and adult blood. The main hematologic parameters from full-term newborn and adult blood are shown in Table 5.1.

5.3.2 Newborn Hemoglobin

At the time of birth, approximately 75% of the hemoglobin is fetal (HbF). As the child grows up, the fetal hemoglobin concentration decreases while the adult hemoglobin (HbA) becomes the main erythrocyte hemoglobin, as shown in Table 5.2. Fetal hemoglobin has an almost 50% larger capacity to transport oxygen than adult hemoglobin. The capacity of the former is to carry 2.08 mL of oxygen per gram of HbF, while the latter has the capacity of 1.39 mL of oxygen per gram of HbA.[16] Fetal hemoglobin also presents higher concentration of 2–3 diphosphoglycerate (2–3-DPG). As 2–3-DPG shifts the oxygen dissociation curve to the right, it increases the oxygen release.[17]

These features are important for transfusional criteria. Theoretically, desired tissue oxygenation can be achieved with smaller increase of hematocrit and, consequently, smaller blood viscosity, due to fetal hemoglobin rich blood. This fact can be interesting in the treatment of anemic patients associated with ischemic disease, or even in patients with sickle cell anemia who need transfusion.

5.3.3 Coagulation Factor Features of Umbilical Cord Blood

The hepatic immaturity of neonates, especially in preterm newborns, and the physiological deficiency of vitamin K, lead to a smaller concentration of pro- and anticoagulant factors in their plasma (Tables 5.3 and 5.4).

Table 5.1 Reference hematologic values in full-term newborns and adults (Adapted from Geaghan[15])

	Newborns		Adults	
	Mean	−2 S.D (or min–max)	Mean	−2 S.D (or min–max)
Blood volume (mL/kg)	86.1		65	(55–75)
Erythrocyte Mass (mL/kg)	43.1		27.5	(25–30)
Hb	16.2	13.5	f:14.0 m:15.5	f:12 m:13.5
Ht%	51	42	f:41 m:47	f:36 m:41
Erythrocytes	4.7	3,9	f:4.6 m: 5.2	f:4 m:5.2
MCV	108	98	90	80
MCH	34	31	30	26
MCHC	33	30	34	31
Reticulocytes (10^6/μL)	0.074	(0.049–0.15)	0.092	(0.058–0.146)
Leukocytes (total)	18.1	(9–30)	7.4	(4.5–11)
Neutrophils	11	(6–26)	4.4	(1.8–7.7)
Lymphocytes	5.5	(2–11)	2.5	(1–4.8)
Monocytes	1.1		0.3	
Eosinophils	0.4		0.2	

Hb hemoglobin, *Hct* hematocrit, *MCH* mean corpuscular hemoglobin, *MCHC* mean corpuscular hemoglobin concentration, *MCV* mean corpuscular volume, *−2 S.D* minus 2 standard deviation, *min* minimum, *max* maximum, *f* female, *m* male

Table 5.2 Erythrocyte hemoglobin concentration from birth to 2 years old, when the concentration remains the same until adulthood (Adapted from Geaghan[15])

Age	HbF%		HbA%	HbA2%	
	Mean	±2 S.D	Mean	Mean	±2 S.D
Newborn	75	61–80	25.0	0	
1 month	60	46–67	39.2	0.8	0.4–1.3
6 months	7	2.7–13	90.5	2.5	2.1–3.1
1 year	2	1.3–5	95.3	2.7	2.0 –3.3
2 years	0.6	0.2–1	96.6	2.8	2.1–3.5

HbA hemoglobin A, *HbA2* hemoglobin A2, *HbF* hemoglobin F, *S.D* standard deviation

Table 5.3 Coagulant factors in full-term and preterm newborn plasma and adult plasma (Adapted from Geaghan[15])

Factor	Full-term newborns		Preterm newborns		Adults	
	Mean	−2 S.D	Mean	−2 S.D	Mean	−2 S.D
Fibrinogen (mg/dL)	246	150	240	150	278	156
F.II (U/mL)	0.45	0.22	0.35	0.21	1.08	0.7
F.VIII (U/mL)	1.68	0.5	1.36	0.21	0.99	0.5
F.IX (U/mL)	0.4	0.2	0.35	0.1	1.09	0.5
F.XII (U/mL)	0.33	0.23	0.22	0.09	0.08	0.52
Antirombin (U/mL)	0.4	0.25	0.35	0.1	–	–
Protein C (U/mL)	0.24	0.18	0.28	0.12	–	–

−2 S.D minus 2 standard deviation

Table 5.4 Coagulation inhibitors in newborn and adult plasma (Adapted from Geaghan[15])

Coagulation inhibitors	Newborns		Adults	
Factor	Mean	Range	Mean	Range
AT.II (antitrombin II)	59.4	42–80	99.8	65–130
Protein C antigen (%)	32.5	21–47	100.8	68–125
Protein C activated (%)	28.2	14–42	98.8	68–129
Protein S (total) (%)	38.5	22–55	99.6	72–128
Protein S (free) (%)	49.3	33–67	98.7	72–128

The smaller volume and reduced concentration of coagulation factors in UCB diminishes the utility of the plasma in correcting coagulation disturbances.

5.3.4 Immunological Features of Umbilical Cord Blood

The placenta barrier protects the fetus against contact with antigens present in maternal circulation and bacterial and viral pathogens very efficiently. The neonate is characterized by a state of true immunological purity. After delivery, the newborn comes into contact with antigenic stimulus of extra-uterus life for the first time. This fact is very important when considering the use of cord blood for transfusion.

Tables 5.5–5.7 show the main immunological features of UCB. It can be observed that IgA levels increase from 4 to 15 times and IgM levels increase from 4 to 30 times, from birth to adult life, whereas total IgG levels increase by just two, and among these,

Table 5.5 Immunoglobulin levels of blood (Adapted from Geaghan[15])

Age	0–30 days	Over 16 years
	Range (95%)	Range (95%)
IgA (mg/dL)	1–20	89–322
IgM (mg/dL)	12–117	59–360
IgG (mg/dL)	221–1,031	632–2,108

Table 5.6 IgG subclasses in preterm and full-term newborn and adult blood (Adapted from Geaghan[15])

IgG subclasses	Preterm	Term	adult
	Range (95%)	Range (95%)	Range (95%)
IgG_1	3.4–9.7	5.8–13.7	4.8–9.5
IgG_2	0.7–1.7	0.6–5.2	1.1–6.9
IgG_3	0.2–0.5	0.2–1.2	0.3–0.8
IgG_4	0.2–0.7	0.2–1.0	0.2–1.1

Table 5.7 Complement levels of blood (Adapted from Geaghan[15])

Complement	0–5 days	Adult
	Range (95%)	Range (95%)
C3	0.26–1.04	0.45–0.83
C4	0.06–0.37	0.11–0.41

IgG_2 is the subclass that increases the most. The level of complement class C3 and C4 does not present differences between neonates and adults. The main difference is in the immunoglobulin level because of the crescent contact with new antigens and pathogens.

5.3.5 Erythrocyte Antigens and Antibodies

Human erythrocytes express polymorphic antigens on their cellular membrane, responsible for hemolytic reactions by incompatibility. The most important antibodies that cause hemolysis are IgM (natural) and IgG (acquired). Notwithstanding, the most important and antigenic blood group is ABH. Natural antibodies against those antigens reach adult levels as early as the third month of extra-uterus life. Anti-A and anti-B antibodies belong to the IgM class and are potent activators of the complement system, causing a severe and potentially lethal intravascular hemolysis.

Healthy neonate blood does not contain acquired antibodies as it has not yet developed natural antibodies against RBC antigens. Newborn erythrocytes do not yet express certain erythrocyte antigens, for example, Kelly, and only express other antigens weakly such as A and B, and are therefore less immunogenic than adult erythrocytes. Table 5.8 shows the most important antigens and antibodies of UCB.

5.4 Hemocomponents from Umbilical Cord Blood

The use of whole blood for transfusion in patients has become an exception and normally whole blood is processed to red cell, platelet, and plasma units before transfusion.[19]

Since blood transfusion in premature or low weight neonates is often necessary,[6-9,11,20] UCB is a good source of hemocomponents for transfusion mainly in newborns

Table 5.8 The main antigens of umbilical cord blood (Adapted from Beutler et al.[18])

Antigen expression	Newborn	1–2 weeks	1 year	Adult
I	Weak	Weak	Strong	Strong after 3 years old
i	Strong	Strong	Undetectable	Undetectable
ABH	Weak	Increasing	Strong	Strong
$Lu^{a \text{ and } b}$	Weak	Weak	Weak	Strong after 15 years old
Lewis	Undectable	Detectable	Strong	Strong

as well as premature infants who generally need to receive more transfusions than full-term infants.[9]

Approximately 15–20 mL of UCB per kg of body weight can be harvested.[6,20] Several factors can influence the volume of cord blood collected. It has been shown that there is a direct correlation of volume of UCB collected to newborn[10,11,20-22] and placental weight,[20,21] and gestational age.[6]

Newborn erythrocytes have high concentration of HbF, whose capacity of carrying oxygen is greater than HbA. The main problem of using UCB is its low volume. However, it can be compensated by using more units.

Neonate plasma is deficient in coagulation factors and it does not as yet have natural antibodies against erythrocyte antigens. Newborn plasma is not therapeutically efficient in correcting bleeding due to its factor deficiency. On the other hand, it is less thrombogenic, which is an advantage when a whole UCB transfusion is needed, or when plasma is used to recover blood volume. The lack of antibodies against erythrocyte antigens, mainly natural antibodies, reduces the risk of hemolysis when neonate plasma is transfused. For this reason, iso group transfusion is not needed when whole UCB is used, diminishing the importance of blood fractionation.

Plasma fractionation by centrifugation is necessary with adult whole blood in order to preserve the activity of coagulation factors. When there is no need to preserve coagulation activity, fractionation of whole blood can be done by sedimentation. As sedimentation does not need expensive whole blood centrifuges, it is a cheaper and easier method and therefore well suited for poor and underdeveloped countries.

It is possible to separate erythrocytes and remove leukocytes from UCB by sedimentation without losing quality when stored up to 35 days.[19]

Even if platelet concentration of newborn blood does not differ from adult blood, the total amount per whole UCB unit is smaller, because of its lower volume harvested. Thus, it seems that the use of UCB platelet for transfusion will have little therapeutic importance.

It can be concluded that erythrocytes are the most interesting components in UCB transfusion practice. The potential use of plasma and platelets from UCB in transfusions is small, because of reduced volume and coagulation activity. The reduced erythrocyte volume per cord blood unit can be compensated using more units and by the abundance of the material. The higher oxygen-carrying capacity of HbF, lower thrombogenicity, lower antigenicity, and an absence of natural antibodies make UCB a very attractive source of RBC for transfusion.

The allogeneic UCB transfusion in adults shows an increase in the number of circulating CD34+ cells in the receptor with transient spontaneous engraftment.[23] Therefore, it is a theoretical risk of GVHD due to implantation of viable nucleated cells,[23,24] which can be significantly reduced by using leukocyte filter (7) or eliminated by irradiation before transfusion.[6]

In spite of theoretical GVHD risk, its incidence is rather low[25] and some studies have shown that this engraftment is not enough to provoke such a risk.[23]

5.5 Stored Umbilical Cord Blood Features and Quality

The mean volume of UCB, which can be harvested from term neonates with normal weight, is between 80 and 90 mL.[26] The volume collected from preterm and low weight newborns is lower, achieving volumes of over 15 mL in 60% of harvests.[20] UCB can be stored as whole blood or, after centrifugation or filtration, fractionated blood.

Bacterial contamination may occur during the harvest. However, with an adequate blood collection technique, this contamination rate can be reduced to less than 2%.[6] Thus, the low risk of possible bacterial contamination of placental blood must be carefully balanced against the benefit of avoiding homologous erythrocytes.[7]

UCB can be stored up to 35 days. Compared with adult erythrocyte stored for the same time period, UCB shows a higher hemolysis rate (1.1 ± 8.8 against 0.2 ± 01% from adult blood), higher free hemoglobin (416.9 ± 254 against 82.8 ± 42.4 mg dL from adult blood), and lower pH (6.1 ± 0.1 against 6.8 ± 0.1 from adult blood). Nonetheless, nonleukoreduced cord blood has nucleated cells while in adult blood these cells can be eliminated (4,200 ± 200 and 0.0 ± 0, respectively).[6] After 2–3 weeks of storage, the potassium level in cord blood also starts to increase significantly.[27] The risk of transfusion-related hyperkalemia will therefore limit the secure storage time of UCB to a maximum of 3 weeks to avoid cardiac arythmias.

During storage of nonleukoreduced UCB, TNF∗ is reduced and TGF-β1 is increased.[27] Alterations in cytokine concentrations during storage of adult allogeneic blood may potentially cause immunomodulation. Why this can happen with UCB is unclear.

5.6 Suggestion for Collection, Preparation, and Storage of Umbilical Cord Blood

UCB use shows some risks when compared with adult blood. Even though there is a higher risk of bacterial contamination at birth collection compared with adult transfusion, this can be reduced by implementing more aseptic collection techniques and testing for bacterial growth.[6]

Scheduled and authorized harvest of full-term and healthy newborn UCB could be a viable suggestion in order to increase and make common practice the use of this material in RBC transfusion.

Sorologic tests can be taken by pregnant women approximately 2 weeks before the delivery in order to avoid harvesting from positive reacting mothers. It is important to establish aseptic collecting techniques and train the obstetricians and staff. Leukoreduction by gravity filtration should be done soon after collection and samples should be sent for microbiological tests. The unit should be stored for no more than 3 weeks and irradiated in the case of transfusion in neonates.

UCB also has immature nucleated cells with engraftment capacity, which can provoke GVHD without leukoreduction, although it has been shown that this risk is minimum.[23,25] Furthermore, it has already been shown that cord blood can be used with safety and at a low risk of immunological and nonimmunological reactions in autologous transfusion in newborns and allogeneic transfusion in children and adults. UCB of healthy full-term neonates with normal weight yields a mean volume of 80 mL of whole blood and from 27 to 30 mL of RBCs after centrifugation. The leukoreduction shows benefits in eliminating nucleated cells and reducing hemolysis and hyperkalemia caused by storage. To diminish transfusional risks caused by hemolysis and hyperkalemia, the period of storage should be reduced from 35 to 21 days.[27] Irradiation before its use eliminates the risk of GVHD, making use of allogeneic cord erythrocytes, a therapeutically useful option especially for preterm and lower weight newborns.

An increase in plasma potassium and a decrease in 2,3-DPG content of erythrocytes during extended storage[6,8] has been shown. Furthermore, morphological changes, including a decreased deformability and an increased osmotic fragility of the erythrocytes, have already been described.[6] Some studies show that 2,3-DPG is totally depleted from erythrocytes after 21 days of storage.[8]

The standard technique for separation of whole blood into plasma and erythrocytes is based on centrifugal force. However, as equipment for blood processing such as centrifuges and the subsequent processing of erythrocytes is expensive and therefore not always available, the use of gravity filter systems have the advantage of removing their necessity. One study showed that placental blood can be separated into its components by gravity with only a hollow-fiber filter system, attaining a quality suitable for later clinical use. One of the advantages of this procedure is that all steps are performed at room temperature. Because no other equipment is necessary and it is possible to use it without electricity, it is our view that this system would be ideal for use in the under resourced world.

5.7 Risk of Infectious Disease due to Allogeneic Umbilical Cord Blood Transfusion

One of the concerns about allogeneic blood transfusion is the risk of viral transmission, although its incidence is rather low. It is estimated that the risk of acquiring human immunodeficiency virus (HIV) is between 1 in 100,000 (0.001%) and 1 in 1 million (0.0001%) per transfusion. For hepatitis B, the risk is 1 in 50,000 (0.002%). Therefore, the risk of viral infections acquired from homologous transfusions does not justify invoking other dangers in an attempt to avoid these rare events.[7]

Despite the small risk of the transmission of infectious diseases through the transfusion of adult blood, the use of UCB diminishes this risk further, because the placenta barrier reduces the chances of vertical maternal-fetal transmission. This is mainly important in places such as Africa, where in some countries more than 50% of the adult population is HIV-positive.

5.8 Therapeutic Use of Umbilical Cord Blood Transfusion

The first autologous UCB erythrocyte transfusion was carried out in 1995 in a neonate.[28] Subsequently, several publications have demonstrated that it is an executable and safe proceeding.[6,10,29,30] Newborns who benefit the most from this proceeding are those with lower weight or preterm neonates, mainly those with cardiopulmonary disease and anemia.[8]

A number of epidemiological and experimental studies have shown that impaired intrauterine growth, resulting in low birth weight, is associated with a variety of adult-onset diseases, including type 2 diabetes, hypertension, hyperlipidemia, cardiovascular disease, stroke, and kidney disease.[25]

A practical limiting factor is that autologous UCB can only fully supply approximately 40% of the transfusional needs of newborns,[20,29] thus in 60% of neonates it is also necessary to use allogeneic blood. UCB use in allogeneic transfusions has been published since 2001. Hundreds of pediatric and adult patients with anemia, associated to several diseases, such as acquired immune deficiency syndrome,[31] ankylosing spondylitis, aplastic anemia,[4,16] benign prostatic hypertrophy,[4] cancer,[16,32] chronic renal failure,[4] diabetes mellitus,[33] leprosy,[24] malaria,[5] rheumatoid arthritis,[4,16,34] systemic lupus erythematosus,[4,16] beta thalassemia,[4,16,35] tuberculosis,[36] and others have already received thousands of allogeneic UCB units, without evidence of immunological or non-immunological reactions.[23,24,31,32,36] Table 5.9 is a resumé of the transfusion clinical trials with RBC of UCB.

Neonates, particularly when extremely preterm, are among the most heavily transfused of all patient groups. It is estimated that 80% of premature neonates with birth weight less than 1.5 kg, and, with rare exception, nearly 100% of extremely preterm infants with birth weight less than 1.0 kg required RBC transfusions every year. A smaller percentage of infants received other blood components such as fresh-frozen plasma, cryoprecipitate, and platelet. Thus, blood component transfusions, particularly erythrocytes, provide a genuine benefit to many preterm infants and are indispensable to the neonatologist.[8]

Many preterm infants who receive blood during the early weeks of life, particularly those with birth weight

Table 5.9 Clinical trials of umbilical cord blood RBC transfusion

Cause of anemia	Transfusion type	Number of units	Number of patients	Age of patients	Year of publication	References
Preterm newborn	Auto	1	1	Newborn	1995	Ballin et al.[28]
Thalassemia, AA, AS, BPH, CRF, RA, and SLE	Alo	174	62	9 - 78	2001	Bhattacharya et al.[4]
Preterm newborn	Auto	52	52	Newborn	2003	Brune et al.[29]
Thalassemia, cancer, AA, AS, RA, and SLE	Alo	413	129	2 - 86	2005	Bhattacharya[16]
Beta thalassemia	Alo	92	14	0.5 - 38	2005	Bhattacharya[35]
Tuberculosis	Alo	106	21	–	2006	Bhattacharya[36]
RA	Alo	78	28	–	2006	Bhattacharya[34]
Cancer	Alo	82	6	–	2006	Bhattacharya[23]
Cancer	Alo	–	72	–	2006	Bhattacharya[32]
DM	Alo	78	39	48 - 74	2006	Bhattacharya[33]
AIDS	Alo	123	16	–	2006	Bhattacharya[31]
Leprosy	Alo	74	16	12 - 72	2006	Bhattacharya[24]
Malaria	Alo	94	39	8 - 72	2006	Bhattacharya[5]

AA aplastic anemia, *AIDS* acquired immune deficiency syndrome, *Alo* allogeneic, *AS* ankylosing spondylitis, *Auto* autologous, *BPH* benign prostatic hypertrophy, *CRF* chronic renal failure, *DM* diabetes mellitus, *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus

lower than 1.0 kg, are given multiple RBC transfusions,[8] which are, generally, correlated to initial hemoglobin value, birth weight, and gestational age.[37] Most RBC transfusions given to neonatal patients are small in volume (10 ± 20 mL/kg).

In neonates with severe respiratory disease, such as those requiring high volumes of oxygen with ventilator support, it is customary to maintain the hematocrit above 40% and hemoglobin concentration above 13 g/dl.[8]

RBC transfusion in newborns has been indicated for: (1) replacement of blood drawn for laboratory tests: (replace if 5–10% of blood volume is removed over a short period); (2) maintenance of optimum hemoglobin and hematocrit in babies with severe respiratory and/or cardiac disease (hemoglobin above 13 g/dL and hematocrit above 40%) evidence that the improvement outcome of transfusion is limited, and (iii) correction of anemia in infants with less severe cardiopulmonary disease or with growth failure (hemoglobin above 10 g/dL and hematocrit above 30%).[9] The risks and benefits of currently used minimal values of hemoglobin and hematocrit to indicate RBC transfusion in newborns have not been tested in randomized controlled clinical trials.

5.8.1 Use of Cord Blood RBCs in Transfusion in Anemia Patients

Anemia in premature newborns with the subsequent need to transfuse allogeneic or autologous red blood cells is a common problem in very low birth weight infants.[9,20,37] Seventy percent of these transfusions are given during the first month of life.[8]

The two most common causes are "physiological" anemia of premature newborns and blood loss due to repeated blood sampling. Anemia of premature newborns results in a lower Hb (6.5–9 g/dL) compared to full-term newborns (10–11 g/dL) and it occurs earlier (4–8 weeks).[9] In extremely low birth weight infants, the causes of anemia and the reasons for RBC transfusions include: the magnitude of blood loss related to the severity and duration of intensive care, erythropoietin treatment failure, and hemodilution caused by rapid weight gain, among others.

Despite limiting the number of donor exposures and transfusion episodes, premature infants still require transfusions of RBC for iatrogenic blood loss and for cardio respiratory instability.[12] Hundreds of infants and adults with anemia have also received allogeneic UCB transfusion such as patients suffering from leprosy,[24] tuberculosis,[36] cancer,[23,32] rheumatoid arthritis,[34] HIV-positive patients,[31] and others.

5.9 Use of Umbilical Cord Blood Transfusion in Sickle Cell Anemia Patients

Most sickle cell anemia patients receive blood during their life. However, one of the potential adverse effects is the high hematocrit and hyperviscosity caused by RBC transfusions,[8] which can cause an increase in the severity of the disease and provoke more sickle cell crisis. To diminish the risks of hyperviscosity due to erythrocytosis, UCB transfusion could be a good approach for these patients.[7] UCB has a high concentration of HbF, which has greater oxygen-binding capacity than normal hemoglobin, and this has been shown to be of considerable therapeutic importance in sickle cell disease or other hemoglobinopathies, since the patient can theoretically receive a smaller volume of blood to receive the same oxygen benefits. HbF will deliver more oxygen to the ischemic core provided there is partial blood flow from subtotal vaso-occlusion or by collateral circulation. The rheological property of term cord blood is also favorable for reperfusion because of lower viscosity.[38]

5.9.1 Use of Umbilical Cord Blood Transfusion in Patients with Malaria

Malaria is an annual killer of over 1 million people mainly in the under resourced world and its essential co-morbidity is anemia, mainly in children.[19,39] The high oxygen affinity and anti-malarial effect of fetal hemoglobin in cord blood are additional advantages for transfusion in malaria patients.[5,30] Without blood transfusions, the patients frequently fail to survive this life-threatening situation.[19] It has been shown that UCB can be used in malaria patients with anemia who need blood transfusions.[39]

5.9.2 Use of Umbilical Cord Blood Transfusion in Patients with Diabetes

Diabetes mellitus (DM) is the most common endocrine disease in all populations and all age groups. Anemia is a common accompaniment of diabetes, particularly in those with albuminuria or reduced renal function, although there are other additional contributory factors. As fetal hemoglobin transport 50% more oxygen than normal hemoglobin, the use of RBC from UCB is theoretically very attractive in patients with DM and anemia since most of them have damaged microcirculation.[33]

Both epidemiological and experimental studies have shown that impaired growth in the uterus due to maternal malnutrition, resulting in low birth weight, is associated with a high incidence of glucose intolerance, insulin resistance, and type 2 diabetes in adult life. Maternal malnutrition is an unavoidable worldwide problem, and therefore, prevention of type 2 diabetes in low birth weight infants who reach adulthood is difficult to achieve. Based on the evidence, it is also proposed that transfusion of human umbilical cord blood to low birth weight infants may offer protection of type 2-DM and other adult onset diseases.[24]

5.9.3 Use of Umbilical Cord Blood Transfusion in Acute Ischemic Stroke Patients

Strokes are a major cause of neurological disability throughout the world. Poststroke functional recovery is limited because of neuronal death and degeneration. Although early reperfusion therapy may improve the outcome, thrombolysis does not reverse ischemic neuronal death and carries the risk of cerebral hemorrhage.[38,40]

Based on some experimental data, human UCB transfusion has been considered possible therapy for ischemic cerebral stroke cases to aid functional recovery. One reason is the higher concentration of HbF in UCB, which has greater oxygen-binding capacity compared with HbA, improving oxygenation in the ischemic tissue. HbF will deliver more oxygen to the surviving neurons in the ischemic penumbra.[38]

Umbilical venous blood also has a high concentration of interleukin-1 receptor antagonist (IL-ra), especially in preterm and in normal term deliveries and is a potent anti-inflammatory cytokine and a target of new clinical stroke trials. Its presence in term newborn UCB suggests that UCB transfusion may potentially attenuate postischemic inflammatory cascade in stroke patients.[38]

Thus, it has been suggested that UCB transfusion could promote better functional recovery in adults with acute ischemic stroke, since UCB transfusion may have the potential to reduce the burden of disability not only in strokes but also in other brain diseases. The collection of cord blood will be parallel with population increase, and as a result, populous countries would be able to use their own resources effectively to treat strokes at a lower cost.[38]

5.10 Conclusions

At present, the placental and the umbilical cord are considered to be biological waste and are usually destroyed. However, UCB is an attractive source of RBC for transfusion for the following reasons: (1) because of its abundance, (2) it can be collected without risks, (3) the fetal hemoglobin has a 50% higher oxygen-carrying capacity, (4) it either does not express or expresses weakly some erythrocyte antigens and is therefore less immunogenic than adult blood, (5) it does not contain or contain very low levels of natural and acquired erythrocyte antibodies.

UCB is easy to collect, filter, and store, which is important in underdeveloped countries or in situations of shortage or war. Maximum time for secure storage should be no more than 3 weeks to avoid the risk of hyperkalemia.

Allogeneic and autologous RBC-UCB has been used in transfusions in a number of clinical situations with very low risk of infection, contamination, or immunological reactions. This makes the use of RBC-UCB in transfusion practice especially interesting in newborns or, for example, in adult patients with ischemic diseases. It is a very viable consideration that the use of UCB transfusion be stimulated in order that many more adult and child patients can benefit from this efficacious clinical approach.

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