

A preliminary report of 123 units of placental umbilical cord whole blood transfusion in HIV-positive patients with anemia and emaciation

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Summary

Cord blood, because of its rich mix of fetal and adult hemoglobin, high platelet and WBC counts, and a plasma filled with cytokine and growth factors, as well as its hypo antigenic nature and altered metabolic profile, has all the potential of a real and safe alternative to adult blood transfusion. Our team's experience (from 1st April 1999 to 1st July 2005) with 123 units of placental umbilical cord whole blood (62 ml-154 ml mean 85 ml \pm 8.4 ml SD, median 82 ml, mean packed cell volume 48.8 \pm 4.2 SD, mean percent hemoglobin concentration 16.3 g/dl \pm 1.6 g/dl SD; after collection the blood was immediately preserved in a refrigerator and transfused within 72 hours of collection) collected after lower uterine cesarean section (LUCS), and the transfusion to 16 consenting HIV-positive patients (12 cases had full blown AIDS) with anemia and emaciation is presented here. On the basis of our preliminary experience of cord blood transfusion, we are of the opinion that umbilical cord whole blood transfusion is safe in HIV-positive patients. This blood has the potential to carry more oxygen than adult blood and it does not trigger any clinical, immunological or non-immunological reaction after its transfusion to an adult host with a HIV-positive status. Apart from the correction of anemia, there was also definite improvement in the energy and fatigue levels in individuals with HIV, i.e., physical functioning, a sense of well-being and weight gain from two to five pounds, within three to ten months of the commencement of transfusion. There was also an immediate rise in CD34 levels of peripheral blood in the HLA-randomized host after transfusion, without any clinical graft vs host reaction.

Key words: Safe; Placental umbilical cord blood transfusion; Immune mosaic HIV-positive patients; Anemia; Emaciation; Transient transplantation transfusion impact.

Introduction

Anemia is a frequent complication of human immunodeficiency virus (HIV) infection, and its incidence is associated with progression of HIV disease, particularly anemia that does not resolve. This, in turn, is associated with a shorter survival rate for HIV-infected patients. The prevalence of anemia decreased in the highly active anti retroviral treatment era, but transfusion was claimed to be positively linked with the risk of death, suggesting a limitation of the use of transfusions in the absence of an emergency situation by some investigators [1]. An alternative could be a once-weekly erythropoietin injection for quality of life which may improve along with the hemoglobin levels in anemic HIV-infected adults receiving antiretroviral therapy [2]. However, the real problem of erythropoietin is the cost, which makes it difficult for many patients to afford treatment, especially in Africa and other parts of the developing world. A second alternative for the treatment of severe anemia is blood transfusion. Anemia in HIV-positive patients may have a role in disease progression and survival. Recovery from anemia has been linked to improved survival outcomes.

Nonetheless, adult whole blood transfusion has been claimed to be associated with accelerated disease progression and mortality in patients with HIV infection, and a review of related literature suggests that the mechanism for negative transfusion-associated outcomes may be transfusion-related immunomodulation [3-5].

Apart from the problem of immunosuppression, adult blood transfusion is problematic in severe anemia as it may trigger cardiac overload and failure unless adequate care and precautions are taken. It was reported earlier that fetal hemoglobin rich placental umbilical cord whole blood, which is readily available from discarded placentae, if collected aseptically after the birth of a healthy newborn at or near term, could be used as a genuine blood substitute [6, 7]. Whether this cord blood can be an emergency and safe substitute for adult whole blood in case of anemia necessitating blood transfusion in HIV-positive patients was the main premise behind the present work.

Case Presentations

In this series, an overview of the cases of 16 HIV patients who were treated with placental umbilical cord whole blood is presented. First a brief background of the patients is given, which may help in gauging the source of HIV infection and the sociological causes of its spread in a developing country like India. This, in turn, may help relevant authorities and institutions in stemming its proliferation. One interesting observation

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is that the females in this study were all apparently infected by their husbands. The couples' children, except in one case, remained unaffected. The males were migrant laborers from the state of West Bengal who had gone to a large metropolis in some other state to work and were generally not accompanied by their families, but returned periodically to their homes on vacation leave. Another noteworthy point is that they all belonged to the poor strata and could not afford expensive treatment. On the other hand, social ostracism implies that they could not turn to their extended families for financial or any other form of support, and depended on the government or some health sector non-governmental organizations for assistance. A third inclusion is that many of the patients also suffered additionally from tuberculosis.

Discussion

My team and I have been investigating issues related to the transplant of ethically collected fetal cell/tissue in adult hosts (with legal consent) since 1999 and have published reports on fetal cell/tissue transplant in different diseases [8-15]. In the present series, the volume of cord blood collected after LUCS varied from 62 ml-154 ml (mean 85 ml \pm 8.4 ml SD, median 82 ml, mean packed cell volume 48.8 \pm 4.2 SD, mean percent hemoglobin concentration 16.3 g/dl \pm 1.6 g/dl SD). After collection, the blood was immediately preserved in the refrigerator and transfused within 72 hours of collection. The work and the clinical follow-up have been ongoing from the 1st of April 1999 to 1st July 2005. Of the 16 HIV-positive patients (12 cases had full blown AIDS) all had severe anemia and emaciation. All cases had a specific suggestive history of heterosexual transmission of HIV. In all cases, the male was infected first (probably from sex workers) and subsequently the wife was infected, and in one case their child was affected as well. We did not come across cases in this series with any history of intravenous drug use, homosexual mode of transmission, blood transfusion-related infection, or any other means of spread. More than 75% of the cases in this series presented with Kochs' infection and extreme weakness, progressive loss of weight with persistent temperature, and episodic diarrhea. These features were followed by progressive loss of hair, generalized itching and maculopapular rashes on the extremities.

We transfused 123 units of freshly collected placental umbilical cord whole blood to 16 volunteers with a HIV-positive status, after getting necessary donor and recipient consent and the approval of the institutional ethical committee. We did not encounter a single episode of any immunological or non immunological reaction during transfusion. Six recipients had B+ blood type, followed by O+ in five patients and three cases had A+ blood type. AB+ blood type was noted in two cases. The age of the group varied from 20 to 40 years; 50% were male and the rest female. One patient received 22 units with five units of cord blood at one time in a row, followed by 17 units, then 16 units, and 10 units; two cases received nine units each, etc. Blood was transfused within a few hours of collection, at the most within 72 hours of collection, to patients on the basis of clinical priority, availability and

cross matching, and after proper screening as per the standard adult blood transfusion protocol of the World Health Organization (WHO) for adult blood transfusion [16]. There was a gap of a few months (4-10 months) between the first and last blood transfusion, for periodic clinical evaluation. All the patients who received more than three units of cord blood, showed subjective and objective improvement in the form of less weakness, improved appetite and a sense of well-being. There was even a gain in weight of three to five pounds within the clinical observation period.

In some cases we did a pre-transfusion and a 72-hour post-transfusion CD34 study from the peripheral blood which indicated a substantial rise. The normal CD34 level range was .09% or lower, but after freshly collected cord blood was transfused, it was noted to be 5.86% (Figure 1) even after 72 hours, without any suggestive feature of clinical graft vs host reaction. The patients did

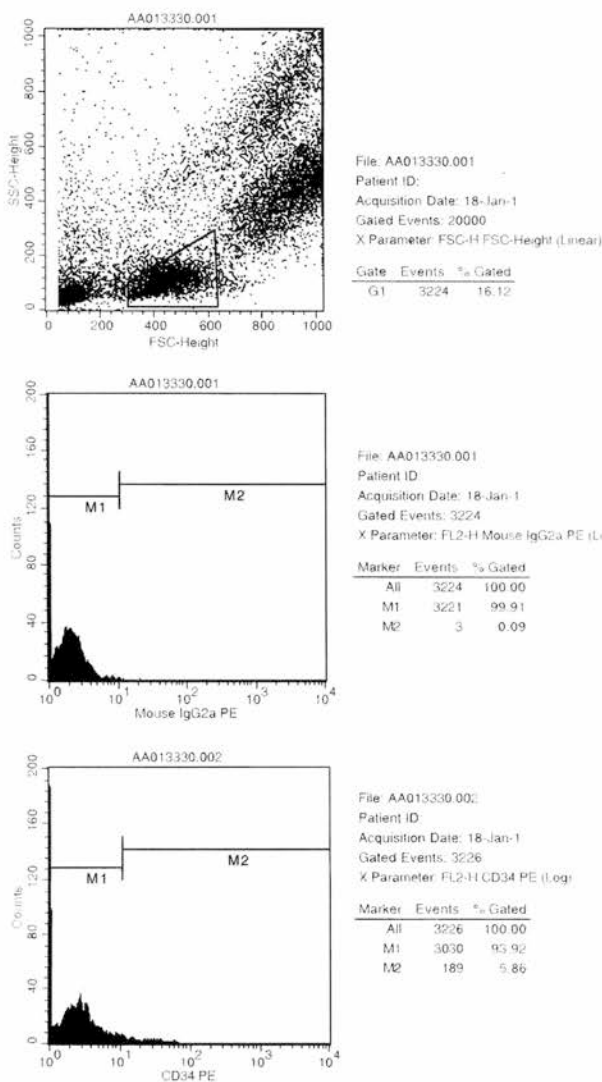


Figure 1. — Flow analysis cytometry report of the peripheral blood CD34 level 72 hours after cord blood transfusion.

Table 1. — List of HIV-positive patients who received cord blood transfusions in the present series.

Patient No. mode of transmission of HIV	Initials, age & sex	Blood group	Primary presentation of the disease apart from anaemia, i.e., Hgb 8 g/dl or less	Transfusion of UCB: No of units	Immediate reaction, viz, fever, chill and rigor, flank pain, back pain, blood in urine, fainting or dizziness	Late reactions like mild or progression to kidney failure, shock or delayed anaemia	Complications like mild to moderate discomfort, anaemia, shock, acute renal shutdown, lung dysfunction	Sense of wellbeing and weight gain	Unknown complication or rare complication autoimmune disease or scleroderma due to microchimersims, etc., with follow-up to date
1 Hetero	M.M. 23 yrs., F	B+	Fever, weight loss and diarrhea	16 units 1 st transfusion on 22/9/03 and last on 28/7/04	Nil	Nil	Nil	Positive	Nil
2 Hetero	S.M. 27 yrs., F	AB+	Fever, and loss of weight	7 units 1 st transfusion on 22/9/03 and last on 26/5/04	Nil	Nil	Nil	Positive	Nil
3 Hetero	M.M. 35 yrs., F	A+	Extreme weakness, fever and maculopapular eruptions	10 units 1 st transfusion on 22/9/03 and last on 26/5/04	Nil	Nil	Nil	Positive	Nil
4 Hetero	B.D. 28 yrs., F	A+	Fever, weakness, loss of hair Pneumocystitis carini	22 units 1 st transfusion on 22/9/03 and last on 27/8/04	Nil	Nil	Nil	Positive	Nil
5 Hetero	P.H. 26 yrs., M	B+	Opportunistic infection Fever, diarrhea, loss of weight and hair loss generalized lymphadenopathy	9 units 1 st transfusion on 28/1/04 and last on 16/4/04	Nil	Nil	Nil	Positive	Nil
6 Hetero	S.R. 40 yrs., M	B+	Weakness, fever, maculopapular rashes, itching	6 units 1 st transfusion on 24/12/03 and last on 27/8/04	Nil	Nil	Nil	Positive	Nil
7 Hetero	U.D. 29 yrs., F	B+	Same as 6	3 units 1 st transfusion on 13/12/03 and last on 12/5/04	Nil	Nil	Nil	Positive	Nil
8 Hetero	S.D. 26 yrs., F	O+	Rashes all over the body and weakness and fever	17 units 1 st transfusion on 13/12/03 and last on 12/5/04	Nil	Nil	Nil	Positive	Nil
9 Hetero	D.B. 20 yrs., M	B+	Weight loss, fever	3 units 1 st transfusion on 17/12/03 and last on 27/8/04	Nil	Nil	Nil	Positive	Nil
10 Hetero	A.M. 23 yrs., M	O+	Maculopapular rashes and weight loss	3 units 1 st transfusion on 24/10/03 and last on 24/12/03	Nil	Nil	Nil	Positive	Nil
11 Hetero	M.G. 30 yrs., M	O+	Weakness and fever	9 units 1 st transfusion on 28/1/04 and last on 27/8/04	Nil	Nil	Nil	Positive	Nil
12 Hetero	S.G. 27 yrs., F	O+	Diarrhea, loss of weight, skin rash	7 units 1 st transfusion on 7/1/04 and last on 28/7/04	Nil	Nil	Nil	Positive	Nil
13 Hetero	T.G. 31 yrs., M	A+	Loss of weight and fever and rashes	3 units 1 st transfusion on 7/1/04 and last on 27/8/04	Nil	Nil	Nil	Positive	Nil
14 Hetero	S.P. 24 yrs., F	AB+	Loss fo weight, diarrhea and fever	4 units 1 st transfusion on 7/1/04 and last on 30/6/04	Nil	Nil	Nil	Positive	Nil
15 Hetero	B.P. 32 yrs., M	O+	Loss of weight, and fever	2 units 1 st transfusion on 28/7/04	Nil	Nil	Nil	Positive	Nil
16 Hetero	T.B. 36 yrs., M	B+	Loss of weight, and fever and loss of hair with episodic intractable diarrhea	2 units, 1 st on 11/01/01 and the last transfusion on 15/1/01	Nil	Nil	Nil	Positive	Nil

Hetero = heterosexual transmission; Positive =

not receive any growth factor or related cytokine stimulation. We are presently studying the impact of cord blood transfusion and the effect of the rise in CD34 in the peripheral blood in advanced immunodeficiency in HLA and sex-randomized adults who did not receive any specific immunosuppressive drug support. We are also studying its relationship with the CD4 and CD8 count of the host system.

In the animal kingdom, swallowing the afterbirth by the mother is a general norm. Even herbivorous animals swallow the placenta after the birth of their babies (e.g., the cow). However, humans do not seem to know how to use this precious afterbirth, which has protected and nurtured babies for so long in the womb. Of late, since 1989, global consciousness has been increasing on the use of umbilical cord blood stem cells as an easily available source of hematopoietic stem cells for bone marrow transplantation [17, 18]. These fetal stem cells (CD34) cause fewer graft vs host reactions after transplantation. Recognition of this potentiality in the scientific world has resulted in the collection and harvesting of these cord blood stem cells in many laboratories all over the world, but these hematopoietic stem cells constitute only .01% of the cord blood. The rest, that is, 99.99% of the cord blood is wasted. This precious wasted gift of Mother Nature is rich in fetal hemoglobin, growth factors and other cytokine-filled plasma, and is moreover protected in the infection-free environment inside the placenta in case of a healthy newborn.

In cases of HIV-infected patients, allogeneic adult blood transfusions have been claimed to have an immunomodulatory effect, and have been associated with the activation of human immunodeficiency virus (HIV) and cytomegalovirus (CMV) *in vitro*, and of stimulating HIV infection in small pilot studies. Retrospective studies suggest that adult whole blood transfusions adversely affect the clinical course of HIV. Data in selected non-HIV-infected patients requiring blood transfusion have suggested clinical benefit with leukocyte-reduced red blood cells (RBCs) [19]. In general, as the HIV disease progresses, the prevalence and severity of anemia increase. Anemia is also more prevalent in HIV-positive women, children, and injection-drug users than in HIV-negative women, children, and injection-drug users. Anemia has been shown to be a statistically significant predictor of progression to acquired immunodeficiency syndrome (AIDS) and is independently associated with an increased risk of death in patients with HIV. Recently, the use of highly active antiretroviral therapy has also been associated with a significant increase in hemoglobin concentrations and a decrease in the prevalence of anemia. Severe anemia did occur infrequently among these patients but was associated with a much faster rate of disease progression. Among patients with similar CD34 lymphocyte counts and viral load, the last value of hemoglobin was a strong independent prognostic marker for death [20]. Treatment of severe anemia with epoetin alpha or use of oxygen-carrying blood substitutes like genetically or chemically modified hemoglobin solutions

or fluoro-carbon compounds is simply unacceptable, not only because of the cost involved in such transfusions but also because of the undesirable level of serious side-effects involved like hypertensive impact or other vascular side-effects [21]. The real problem in the developing world of Asia and Africa is the cost involved in the procurement of safe HIV, hepatitis (B/C), and malaria-free blood, screened at the nano or molecular levels by PCR technology. It should be pointed out that HIV in most cases cannot cross the placental barrier, and the placental umbilical cord blood of a healthy newborn, as per our experience, is safe (infection free). We also should reiterate that aseptically collected cord blood after the birth of healthy newborns is very rich in fetal hemoglobin content, growth factors, and is hypoimmune in nature because of the formidable placental barrier. It may be noted further that the baby of a HIV-positive mother is infected mainly as a result of placental breaks or some extra placental mode of transmission of the infection [22].

Conclusion

In a report of the WHO, it was revealed that there are about 500,000 pregnancy-related deaths globally, of which at least 25% maternal deaths are due to a loss of blood [23]. An estimated 13 million units of blood worldwide are not tested against human immunodeficiency viruses or hepatitis viruses, and in some developing countries, 80% of the blood supply comes from paid donors or replacement donors (family friends or acquaintances), even when the number of infected persons in the population is high [24]. The requirement for safe, infection-free blood is on the increase, and this is where the potential of placental umbilical cord whole blood needs to be underscored.

In India alone, more than 20 million annual registered births take place and the placenta is regarded generally as biological waste everywhere. Instead of simply disposing of this precious blood in dustbins or incinerators, if it is collected aseptically from the placenta and used in cases of severe anemic victims of HIV with progressive emaciation, this HIV-related anemia can be improved with cord blood transfusion as in all the 16 cases in the present study. There was also a definite improvement in the energy and fatigue levels in individuals with HIV, i.e., physical functioning, sense of well-being and weight gain from two pounds to five pounds within three to ten months of the commencement of transfusion, irrespective of background treatment. The implication is that it may help in prolonging life, delay progression towards full blown AIDS, and stimulate the system to fight the disease.

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