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Original Article

Transfusion Practice, Post-Transfusion Complications and Risk Factors in Sickle Cell Disease in Senegal, West Africa

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Abstract. ***Context and Objectives:*** **Blood transfusions (BT) remain a mainstay of therapy for patients with sickle cell disease (SCD) but pose significant clinical challenges. We aim to assess infectious markers, red cell alloimmunization, and iron overload secondary to BT in SCD patients.**
Materials and Methods: **This case-control study included 253 SCD (153 SCD-transfused and 100 SCD non-transfused). We evaluated the transfusion practice (modalities, indications), post-transfusion complications (infections, alloimmunization, iron overload), and risk factors of these complications (socio-demographic, clinical, biological).**
Results: **Median age was 28.5 years (5 - 59). The sex ratio was 0.86. Homozygous SCD was the most common (95.3%). Simple BT was performed in 92.8% and transfusion exchange in 18.9%. Transfusion indications were dominated by acute anemia (57.06%) and vaso-occlusive crisis (VOCs) (14%). Red blood cell concentrates (RBCSs) were administered to 93.46%. The median RBCs received per patient was 10 (2 - 48). The prevalence of VHC in SCD-transfused was 1.33% and 2% for VHB. Anti-HIV antibodies were not found. Red cell alloimmunization frequency was 16%. The most common alloantibodies were anti-rhesus (34.19%) and anti-Kell (23.67%). Iron overload was detected in 7.84%. The number of RBCs transfused was the only risk factor for alloimmunization (p = 0.03) and iron overload (p = 0.023). BT frequency was not related to infectious transmission.**
Conclusion: **BT therapy is still a risk for SCD polytransfused patients despite advances in blood safety. Although infectious transmission has rare, the risk of alloimmunization and iron overload is high in these patients.**

Keywords: Blood transfusion; Sickle Cell Disease; Alloimmunization; Iron overload.

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Introduction. SCD is one of the most common worldwide hereditary disorders characterized by the substitution of hemoglobin A (HbA) with the abnormal HbS. In Africa, 10% to 40% are carriers of HbS, and each year 200 000 to 300 000 newborns have the homozygous form.[1] SCD is characterized by high morbidity and significant mortality at the onset of acute or chronic complications whose treatment often resorts to BT.[2]

BT is currently a major therapeutic option indispensable in the management of severe forms of SCD.[3,4] It exists in three methods to treat SCD anemia: simple BT, punctual transfusion exchange, and long-term transfusion exchange.[5,6]

Despite the benefits, multi-transfused patients are at an increased risk of complications of red cell alloimmunization, iron overload, and blood-transmitted infections.[7,8,9] The frequency of these complications correlates with RBCs units transfused.[3,4] The presence of one of these complications is a major risk factor for morbidity and mortality in SCD patients requiring specialized therapeutic management.[8,10] Preventing these complications can be achieved by optimization of BT indications, extensive phenotyping of RBCs and patient's blood group, and strengthening infectious blood safety.[11,12] Systematic screening for these complications in SCD-polytransfused is recommended by screening for irregular agglutinins, for infectious transmitted (HIV, VHB, VHC) before and after BT, and ferritin assay even if serum ferritin constitutes an indirect marker to detect post-transfusion iron overload.[13,14,15] In Africa, there are many shortcomings in transfusion availability and safety. These constraints could have consequences in polytransfused patients such as SCD patients. Unfortunately, data on the frequency of post-transfusion complications are scarce, especially in Senegal.

The objective of this study was to report on the practical aspects of BT and post-transfusion complications in SCD patients.

Materials and Methods. The study included 253 SCD patients (homozygous SS, heterozygous SC, Sβ0 thalassemia, Sβ+ thalassemia) consisting of 153 transfused and 100 non-transfused SCD.

SCD-transfused had undergone at least two transfusions during follow-up; blood samples were taken at least one month before from any vaso occlusives crisis (VOCs) or infections. VOCs were defined as bone pain that lasted 48 hours or required hospitalization. All patients were diagnosed by hemoglobin electrophoresis at alkaline pH, regularly monitored every three months, and a medical record included socio-demographic, clinical, and biological data. Informed consent was obtained for all patients before the samples.

This case-control study was carried out at the Clinical Hematology Department (Dakar, Senegal) over six months. Three samples (5ml) were taken; EDTA samples for detection and identification of irregular antibodies, citrate samples for viral hepatitis B (HBsAg), hepatitis C (VHC antibodies), and HIV (HIV 1 and 2 antibodies, and P24 antigen), and a serum sample for ferritin assay. Blood samples collected were immediately centrifuged at 3500 rpm. The serum was aliquoted and stored at -80°C.

Viral markers screening (HBsAg, VHC antibodies, HIV antibodies) was performed using chemiluminescence methods (Architect i1000sr, Abbott, USA). Searching for irregular antibodies was carried out by gel filtration test (Bio-Rad reagents, USA). Ferritin assay was performed by immunoassay (PLC Axsym, Abbott, USA). The reference values of ferritin level were defined between 7 and 250 ng/ml (Women) and 20-300 ng/ml (Men). Iron overload was defined when ferritin level was greater than or equal to 1000 ng/ml.

Socio-demographic variables were age and sex. Clinical variables consisted of the duration of follow-up, number of VOCs, acute complications (acute anemia, priapism, acute chest syndrome, infections, stroke), chronic complications (biliary lithiasis, leg ulcer, osteonecrosis, cardiac failure, renal failure). Laboratory variables consisted of blood count and hemoglobin electrophoresis data. Transfusion data were the frequency of transfusions, type of blood product, transfusion indications, and transfusion modalities. In addition, risk factors for the occurrence of transfusion complications were studied.

Data were collected and analyzed using Epi Info version 3.5.4. Means were calculated with a 95% confidence interval. Chi2 test was used to study the frequency data (significance of $p < 0.05$). In addition, the correlation coefficient (r) between ferritin level and RBCs number received was determined (r between -1 and 1).

All patients signed an informed consent form prior to participation in the study. For minors, the signature was obtained from one of the parents.

Results.

SCD Patients Baseline Characteristics. The mean age was 28.5 years (5 - 59), and the sex ratio was 0.86. Homozygous SCD was more common (95.3%), $S\beta^0$ thalassemia (2.62%), SC form (1.31%), and $S\beta^+$ thalassemia (0.65%). The mean duration of follow-up was 9.1 years (2 - 26). The mean number of VOCs per year was 2 (1 - 6). Acute complications consisted of anemia (63.98%), infections (26.69%), priapism (5.51%), stroke (2.12%), acute chest syndrome (0.85%) and renal failure (0.85%). Chronic complications were found in 39.87% of SCD-transfused and consisted of femoral head osteonecrosis (27.87%), biliary lithiasis (32.79%), leg ulcers (16.39%), pulmonary arterial hypertension (16.39%), and renal failure (6.56%). We had no statistical difference in baseline characteristics

Table 1. Baseline characteristics of SCD-transfused and SCD non-transfused patients.

Parameters	SCD-transfused (n=153)	SCD non-transfused (n=100)	p
Age (years)			
≤ 20	34	22	0.78
> 20	119	131	
Sex (sex ratio: 0.86)			
Male	71	46	0.73
Female	82	54	
SCD profile			
Homozygous	145	95	0.6
Others (SC and Sβ thalassemia)	08	05	
VOCs/an			
Mean	2.62	4.09	0.4
Ecart type	2.5	2.99	
Hospitalisations			
Mean	5.9	0.21	0.74
Ecart type	4.04	1.61	
Chronic complications			
Mean	0.6	0.27	0.9
Ecart type	0.4	0.08	
Basic hemoglobin level (g/dl)			
Mean	7.71	8.84	0.93
Ecart type	1.59	1.81	

comparing transfused and non-transfused SCD patients **(Table 1)**.

Blood Transfusion Practice. According to transfusion methods, simple transfusion was performed in 92.81%, transfusion exchange in 18.95%; 14.37% of the patients were submitted to a blood transfusion program. Transfusion indications consisted of acute anemia (57.06%), prolonged VOCs (14%), pregnancy management (10.5%), surgery (7%), leg ulcers (4.2%), infections (2.8%), priapism (1.4%), acute chest syndrome (2.1%) and stroke (0.7%). RBCs were administered to 93.46% and whole blood to 6.54%. Mean number of RBCs transfused by patient was 10 (2 - 48); 43.14% had received between 2 and 5 RBCs **(Figure 1)**.

Post-Transfusion Red Cell Alloimmunization (RCA). The prevalence of RCA was 16%. Anti-Rhesus and anti-Kell

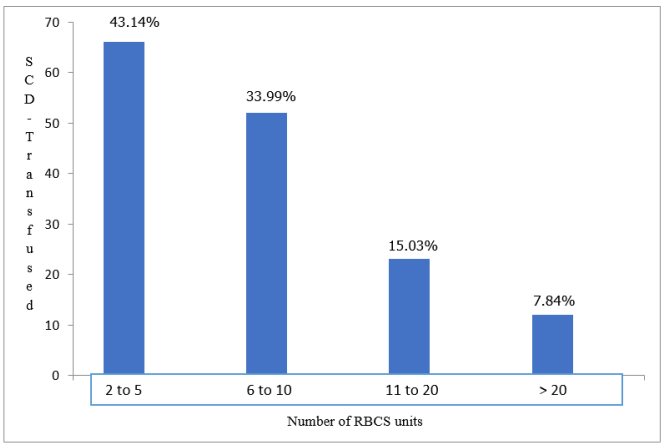

Figure 1. SCD-Transfused patients and number of RBCS received.

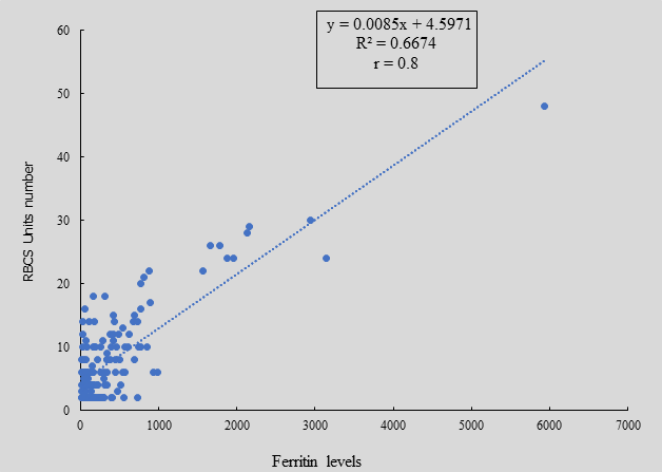

Figure 2. Correlation between RBCS units received and ferritin levels.

alloantibodies were predominant with 34.19% and 23.67% respectively **(Table 2).**

According to the distribution of alloantibodies, 14 SCD-transfused had a single alloantibody (58.3%), 5 patients had two alloantibodies (20.83%) and 5 other patients had three alloantibodies (20.83%).

Post-Transfusion Iron Overload. Median value of ferritin level was 339.5 ng/ml (16 - 5941). Twelve patients (7.84%) had ferritin levels more than 1000 ng/ml and received more than 20 RBCSs. We observed that ferritin level was correlated of blood transfusions frequency (r = 0.8) **(Figure 2)**.

Transfusion-Transmitted Infections (TTI). The prevalence of VHC in SCD-transfused was 1.33% and 1% in non-transfused (p = 0.64). The prevalence of VHB was 2% in SCD-transfused and 3% in non-transfused

Table 2. Frequency and specificity of anti-erythrocyte alloantibodies.

Blood groups Systems (n=7)	Allo-antibodies (n=24)	Number (n=38)	Frequency (%)
Rhesus (n=13 ; 34.19%)	anti RH1	05	13.15
	anti RH3	01	2.63
	anti RH4	01	2.63
	anti RH2	04	10.52
	anti RH (Cw)	02	5.26
Kell (n=9; 23.67%)	anti kpb	04	10.52
	anti k	04	10.52
	anti K	01	2.63
Duffy (n=4; 10.52%)	anti Fya	04	10.52
Kidd (n=1; 2.63%)	anti kb	01	2.63
Lewis (n=2; 5.26%)	anti Lea	01	2.63
	anti Leb	01	2.63
MNSs (n=2; 5.26%)	anti S	01	2.63
	anti M	01	2.63
Lutheran (n=7; 18.41%)	anti Lua	03	7.89
	anti Lub	04	10.52

Table 3. Risk factors associated with infectious markers, RCA and iron overload.

Parameters	**Patient's characteristics**		**p**
Risk Factors of RCA	**SCD alloimmunised (n=24)**	**SCD Non-alloimmunised (n=126)**	
Age (<20 years /≥ 20 years)	3/21	24/102	0.4
Sex (M/F)	10/14	58/68	0.48
VOCs (< 3 VOCs/≥ 3 VOCs)	84/59	9/1	0.31
RBC units received (< 20/≥20)	17/7	100/26	0.03
Risk Factors of iron overload	**Ferritin levels**		
	(1000 ng/ml, n=141)	**(≥ 1000 ng/ml, n=12)**	
Age (<20 years / ≥ 20 years)	29/109	4/8	0.27
Sex (M/F)	69/74	7/5	0.18
VOCs (< 3 VOCs/ ≥ 3 VOCs)	84/69	9/4	0.31
RBC units received (<20/ ≥20)	141/0	0/12	0.023
Risk Factors of infectious markers	**SCD-transfused (n=150)**	**SCD non-transfused (n=100)**	
Anti HCV antibodies	2(1.33%)	1 (1%)	0.648
HBs Ag	3 (2%)	3 (3%)	0.456
Anti-HIV antibodies	0	0	

(p = 0.45). Anti-HIV antibodies were not found neither in SCD-transfused than non-transfused **(Table 3)**.

Risk Factors Occurred Post-Transfusion Complications. The number of RBCs transfused was the only risk factor for RCA (p=0.03) and for iron overload (p=0.023). In this study transmission of infectious agents was not observed after blood transfusions **(Table 3)**.

Discussion. BT is an essential treatment in the management of SCD. Its usage is different from one country to another depending on the type of indication.[12,16,17] The objective of BT in SCD is not only correct chronic anemia but also to decrease HBS level and therefore to prevent or treat SCD complications whereas in case, of a simple or a transfusion exchange, either in an acute context or during a transfusion program.[3,6] Iterative transfusions are exposed to RCA, infectious and iron overload which pose a great risk of morbidity and mortality for SCD patients.[4,5]

In this study, simple transfusion was performed in the majority of cases and few patients had a chronic transfusion program. We confirm that our patients are less transfused as compared to other SCD cohort in Africa and in the world.[16,17] The lower severity of the Senegal's haplotype means that patients have few symptoms with less than 3 VOCs per year and transfusion indications dominated by acute anemia and prolonged VOCs, which are more random than scheduled.[12]

BT is an important treatment for some complications of SCD. On the contrary, transfusion may lead to alloimmunization to red blood cell antigens, with such alloantibodies putting patients at risk for acute or delayed hemolysis and increasing difficulty finding compatible RBCs. In addition, SCD patients are more susceptible to developing RBCs alloantibodies than non-SCD multiply-transfused for not completely understood

reasons.[18,19]

The phenotypic and antigenic disparity between blood donors and SCD patients partly explain the appearance of RBCs alloantibodies.[20] In our study, the RCA rate was 16%. RCA frequency has been shown to increase with the BT.[10,15,21] In Africa, where SCD-patients are rarely on a long-term transfusion, RCA rates are lower.[23,24,25] Unlikely in developed countries, in which SCD-patients receive more RBCs, alloimmunization is higher, often reaching half of SCD-patients.[15,26] These high rates of RBCs in developed countries could be explained by genetic differences in blood group antigens distribution between black SCD-patients and Caucasian blood donors.[18,27] Extended phenotyping blood group systems between blood donors and SCD-patients would reduce the risk of RCA.[22,28] Thirty-eight different antibodies were identified in 24 SCD-transfused with positive irregular antibodies detection. These alloantibodies were mainly directed against Rhesus and Kell systems antigens. Anti-Rhesus and anti-Kell specificities were reported by most studies in Africa or developed countries.[21,29] The high immunogenicity of these two systems other than the ABO system could partially explain the high incidence.

Given the importance of polymorphism in blood group systems, the number of epitopes defining an erythrocyte antigen, BT may only be one of many RCA risk factors.[18] BT remains a critical component of care for acute and chronic SCD complications. Randomized clinical trials demonstrated the benefits of transfusion therapy to prevent primary and secondary strokes and post-operative acute chest syndrome. Despite overall improvements in blood inventory safety, adverse effects of BT are prevalent among SCD-patients and include RCA, acute and delayed hemolytic BT reactions.[9]

BT plays a prominent role in the management of SCD-patients but causes significant iron overload. As transfusions are used to treat severe complications in SCD, it remains difficult to distinguish whether organ damage is a consequence of iron overload or is due to the complications treated by BT. Better BT management has resulted in increased survival, but prolonged exposure to iron puts SCD-patients at greater risk for iron-related complications that should be treated.[13,30] Post-transfusion iron overload causes serious organ damage. Excess iron accumulates in the parenchymal tissues of different organs and causes degenerative lesions due to its toxicity.[31,34,35] Less than 10% of SCD-transfused received more than twenty RBCs units during follow-up. All these patients had a very high ferritin level (> 1000ng/ml). Literature data show that organs' iron overload risk appears when ferritin level is greater than 1000ng/ml,[32] confirming our hypothesis that iron overload is correlated with the frequency of RBCs transfused.[33] However, it should be noted that serum ferritin assay is a good sensitivity marker but of poorer specificity for detecting iron overload in SCD-polytransfused patients because the inflammatory phenomena are more frequent in SCD.[35] The choice of serum ferritin assay as iron overload evaluation method in our study is guided by the fact that this method is more accessible and less costly than others. However, it can have drawbacks because hyperferritinemia can be related not only to organs' iron overload but also to pathologies frequent in SCD like liver disease, inflammation or VOCs.[36] Another alternative would be the measurement of unbound plasma iron which evaluates toxic iron fraction, but unfortunately, this test is not available in current practice.[37] Direct methods such as the determination of the intrahepatic iron concentration by hepatic biopsy, magnetic susceptometry or nuclear magnetic resonance imaging (MRI), and myocardial iron overload by MRI make it possible to accurately assess the organs iron overload.[30] Direct methods are more reliable but rarely accessible, so serum ferritin assay is more widely used in Africa.[32,38]

SCD-patients often require RBCs transfusion for clinical complications and then may be exposed to transfusion-transmitted infections.[14] The prevalence of VHB and VHC was low in SCD-transfused in Senegal, and no HIV antibodies were found in any patient. This prevalence is much lower than those found in other countries in Africa.[43,44] This low prevalence is explained by the progress in the medical selection of blood donors and the strengthening of infectious transfusion safety through the systematic screening of these infectious agents.[11] Comparing the prevalence of infections in the Senegalese population, we find that HBsAg was lower (11%) and anti-HCV (2.2%) and anti-HIV antibodies (0.7%) were slightly higher than in other African countries.[45] We confirm that TTI is more frequent in Africa.[46] VHB is more common, affecting more than 20% of SCD-polytransfused in some countries,[47,48] followed by VHC.[49] HIV antibodies were not found in this study but were present in studies carried out in several Africa countries with sometimes very high rates.[48,50] This infectious risk in multi-transfused patients is lower in developed countries.[51,52] Establishing infectious blood safety by the genomic screening of infectious markers is the real goal. In Africa, infectious tests which are used do not make it possible to cover the serological period resulting in a persistent residual risk of TTI.[46,52]

Risk factors of RBCs transfused were age, gender, chronic complications, mean baseline hemoglobin level, and number of RBCs-transfused. The only risk factor associated with RCA and iron overload was the number of RBCs transfused. No factors were associated with TTI occurrence by comparing SCD-transfused and non-transfused.

The pathogenesis of alloimmunization is not well understood, and initiatives that aim to reduce the

incidence of alloimmunization are generally expensive and either ineffective or unproven. Future reductions in the costs associated with genotype matching could make a largescale program economically feasible. Novel techniques to identify patients at the highest risk for alloimmunization could improve the cost-effectiveness of antigen matching programs.[39] Judicious use of BT, optimization of red cell antigen matching, and the use of erythrocytapheresis and iron chelation can minimize adverse effects. Early recognition and management of hemolytic transfusion reactions can avert poor clinical outcomes.[9] Identifying genetic markers may help predict which patients are at risk of forming alloantibodies. This study found 19 moderately associated SNPs, among others, SNPs in TLR1/TANK and MALT1 were associated with a higher alloimmunization risk, while SNPs in STAM/IFNAR1 and STAT4 conferred a lower alloimmunization risk.[40]

The strong correlation between ferritin level and RBCs received is confirmed in some studies,[32] while others emphasized a lack of relationship between the two parameters.[16,38] Therefore, ferritin assay must be serially performed, and the screening must be made in the basal state without VOCs. The prevention of post-transfusion iron overload is based on the optimization and regulation of BT in managing chronic anemia.[41] In addition, Erythrocytapheresis reduces iron overload and allows a longer interval between procedures without a higher RBCs requirement from the second year on automated RBCs exchange.[42]

Conclusions. Post-transfusion iron overload and RCA strongly correlate with BT frequency, which is not the case with infectious agents (HIV, HBV, HCV). So, we recommend optimization of transfusion practices, extensive phenotyping blood groups, serial ferritin screening after twenty RBCs-transfused, and TTI screening before and after transfusion for improved blood safety in SCD-patients.

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