ORIGINAL ARTICLE

Red blood cell exchange in children with sickle cell disease

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Abstract

The aim of our study was to assess the efficacy of red blood cell exchange (RBCx) using a Spectra Optia® automated apheresis system in children with sickle cell disease (SCD). We used automated RBCx to treat acute and chronic complications in 75 children with SCD who had a median age of 10 years [7–13]. We analyzed 649 RBCx sessions. Peripheral venous access was limited in a number of the children, and thus a femoral double-lumen central venous catheter was required. We recommend heparin locking with 500 units in each lumen of the catheter. To prevent complications, we ensured that all patients had achieved a post-RCE HbS level of $< 30\%$. For chronic transfusion, with a post-RCE Hb level of approximately 10–11 g/dL, a blood exchange volume of ≥ 32 mL/kg, and an interval between each RBCx procedure of ≤ 30 days, the residual HbS level was maintained below 30%. For acute transfusion, a post-exchange Hb level ≥ 10 g/dL ($p < 0.001$) and a total exchange volume ≥ 35 mL/kg ($p = 0.001$) were the best way to reduce HbS to $< 30\%$. AUC was 0.84. Our results show that erythrocytapheresis was useful and safe for children with SCD.

Keywords Erythrocytapheresis · Red blood cell exchange · Sickle cell disease · Target HbS level · Heparin locking

Introduction

Sickle cell disease (SCD) refers to a group of autosomal recessive genetic disorders characterized by the synthesis of abnormal haemoglobin: sickle haemoglobin S. This is the result of the substitution of a single amino acid (Glu $\rightarrow$ Val) at the sixth position of the β-chain of normal haemoglobin (HbA) [1, 2]. This single point mutation leads to polymerization of HbS and red cell sickling under deoxygenated conditions. Homozygous SS is generally considered to be the most severe form of SCD. Compound heterozygotes, in whom HbS is combined with a different mutation in the second β-globin gene, such as HbC, D, OArab, or β-thalassemia can also be affected, with variable genotypes. SCD can result in severe complications including chronic pain, end-organ dysfunction, stroke, life-long suffering, poor quality of life, and early mortality. Treatments include medications to reduce pain and to prevent complications (e.g., hydroxyurea), and blood transfusions, as well as a bone marrow transplant in patients who have a related donor [3, 4].

Red blood cell (RBC) transfusions are often used to treat acute complications of SCD. The purpose of RBC transfusion is to increase oxygen distribution to the tissues and/or to replace the rigid sickle-shaped RBCs with healthy deformable RBCs [5]. Transfusion can also be part of a regular long-term transfusion program to prevent SCD complications. When the goal is reduction of the HbS level, exchange transfusion is the therapy of choice [6, 7] as it allows for better control of the blood volume and viscosity, in addition to decreasing the risk of iron overload [8]. A red blood cell exchange (RBCx) can be accomplished manually by bleeding and transfusion or through the use of an apheresis device that separates the plasma from the RBCs, removes and replaces the patient's red blood cells, and then returns the plasma to the body [9–12].

The aim of our study was to describe the efficacy of RBCx procedure using a Spectra Optia® automated apheresis system [13–15] in children with SCD.

In memoriam of Thierry Basset.

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Materials and methods

Study site

Cayenne Hospital is a 510-bed general medical centre that is a referral and teaching hospital, and it runs the only sickle cell centre for children and adults (created in September 2014) in the country. The study population was part of a pre-existing cohort, improving the quality of management of SCD in French Guiana: "Epidemiology of predictive factors of acute clinical events," that enrolled approximately1000 patients.

Study design

Before 2012, transfusion exchanges were partial exchanges by removing 25 mL/kg of blood from the patient and administering 25 mL/kg of donor RBCs and 15–20 mL/kg of normal saline with an interval of 4–6 weeks between two exchanges. Since the implementation of the Spectra Optia®system in our department in April of 2012, we have exclusively used the Spectra Optia® apheresis system for RBC exchange. The Spectra Optia® automated apheresis system is manufactured and supplied by Terumo Medical Corporation. It has several applications relating to the in-situ separation of blood components, including automated RBE exchange and depletion exchange in adults or children with sickle cell disease. Since 2017, for patients with abnormal transcranial Doppler (TCD) velocities, we provide a transfusion exchange program for a year before switching to hydroxyurea (HU) or hydroxycarbamide [16, 17].

Exchange transfusion procedure

The vascular access consisted of either peripheral vein or femoral central double-lumen venous catheterisation. Using each patient's height, weight, gender, pre-RBCx Hct, pre-RBCx HbS, post-RCE Hct goal, and post-RBCx HbS goal, the volume of RBCs to be used in each procedure was calculated automatically when their weight was > 25 kg. For the patients weighing less than 25 kg, the volume of RBCs in milliliters was calculated by the formula Weight × 70. The RBCx were performed by a nurse, with constant medical supervision, as previously described [16, 17]. Given the frequent presence of clots in the lumen of the central catheter, which makes the procedure difficult; we decided to administer heparin-lock solution, with 500 units in each lumen of a double-lumen central venous catheter.

Automated depletion/RBCx protocol

For patients receiving chronic transfusions, when the hemodynamic state of the patient as well as the hematocrit level allow it (hemoglobin level ≥ 10 g/dL), we use the isovolemic hemodilution approach for the erythrocytapheresis procedure by combining two protocols, the depletion of red blood cells followed by transfusion exchange. This helps to reduce the blood consumption of donors while maintaining the efficiency of the exchange. We use this procedure, as described in previous publications [18, 19]. However, this procedure is not advised for acute indications for RBCx or recent history of stroke or transient ischemic attack, severe vasculopathy, or severe cardiopulmonary disease.

Data collection

Since April 2012, we have prospectively recorded all of the information regarding exchange transfusions in adults and children with SCD at our centre in an Excel database. All of the patients underwent a complete blood count, determination of the levels of ferritin, LDH, and serum electrolytes, as well as haemoglobin electrophoresis, hepatitis B, C, HIV serologies within the 24–72 h prior to each RCE procedure. Our SCD population exclusively received transfusions with blood systematically matched for ABO, Rh, C, c, E, e, and Kel antigens. After each RCE procedure, the following parameters before and after the RCE were recorded: RBCx, Hb, HbS, ferritin, and LDH levels. The other parameters were the indication for RCE, the intravenous access, the RBCx duration, the quantity of blood exchanged in ml/kg, the interval between two RCE procedures, adverse events, and complications.

Ethical and regulatory aspects

The parents or authorized representatives of the patients provided written and informed consent to participate in this research. The study cohort was presented to the Cayenne General Hospital Ethical Committee (Number 1-2017-V2) and the database was declared to the French Data Protection Authority (Number 3Yj157849 3#).

Statistical analyses

The data were analysed using STATA 15.0 (Stata Corp LP, College Station, TX, USA) software. The results are expressed as medians ± the standard deviation. Fisher's exact test was used to study the categorical variables while the Kruskal–Wallis test was used to study the non-Gaussian variables. The factors associated with the outcomes were analysed by unconditional multiple logistic regression. For all of the tests, a p value of 0.05 or less was considered statistically significant. We used a stepwise univariate model to calculate the best blood exchange quantity, the best post-Hb level, and the best interval between RBCx procedures.

Results

Seventy-five children, with a median age of 10 years [7–13], were enrolled. There were 30 females and 45 males, of whom 64 had the SS genotype (85%), 8 were SC (11%) and 3 were S-βThalassemia (4%). The transfusions were carried out manually 23 times (3%) and by automated RBCx 626 times (97%). Figure 1 shows the distribution of the RBCx procedures performed at our centre since 2012.

Exchange transfusion indications

The preoperative prevention was the first indication, followed by acute chest syndrome (Table 1). For the preoperative prevention, all of the patients had achieved a post-RBCx HbS level of < 30%, as this is a mandatory condition imposed by the anaesthesiologist.

Side effects and complications

The side effects and complications are summarized in Table 2. In patients who required a central line, no perioperative complications were observed. However, three episodes of deep vein thrombosis requiring heparin treatment occurred in three patients. These thromboses occurred in children aged 11, 12, and 13 years, in whom we were obliged to maintain the catheter for more than 12 h after the end of

Table 1 Exchange transfusion indications

Indication	Number	%
Preoperative	40	35
Acute chest syndrome (ACS)	27	24
Prevention before a long flight	11	10
Primary stroke prophylaxis	10	9
Secondary stroke prophylaxis	9	8
Prevention of recurrent pain	7	6
Repeated VOC/ACS despite HU	3	2.6
Acute stroke	2	1.8
Priapism	2	1.8
Liver complications	1	0.9
Retinopathy	1	0.9

the erythrocytapheresis procedure. In two cases of unilateral thrombosis of the femoro-popliteal vein, the evolution was rapidly favorable after removal of the catheter and anticoagulant treatment. The third patient presented a bilateral ilio-femoral-popliteal vein thrombosis, complicated by a right pulmonary embolism, despite catheter removal.

Intravenous access

A femoral central catheter was used 353 times (54%) and the peripheral vein 296 times (46%). None of the patients had an arteriovenous fistula. We frequently used Doppler ultrasound to find the vein.

Chronic transfusion for primary and secondary stroke prevention

Between 2012 and 2019, 19 children (13 boys and 6 girls), with a median age of 8 [7–10] years were placed on chronic transfusion for stroke prevention at our centre. Of these, 17 had homozygous SCD and two had sickle β^0-thalassaemia. Nine had a history of stroke and ten an abnormal transcranial Doppler (TCD) velocity (and normal magnetic resonance imaging (MRI) brain scan). One patient developed red blood cell alloantibodies. Of the 17 patients, 4 required iron chelation. For 24% of the patients, the HbS level was below 30%.
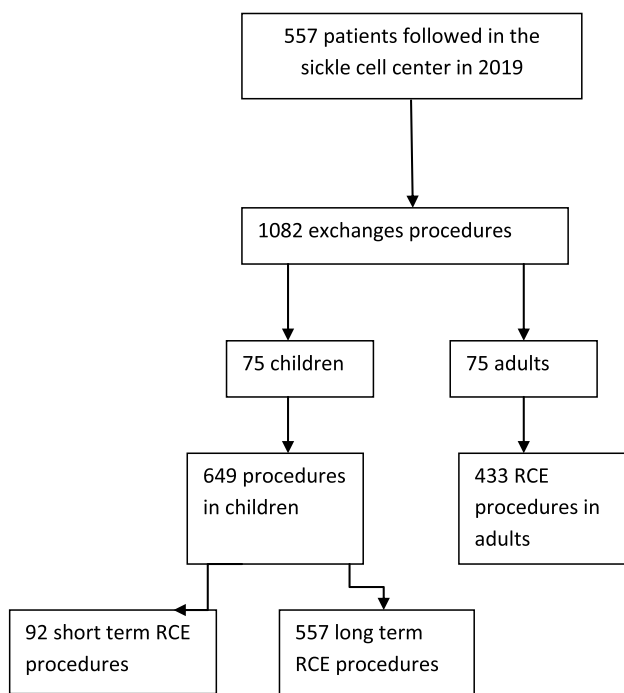

Fig. 1 Flowchart for our cohort

Table 2 Adverse effects and complications of RCE

Side effects and complications	Number	%
Iron overload	9	45
Non-haemolytic transfusion reaction	4	20
Thromboembolic complications	3	15
Allergic reaction	2	10
Acute haemolytic transfusion reaction	1	5
Presence of blood clots in the central catheter	1	5

The target median HbS level was 47% [30–53]. None of the 8 patients with a history of stroke experienced a stroke recurrence. Among the nine patients with abnormal TCD, we controlled TCD every 3 months and prescribed hydroxy-carbamide before stopping RBCx procedures, one year after the normalization of the TCD. But one of them presented an ischemic stroke 6 months after stopping RBCx procedures and 2 others again have a pathological TCD respectively 6 months and 1 year after stopping the RBCx procedures. In these 3 children, we took over the RBCx procedures.The other indications for chronic RBCx concerned two 9 and 11-year-old girls for recurrent VOC and a 12-year-old boy for recurrent ACS, respectively, despite a well-conducted treatment with HU.

To understand why there were relatively few patients with a residual HbS level below 30%, we performed a logistic regression in order to determine the optimal target post-RBCx levels for haemoglobin, the haematocrit, and the interval between two RCE procedures to reduce the HbS level below 30% (Table 3). Based on the results of stepwise logistic regression, we came to the conclusion that the apheresis machine should be programmed with the aim of achieving a post-exchange Hb level of approximately 10–11 g/dL (or a post-exchange haematocrit at ~ 30%) ($p < 0.001$). The best total exchange volume to maintain a residual HbS level of < 30% was > 32 mL/kg of body weight ($p = 0.006$). The best interval to maintain residual HbS level of < 30% between each RBCx procedure was ≤ 30 days ($p < 0.001$).All of the patients undergoing chronic transfusion were given extensively matched units of packed red blood cells. One patient developed red blood cell alloantibodies. None of the patients underwent seroconversion for hepatitis B.

Transfusions for treatment of acute events or similar

Certain situations required an urgent reduction in HbS%. This concerned ACS in 27 cases, prophylaxis before a long flight in 11 cases and current pain in 7 cases (Table 1). Among the other situations of occasional transfusion, there was preoperative erythrapheresis. We had no recurrence of ACS nor VOC, as long as the patient was in the chronic transfusion program. We also performed a multiple logistic regression in order to determine the optimal target post-RBCx levels for haemoglobin, haematocrit, and

the total blood RBCx volume allowing to reduce the HbS level below 30%. This analysis showed that in the case of acute RBCx, in order to reduce the rate of HbS < 30%, the apheresis machine should be programmed with the aim of achieving a post-exchange Hb level ≥ 10 g/dL (or a post-exchange haematocrit at ≥ 30%) ($p < 0.001$) and the total exchange volume ≥ 35 mL/Kg of body weight ($p = 0.001$). In this multivariate model, the area of the ROC curve was 0.84 (Fig. 2).

Transfusion-acquired infections

We had no cases of contamination by hepatitis B, C, HIV, HTLV1 and 2, Parvovirus B19 or plasmodium.

LDH and ferritin levels

The median ferritin level was 77 μg/L (Interquartile range IQR 36–342) before and 62 μg/L (29–254) after the RBCx procedure. There was also a decrease in LDH, with a median level of 466 IU/L (IQR 295–583) before and 396 IU/L (263–476) after.
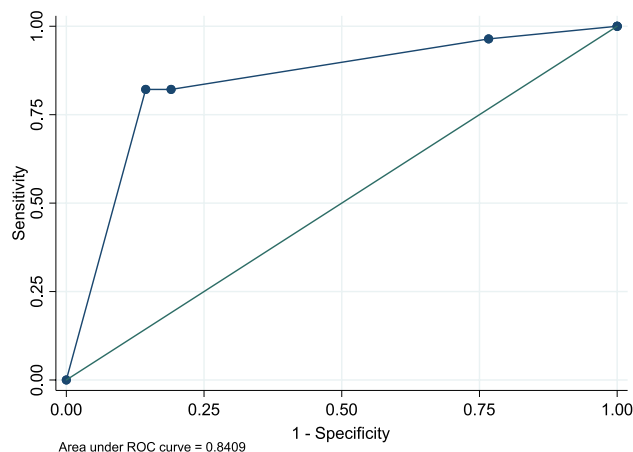
Fig. 2 ROC curve testing our multivariate model. The area under the ROC curve was close to 1, confirming the quality of the model. The ROC analysis is used here to quantify how accurately our medical diagnostic test (post-exchange Hb level ≥ 10 g/dL (or a post-exchange haematocrit ≥ 30%) and total exchange volume ≥ 35 mL/kg) can discriminate between post-HbS level < or > 30%

Table 3 Logistic regression: what are the target Hb (or Ht) levels, the volume of RBC, and the interval between two procedures

Variables	Residual HbS < 30% n (%)	Residual HbS ≥ 30% n (%)	OR (95% CI)	p
Interval between ERC < 30 days	142 (24)	443 (76)	0.37 [0.22–0.62]	< 0.001
Volume of exchanged blood > 32 mL/kg	395 (68)	190 (32)	2.03 [1.2–3.37]	0.006
Target haemoglobin level > 10 g/dL	155 (27)	430 (73)	14.3 [3.5–59.4]	< 0.001

Discussion

Controlled studies have shown that TCD is effective at identifying children at high risk for stroke [20, 21]. The Stroke Prevention Trial in SCD, by Adams et al. found a 92% reduction in the annual incidence of primary stroke in children with an abnormal TCD velocity [22]. Currently, the standard care to reduce the incidence of primary and secondary stroke is chronic exchange transfusion allowing the target HbS level to be maintained at < 30%. Although the methods of transfusion in these trials included simple transfusion and RCE, in our centre, we opted for erythrocytapheresis, as apheresis machines have been available in our hospital since 2012. In addition, erythrocytapheresis reduces iron overload and it allows for a longer interval between the RCE procedures [8]. The main problem, however, with this procedure is the significantly increased blood requirements [23]. In French Guiana, uncertainty regarding the safety of blood products led to the cessation of blood donations in April 2005 [24]. Approximately two-thirds of the supply of packed RBC in French Guiana comes from mainland France and one-third comes from the Guadeloupian French Blood Establishment. Thus, erythrocytapheresis could have been affected at our centre. Fortunately, we have not experienced any problems to date with the blood supply. Despite the disparity between the donors and the recipients, only one patient in our study developed new RBC antibodies. However, none of our patients experienced seroconversion for hepatitis B, hepatitis C, or HIV. These findings support the feasibility of chronic transfusion in patients with SCD at our centre. In accordance with the literature, long-term transfusion therapy has been associated with complications, such as transfusional iron overload, transfusion reactions, thromboembolic complications, and allergies [25]. These side effects were minimal, however, because we exclusively used the automated apheresis system. In addition, the use of heparin locking allowed us to minimize the risk of thrombosis. We consequently highly recommend the use of this procedure. We did not compare the overall costs between manual exchange transfusion and erythrocytapheresis. Several authors have claimed that the cost of erythrocytapheresis is not higher than that of manual exchange transfusions [26, 27].

We set a target HbS level of 30%. In our study, only 24% of the patients achieved an HbS level below 30% after chronic transfusion, despite the use of erythrocytapheresis. This could be due to a lack of homogeneity in our practices. However, higher HbS levels prior to the next exchange transfusion have frequently been reported [28–30], thereby underscoring the difficulty with complying with the recommendations. Moreover, the statistical

analysis showed that with a post-exchange Hb level of approximately 10–11 g/dL, a blood exchange volume of ≥ 32 mL/kg, and an interval of ≤ 30 days between each RBCx procedure, the residual HbS level can be maintained below 30%. It is often difficult though to attain this level. However, the optimal pre-exchange Hb level for stroke prevention has not been clearly defined. Cohen et al. have confirmed that a target pretransfusion HbS level of 50% imparts a high level of protection against recurrent stroke in SCD [31]. Moreover, in the SWiTCH study in the United States, pretransfusion HbS levels ranged between 22 and 51% in the various centres [32]. Some studies have reported a target HbS level of > 30% during stroke recurrence [33, 34]. Despite a target HbS level of 47%, we did not encounter a single stroke recurrence.

Although chronic transfusion is presently the only proven therapy for primary or secondary stroke prevention in sickle cell children, recent studies have demonstrated the efficacy of HU in maintaining normal TCD velocities after at least 1 year of chronic blood transfusion [35]. These studies are promising, as the duration of chronic transfusions is unknown when the child lacks a compatible HLA donor for a hematopoietic stem cell transplantation. Indeed, as in the case with other therapeutic aphereses, good vascular access is required, although this can often be difficult to obtain in paediatric sickle cell patients requiring a chronic exchange transfusion program. Regarding the punctual transfusion, our results were satisfactory. We had no difficulty achieving hemoglobin S < 30%. Also, a multivariate model now allows us to improve our transfusion performance. Whenever possible, peripheral access is ideal for RBCx because it is safer. With patients for whom peripheral venous access is impossible, a double-lumen femoral catheter (used for very short-term access) with a high flow is needed, and this can be associated with infections, thrombosis, and difficulties with blood withdrawal [36–38]. In addition, the use of femoral lines is not standard or required in the majority of patients. Arteriovenous fistulas have been suggested [38, 39], but there has been a paucity of data to date in the literature regarding their use in children with SCD [38, 40].

Conclusion

Erythrocytapheresis is useful and safe for patients with SCD who require a chronic exchange transfusion program. However, the optimal pretransfusion HbS level for stroke prevention remains unclear. Despite a target HbS level of 47%, we did not encounter a single stroke recurrence. In the case of acute RBCx, to reduce the rate of HbS < 30%, the apheresis machine should be programmed with the aim of achieving a post-exchange Hb level ≥ 10 g/dL (or a post-exchange haematocrit at ≥ 30%) and the total exchange volume ≥ 35 mL/

Kg of body weight. We recommend the use of heparin locking, with 500 units in each lumen of a double-lumen central venous catheter. This procedure is less time consuming for nurses and patients and it improves the iron overload. It can also be performed successfully in children without having to resort to using a central line.

Declarations

Conflicts of interest The authors declare that they have no competing interests.

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