Red Blood Cell Exchange in children with Sickle Cell Disease in French Guiana

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Running title: Transfusion Exchange in Sickle Cell Disease

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Abstract

The aim of our study was to describe our experience using a Spectra Optia® automated apheresis system in children with sickle cell disease (SCD). We used automated red blood cell exchange (RCE) to treat acute and chronic complications in 75 children with SCD who

 doi:10.20944/preprints202007.0627.v1

had a median age of 10 years [7-13]. We analysed 649 exchange sessions. Peripheral venous access was limited in a number of the children, thus requiring a femoral central double-lumen venous catheter (CVC). We recommend the use of heparin locking, with 500 units in each lumen of a CVC. This method was well tolerated, with few complications during the procedures. For preoperative prevention, all of the patients had achieved a post-RCE HbS level of <30% since this is a mandatory condition imposed by the anaesthesiologist. 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 RCE procedure of ≤30 days, it was able to maintain the residual HbS level below 30%. Despite a target pre-exchange HbS level of 47%, we did not encounter a single stroke recurrence. Erythrocytapheresis is 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→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

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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 (RBE) exchange 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 our experience using a Spectra Optia® automated apheresis system in children with SCD [13, 14].

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 approximately1,000 patients.

Study design

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

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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) [15, 16].

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-RCE Hct, pre-RCE HbS, post-RCE Hct goal, and post-RCE 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 millilitres was calculated by the formula Weight x70. The RCEs were performed by a nurse, with constant medical supervision ,as previously described [15, 16]. 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.

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, in the 24-72 hours 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: RCE, Hb, HbS, ferritin, and LDH levels. The other parameters were the indication for RCE, the intravenous access,

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the RCE 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 RCE 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 RCE 626 times (97%). Figure 1 shows the distribution of the RCE procedures performed at our centre since 2012.

Exchange transfusion indications

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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-RCE 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.

Intravenous access

A femoral central catheter was used 353 times (54%) and the peripheral vein 296 times (46%) (Figure 2). None of the patients had an arteriovenous fistula. We frequently used Doppler ultrasound to find the vein (Figure 3).

Patients with chronic transfusion

Between 2012 and 2019, 17 children (12 boys and 5 girls), with a median age of 8 [7-10] years were placed on chronic transfusion for stroke prevention at our centre. Of these, 16 had homozygous SCD and one had sickle β^0-thalassaemia. Eight had a history of stroke and nine an abnormal transcranial Doppler (TCD)velocity. 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%.The target median HbS level was 47% [30-53]. None of the patients experienced a stroke recurrence. In order 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-RCE levels for haemoglobin, the haematocrit, and the interval between two RCE procedures to reduce the HbS level below 30%. Based on the results of stepwise logistic regression (Table 3), we came to the conclusion that the apheresis machine should be programmed with the aim of achieving a post-exchange Hb level of

 doi:10.20944/preprints202007.0627.v1

approximately10-11 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 RCE 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.

Discussion

Controlled studies have shown that TCD is effective at identifying children at high risk for stroke [17, 18]. 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 [19]. Currently, the standard care to reduce the incidence of primary and secondary stroke is discontinuing chronic 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 [20]. The main problem, however, with this procedure is the significantly increased blood requirements [21]. In French Guiana, uncertainty regarding the safety of blood products led to the cessation of blood donations in April 2005[22]. 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

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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 [23]. 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 [24-26]. 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 [27-29], 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 RCE 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 [30]. Moreover, in the SWiTCH study in the United States, pretransfusion HbS levels ranged between 22 and51% in the various centres [31]. Some studies have reported a target HbS level of > 30% during stroke recurrence [32, 33]. 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 [34].

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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. Whenever possible, peripheral access is ideal for RBCs 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 [35-37]. Arteriovenous fistulas have been suggested, [37, 38] but there has been a paucity of data to date in the literature regarding their use in children with SCD [37, 39].

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. 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.

Acknowledgements

The authors would like to thank Pr Mathieu NACHER from the INSERM U1424 of Cayenne Hospital, Rue des Flamboyants, BP 6006, 97306 Cayenne Cedex, French Guiana, for his advice and corrections.

 doi:10.20944/preprints202007.0627.v1

Authorship contributions

NE analyzed the data and drafted the manuscript, VV, EM, EC, MP, PS and FM collected the data, provided necessary logistic support and have read the manuscript. NE and FM provided critical comments on the manuscript. I confirm that all authors read and approved the final manuscript.

Disclosure of conflicts of interest

The authors declare that they have no competing interests

Funding and resources

There is no fund related to this study.

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