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Research Article

Implementation of Automated Red Blood Cell Exchange as a Transfusion Treatment for Sickle Cell Disease Patients in A Low-Middle Income Country

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Abstract

Background/Objectives: Sickle cell disease (SCD) is a prevalent genetic disorder characterized by the presence of hemoglobin S (HbS), leading to significant health complications. This study details the implementation of an automated red blood cell exchange (aRBCx) program at HEMOCE, a public blood center in Ceará, Brazil, aimed at improving management for SCD patients. **Methods**: The program was established with comprehensive protocols for patient selection, donor compatibility, and transfusion logistics, ensuring effective and safe procedures. This is a retrospective study that analyzed data on patients and procedures performed to assess the safety, feasibility and effectiveness of the aRBCX program. **Results**: From August 2023 to December 2024, 19 patients underwent 146 aRBCx procedures, using a sum of 1072 red blood cells (RBC) units. The indications for aRBCX in the study population were: secondary stroke prevention, pregnancy, recurrent vaso-occlusive crises (VOC) and acute stroke**.** Only two procedures occurred via a central line and all other 144 procedures occurred via single needle peripheral venous access with intermittent flow. Results indicated a significant reduction in hemoglobin S levels (from 48,9% to 16,0% p< 0,0001), and stable hematocrit levels (mean pre and post hematocrit were 29.0% and 28,9% respectively), with minimal adverse events reported. **Conclusions:** The successful implementation of automated RBCx at HEMOCE demonstrates the effectiveness of this approach and the feasibility of introducing it in public healthcare settings in low-middle income countries.

Keywords: Sickle cell disease, Red blood cell transfusion, Automated red blood cell exchange, Chronic transfusion, Pregnancy, Alloimunization

Introduction

Sickle cell disease (SCD) includes a group of inherited hemolytic disorders characterized by the presence of hemoglobin S (HbS). Under low-oxygen conditions, HbS polymerizes, causing red blood cells (RBCs) to take on a characteristic sickle shape. The most common and severe form of SCD is the homozygous presentation, known as sickle cell anemia (HbSS) [1]. Other forms of SCD arise when a different abnormal hemoglobin gene is co-inherited with HbS. These include HbSC and HbSβ-thalassemia, as well as less common genotypes such as HbSD [1]. SCD is one of the most prevalent genetic disorders worldwide, with an estimated 515,000 infants born with the condition each year [2]. Globally, individuals with SCD face premature mortality and debilitating chronic complications that significantly impair their quality of life. Notably, it ranks among the top fifty leading causes of non-communicable deaths worldwide, particularly in African nations [3]. Effective SCD management requires frequent transfusions, necessitating complex coordination to minimize complications such as iron overload and alloimmunization. The American Society of Hematology (ASH) guidelines advocate for aRBCX as a preferable option over simple transfusion or manual red blood cell exchange (mRBCX) for individuals with SCD requiring chronic transfusions. Furthermore, studies demonstrate that automated aRBCX is more efficient in lowering anomalous Hb levels, leading to reduced hospital admissions and enhanced disease control. The choice of treatment should consider factors such as clinical indication, baseline and target hemoglobin levels, HbS percentage, patient age, iron overload status, adherence to iron chelation therapy, and red blood cell availability [4]. According to the American Society for Apheresis (ASFA), aRBCX is recommended for individuals with SCD in certain situations: secondary stroke prophylaxis, pregnancy, preoperative management, recurrent VOC, acute stroke and severe acute chest syndrome [5]. The aRBCX can be performed in two ways: the classic exchange using only RBC units or depletion followed by exchange. The depletion/exchange or isovolemic hemodilution red cell exchange occurs through isovolemic RBC reduction (replacement of a portion of the patient's RBC volume with normal saline or albumin) followed by standard exchange with RBC units. Previous studies demonstrated that depletion/exchange procedures can be safely used in patients with SCD undergoing chronic transfusion with benefits of decrease RBC usage and increased post procedure Hct [6].

The literature highlights challenges with venous access for aRBCX, noting that 16% of patients temporarily discontinued the protocol due to the need for central access, resulting in discomfort and limited tolerance. Despite this, some measures can be taken to optimize the use of peripheral venous access, such as ultrasound-guided insertion [7]. In Ceará, there are 747 registered cases of SCD, although this figure is likely to be much higher due to underreporting. Ceará is in Northeast Brazil and has a population of nearly 9 million. It is among the six poorest states in the country, with an average annual per capita income of around R$13,992. (about USD 2,590) [8]. HEMOCE is the state public blood centre, responsible for coordinating the hemoglobinopathy program in the state. Its network includes five hemotherapy regions, comprising one central coordinating centre, in Fortaleza, the capital city, and four regional blood centres. A total of 570 patients receives ongoing care at HEMOCE.

The implementation of automated red blood cell exchange (aRBCx) at HEMOCE is part of an effort from global therapeutic strategies to identify aRBCX as a consensus for standard intervention for the treatment of acute and chronic complications of SCD [3]. The aim of this program is applying a significant advanced technology in

transfusion medicine, particularly for SCD patients unresponsive to other transfusion modalities such as top up or partial manual exchange transfusion. aRBCx offers a controlled approach to removing sickle cells while preserving oxygen-carrying capacity, reducing iron accumulation, and minimizing transfusion-related complications [9]. It is crucial to emphasize the great need to report data on the implementation of an aRBCX program in Ceará, Brazil, given the limited data availability of this exchange transfusion modality nationwide. By sharing these findings, we can demonstrate the feasibility of introducing this treatment option in public healthcare settings not only in Brazil but also in other low-middle income countries. This single center study outlines the planning, coordination, and execution of aRBCX at Hemoce, focusing on patients selection, donor compatibility and transfusion logistics. It also evaluates the characteristics of the patients and procedure-related data, aiming to assess the efficacy, safety, and feasibility of the aRBCX program.

Materials and Methods:

The aRBCx program at HEMOCE was established with several core components: (Figure 1)

1. Protocol Development: Written protocols guided each step of the aRBCx process, from venous access placement to monitoring patient vitals and managing transfusion reactions. Protocols included patient selection criteria, aRBCx targets for hemoglobin (Hb) and HbS (or HbSC), and management of reactions to RBCs and citrate.

2. Patient Selection: Eligibility criteria were established to identify SCD patients who would benefit most from aRBCx. Indications for aRBCX followed ASFA guidelines both for chronic and episodic procedures. Priority was given to those who had experienced new acute neurological events during their chronic transfusion protocol, whether through top-up or manual RBCx. During the selection process, the risks and benefits of the RBCx procedure were thoroughly explained to the patients. Lacking viable peripheral access was a exclusion criteria. Additionally, previous alloimmunization history and availability of antigen-negative RBCs for the identified alloantibody were critical in determining eligibility.

3. Donor Selection and Recruitment: Extended phenotyping was prioritized to ensure compatibility, with efforts to recruit previously matched donors for patients in the program. All RBCs were leucodepleted, phenotypically matched for D, C/c, E/e, Kell antigens and antigen-negative for alloantibodies. Double RBC collections helped meet the needs of patients with hard-to-match phenotypes, reducing time between transfusions and improving resource availability. The recruitment team collaborated with the Immunohematology Laboratory to develop strategies for maintaining an adequate pool of compatible RBCs for scheduled patient appointments.

4. Informatics Support: A customized system was developed to ensure all patient data was available to the Immunohematology team. This system included blood type, extended phenotype, alloimmunization history, and previous transfusion records, highlighting available RBC units from previous donors throughout the state. This enabled mobilization of compatible units, reducing exposure to new donors and decreasing the risk of alloimmunization.

5. Training: Staff received training from Terumo Blood and Cell technologies, the company providing the apheresis machine (Spectra Optia), with protocols established to standardize procedures and ensure adherence to best practices. Training covered RBCx equipment, patient management strategies, and emergency response for potential complications.

6. Laboratory Support and Logistics: HEMOCE's laboratories prioritized sample processing for SCD patients requiring transfusion, fast-tracking results, and ensuring accurate matching to meet urgent transfusion needs.

7. RBC units segregation: Blood processing and distribution teams worked to segregate extended phenotype-matched RBC units specifically for aRBCx patients, crucial for avoiding alloimmunization risks and minimizing procedural delays.

8. Automated Exchange Procedure: aRBCx procedures were conducted mostly at HEMOCE's Transfusion Outpatient Clinic, equipped with trained staff to manage these complex exchanges efficiently. Patients who required urgent aRBCx therapy due to acute conditions were managed during hospitalization in tertiary facilities and HEMOCE's team and equipment were relocated to where the patients were hospitalized.

9. Statistical Analysis: A limited statistical analysis was performed as this is a retrospective study. Numerical data are presented as median, minimum and maximum values, and standard deviation. Unpaired two tailed T-test were applied, when necessary. Categorical data are presented as absolute values and frequency. The main data analyzed include patients characteristics (age, sex, weight, height, sickle cell disease genotype, and indication for aRBCX) and procedure-related data (modality, intervals between procedures, procedure duration, achieved levels of anomalous Hb - S or S+C, pre- and post-procedure hematocrit and ferritin levels, as well as the number of red blood cell units and volume of anticoagulant used).

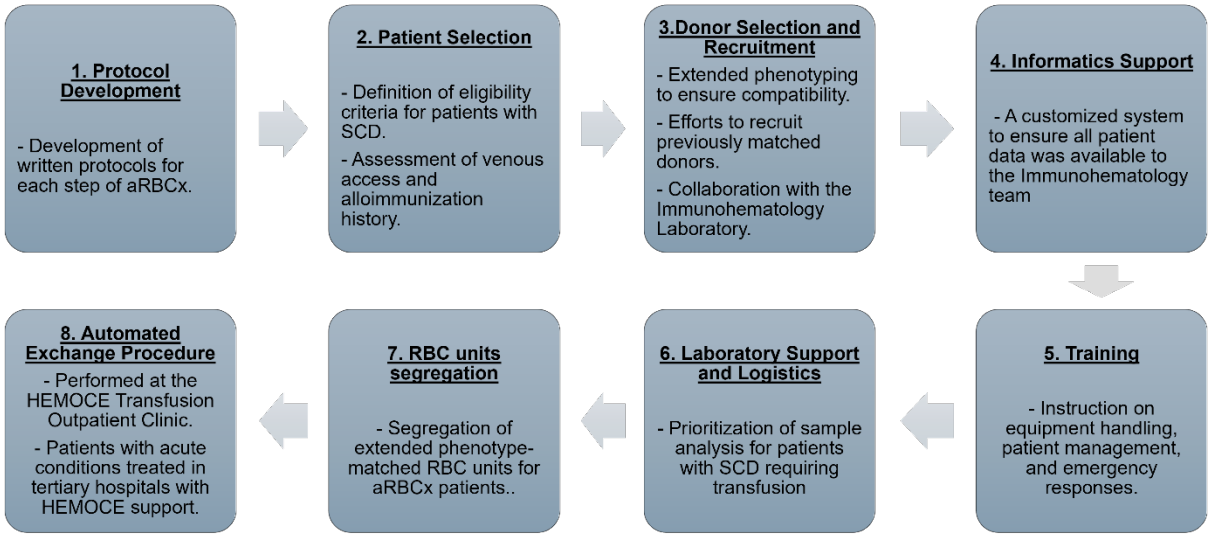

Figure: 1 Phases of automated red blood cell exchange implementation

Results

Nineteen patients were submitted to a total of 146 aRBCx procedures from August 2023 until December 2024, using a sum of 1072 RBCs units. The demographic patient parameters and the details of the aRBCx procedures are summarized in Tables 1 and 2.

The median of RBC units per procedure was 7 (3-12). The Spectra Optia apheresis machine calculated the required volume of RBC units for each procedure, considering factors such as abnormal Hb, hematocrit, patient weight and height, and the specific procedure type (exchange or depletion/exchange).

The age of the patients at the time of their first procedure varied between 18 and 50 years. The median age was 25 years. Five patients (26,3%) were male and fourteen (73,7%) were female. Regarding the anthropometric characteristics of the patients, the mean weight was 55 ± 14 kg, while the mean height was 161.2 ± 9 cm. Seventeen (89.5%) of the patients had genotype SS or Sβ^0, and two (10.5%) were SC.

The indications for aRBCX in the study population were diverse. The most common indication was secondary stroke prevention, observed in twelve patients (63.2%). Pregnancy was the indication in 5 patients (26.3%), which were selected due to complications in previous pregnancies (stillbirth, premature birth with severe intrauterine growth restriction) or recurrent vaso-occlusive crises (VOC). Lastly, one patient (5.3%) underwent the procedure due to recurrent VOC, while another one (5.3%) required aRBCX for the management of an acute stroke.

Depletion/exchange was employed in 24 aRBCX procedures, when it was feasible in patients who present with higher pre-procedure hematocrit, whereas only exchange was performed in the remaining 122 procedures.

All patients underwent the following tests before and after each aRBCX: complete blood count, quantification of HbS by High Performance Liquid Chromatography (HPLC), and serum levels of ferritin, calcium, sodium, potassium, and magnesium. Electrolyte replacement was performed in case of low serum levels or symptoms of hypocalcemia. Due to the high incidence of hypotensive reactions after aRBCx, all patients received volume expansion with intravenous 0.9% saline solution.

Adequate vascular access is essential for aRBCX to allow for high flow rates and various forms of access are used including peripheral veins and central venous access devices. aRBCX usually requires two vascular access for concurrent blood withdrawal and return, which can be a challenge in apheresis procedures. A single-needle red cells exchange has been developed to alternates blood withdrawal and return and to ensure a successful procedure in patients with poor peripheral access [10]. During our aRBCX implementation, only two procedures occurred via a central line. These patients were hospitalized due to acute complications (ischemic and haemorrhagic stroke). The patient who presented with a haemorrhagic stroke was already on secondary stroke prophylaxis (previous history of ischemic stroke) and had significant cerebral vasculopathy (Moyamoya). All other procedures,144, occurred via single needle peripheral venous access with intermittent flow. Research findings suggest

that single needle aRBCX is a viable option, effectively reducing the anomalous hemoglobin levels [11]. Retrospective comparison data of automated and manual exchange procedures in paediatric and adult patients have demonstrated that aRBCX procedures were more likely to rapidly removes RBCs containing HbS and replaces them with normal (HbA) RBCs, achieve HbS% and Hct% targets and manage iron overload and blood viscosity [12-16]. Consistent with this, our aRBCX implementation cohort data demonstrated that, the mean pos procedure FCR (fraction of remaining cells) was 32%, and mean pre and post hematocrit were 29.0% and 28,9% respectively. The mean pre and post HbS procedure (or HbS plus HbC) were 48,9% and 16.0% (p<0,0001). The median interval between sessions was 39.5 ± 13.5 days. Additionally, the mean duration of the procedure was 124.5 ± 39.6 minutes.

In our cohort, data demonstrated that from 10 patients who started the aRBCx protocol between August and December 2023 and were still in the protocol in December 2024, the median serum ferritin levels before the first procedure was 519,5ng/mL. The median serum ferritin level of these group in December 2024 was 186,5ng/mL. The volume of anticoagulant (AC) administered to the patient had a mean of 202.1 ± 72.9 mls. Adverse events occurred in 16 of 146 procedures (10,9%), which included 03 mild allergic transfusion reactions, 01 hematoma at the puncture site and 12 vasovagal reactions. None of these adverse events were considered severe. The most common complication in our results was vasovagal reactions, accounting for 12 of the 16 adverse reactions observed. Notably, 7 of the 12 vasovagal reactions (58%) occurred in only 2 patients. The incidence of vasovagal reaction in depletion/exchange modality was 20,8% (5 of 24 procedures) and the incidence in exchange modality was 5,73% (7 of 122 procedures).

Among the 19 patients who received aRBCx, alloimmunization occurred in 02 patients, resulting in the suspension of transfusions for one of them - a RhD positive who developed an anti-D.

One patient receiving ongoing care at HEMOCE and with indication for chronic transfusion continues to perform manual exchange. He did not switch to the aRBCx protocol due to alloimmunization. Four patients with indication did not start chronic transfusion (top up, manual or aRBCx), three of them due to lack of peripheral access and one due to alloimmunization.

Patient Characteristics	
Patients enrolled	19
Age (yo) median (MIN-MAX)	25 (18-50)
Sex (male : female); n (%)	5 (26,3) :14 (73,7)
Weight (kg) mean ± SD	55 ± 14
Height (cm) mean ± SD	161,2 ± 9
Genotype:	
SS/Sβº n(%)	17 (89,5%)
SC	2 (10,5%)
Indications n (%):	
- Secondary stroke prevention	12 (63,2%)
- Recurrent vase-occlusion crises	1 (5,3%)
- Acute stroke	1 (5,3%)
- Pregnancy	5 (26,3%)

Table: 1 Demographic and Clinical Characteristics of Patients Undergoing Automated Red Blood Cell Exchange Implementation

Procedure Characteristics	
Number of RBCX procedures	146 (Aug 23- Dec 24)
- RBC exchanges	122 (83,6%)
- RBC depletion/exchanges	24 (16,4%)
Interval between sessions (days), median (SD)	39,5 (13,5)
Duration of Procedure (min), (mean ± SD)	124,5 ± 39,6
Pre-RBCX Anomalous Hb (S or S+C)%, mean (range) (SD)	48,9 (22 - 95,7) (12,9)
Post-RBCX Anomalous Hb (S or S+C)%, mean (range) (SD)	16,0 (6,3-47,5) (8,18)
Pre-HT (%), mean (range) (SD)	29,0 (19,7 – 40,4) (3,77)
Post-HT (%), mean (range) (SD)	28,9 (19,5 – 34,9) (2,57)
Pre-RBCX protocol Ferritin (ng/L), median (range) (SD)	519,5 (46 - 2497) (702,00)
Post-RBCX protocol Ferritin (ng/L), median (range) (SD)	186,5 (4-1636) (609,8)

RBC utilization; units/procedure, median (range) (SD)	7 (3-12) (1,9)
AC to patient (ml), mean ±SD	202,1 ± 72,9

Table: 2 Details of the automated Red Blood Cell Exchange Procedures

Discussion

Since implementation in 2023, aRBCx has been successfully carried out for eligible SCD patients at HEMOCE, resulting in improved control over hemoglobin. The program's donor coordination efforts have also established a robust network of matched donors, ensuring better preparedness for future transfusion needs. One of the notable aspects is that depletion/exchange was used in 24 RBCx procedures, in patients with higher pre-procedure hematocrit. This approach reduces the volume of RBC used and minimizes potential complications associated with higher baseline hematocrit levels. However, the majority of procedures -122 - were conducted using only exchange transfusion protocol, indicating that depletion/exchange may not always be a feasible option depending on individual patient parameters. Peripheral venous access difficulty is a common challenge for patients undergoing chronic transfusions [17]. Three patients currently followed at HEMOCE are unable to receive chronic transfusions due to this issue. Safe solutions for these patients, such as implantable catheters or future implementation of ultrasound, should be considered, always weighing the benefits and risks, like infections and thrombosis [7]. Procedural efficiency was demonstrated by a significant reduction in anomalous hemoglobin levels, as evidenced by the results. ASFA recommends a target anomalous hemoglobin level of <30% and a hematocrit of 30 ± 3% (≤ 33% to prevent hyperviscosity) [5]. These outcomes suggest that aRBCx was effective in reducing sickle hemoglobin burden, which is critical for mitigating disease complications.

Earlier research has indicated that aRBCx is not linked to substantial iron accumulation [9]. This is consistent with the findings presented, represented by the serum ferritin levels shown earlier. A longer follow-up period for these patients is necessary to evaluate the effects of aRBCX in reducing the need for iron chelation therapy. Data from our study suggest that RBCx is a safe procedure. The absence of severe complications reinforces the safety of RBCx, particularly when appropriate monitoring and supportive measures, such as intravenous fluid expansion, are implemented to mitigate common side effects like hypotensive reactions. Consistent with this, Dimitris A. Tsitsikas et al (2016), found in a cohort of 50 patients that the most common adverse event was vasovagal symptoms, that occurred in 17 (35%) patients. Reducing the rate of the anticoagulant infusion for subsequent procedures resolved or improved the problem. In our practice we use strategies such as: encouraging oral hydration at home, performing intravenous fluid expansion after the procedure, and reducing the anticoagulant infusion rate.

Alloimmunization in SCD can occur in rates as high as 65% with ABO and D matching alone and 11% with Rh and K matched units [18]. Although automated RBCx requires a larger volume of RBCs, leading to increased donor exposure, selecting Rh- and K-matched units appears to mitigate the risk of alloimmunization, making it comparable to simple transfusion [19]. Further more, even patients who are alloimmunized and receive chronic transfusions in a stable condition have a lower risk of developing new antibodies than those who undergo sporadic transfusions for acute conditions [20,21]. Although the implementation of aRBCX can be a challenge in middle-poor income countries, the Brazilian government recently included, in the national therapeutic guidelines, the aRBCX as a transfusion modality to treat patients with SCD [22]. HEMOCE implementation can be seen as a model of this advancement in transfusion therapy [23-25].

Challenges and Future Directions: The introduction of aRBCx at HEMOCE highlighted several challenges, including the need for extended phenotype-matched donors, particularly for patients with rare phenotypes or high alloimmunization levels. High demand for compatible blood products strains HEMOCE's resources, prompting ongoing efforts to streamline laboratory processes and minimize waste. Plans for aRBCx expansion are in place, including extending access to regional blood centers and pediatric patients primarily treated at a tertiary hospital in the capital. Securing reliable venous access for patients also remains a priority. Additionally, futher studies analyzing the impact of aRBCX on clinical outcomes and quality of life in patients with sickle cell disease are being under investigation for future publication.

Conclusions

The successful implementation of aRBCx at HEMOCE demonstrates the feasibility and effectiveness of this approach for managing SCD in resource-limited settings.

The presented data are consistent in demonstrating that aRBCX is safe, effective in reducing HbS levels, and viable for implementation and continuation in public blood centers across Brazil. Through targeted donor matching, comprehensive staff training, and coordinated logistical support, HEMOCE has established a transfusion model adaptable to other centers. This experience underscores the importance of a multidisciplinary approach and continual adaptation to the evolving needs of transfusion medicine in Brazil.

Futher research analyzing the impact of aRBCX on clinical outcomes in patients with sickle cell disease are being under investigation for future publication.

Author Contributions: DMB wrote the first draft of the manuscript; DMB, FLNB, LEMC and LMBC designed the research study; All authors acquired and analysed specific data; DMB and FLNB supervised the research and edited the manuscript; All authors reviewed and approved the final version of the manuscript.

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Institutional Review Board Statement: The study was approved by the local research ethical committee (CAAE: 85864024.2.0000.8152).

Informed Consent Statement: Patient consent was waived due to retrospective nature of the study.

Data Availability Statement: Raw data were generated at HEMOCE and are available from the corresponding author on request.

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Conflicts of Interest: The authors have no conflicts of interest relevant to the manuscript.

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