Comparative efficacy in red blood cell exchange transfusions with different apheresis machines in patients with sickle cell disease

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Abstract The purpose of this study is to compare the efficacy and side effects of two red blood cell exchange (RBCX) transfusion systems in sickle cell disease (SCD). The data is collected retrospectively from the January 2010 to March 2015. 447 RBCX transfusions were performed to 165 patients. Side effects, clinical and technical efficacy were compared in between procedures with Cobe Spectra (CS) and Spectra Optia (SO) systems. Furthermore a subgroup analyses was performed for 40 patients who had RBCX transfusions with both system at least two times. Vasoocclusive crises, preoperative period and foot ulcers (49.6, 13, and 15.2% respectively) were the common indications of RBCX transfusion. While the levels of post-RBCX HbS and the actual fraction of cells remaining (FCRa) were found significantly higher in the SO compared to CS system ($p = 0.018$ and $p = 0.016$ respectively), the rate of targeted hemoglobin S (HbS) levels ($< 30\%$) were same in both. The length of procedure and replacement volume were significantly lower in SO compared to CS system ($p = 0.025$ and 0.044 respectively). Subgroup analyses of 40 patients did not reveal any statistically significant differences regarding post-procedure HbS levels, FCRa levels, replacement volume and

procedure duration. The inter-rater correlation coefficient for FCRa was calculated to be 0.82. Serious adverse reactions were not observed from either system. Both systems are efficiently achieved the targeted post-procedure HbS level. The recently introduced SO apheresis system is as effective and safe as the CS system, which has been used for all indications of SCD for years.

Keywords Sickle cell disease · Red blood cell exchange · Cobe Spectra · Spectra Optia

Introduction

Sickle cell disease (SCD) is an inherited single-gene autosomal recessive, life-threatening disorder with a chronic inflammatory process [1–4]. In the pathogenesis of the disease, abnormal hemoglobin S (HbS) levels occur because glutamic acid in the 6th position of the beta globin chain is replaced by valine. While normal Hb dissolves in red blood cells (RBCs) and does not polymerize, HbS is a tetramer comprising $\alpha_2\beta_2^S$ globin chains and has low dissolubility. Therefore, vasoocclusive events (e.g., painful crises, predisposition to thrombosis, hemolytic attacks) are frequently observed. In some ethnic groups in the Mediterranean region, abnormal Hb incidence can be as high as 9.6% [5].

Many clinical symptoms of SCD are related to increased blood viscosity, which is reduced even further due to factors such as stiffness of RBC membranes, polymerization of Hb, and elevated intracellular Hb levels. Increased viscosity of sickle cells to the endothelium of the vessel leads to a reduction in the perfusion of tissues, resulting in decreased oxygen saturation and continuation of the vicious cycle that leads to sickling [6, 7]. Repeated or

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prolonged sickling progressively damages the RBC membrane and is of primary importance in the pathophysiology of SCD [8]. Patients with SCD may experience disease-specific crises (sequestration crisis, aplastic crisis, painful crisis and hemolytic crises) triggered by various factors (infection, dehydration, stress, menstruation, alcohol use, cold exposure, pregnancy, etc.). These events may result in serious mortality. Measures such as lifestyle changes, vaccination, penicillin prophylaxis and prophylactic transfusions have been applied to prevent complications of the disease. Treatments for complications in painful crises include non-steroidal anti inflammatory drugs, opioid analgesics low-flow oxygen delivery via nasal cannula, sufficient hydration, infection treatment, basic transfusion and red blood cell exchange (RBCX). The purpose of the RBCX procedure is to lower the level of HbS to 30% and less and to increase the level of HbA instead. RBCX is performed with an automatic cell separator. The indications of RBCX for patients with SCD are presented in the guidelines of the American Society for Apheresis (ASFA) and particularly its use in vasoocclusive crisis, acute chest syndrome, and organ failure can be lifesaving [9].

The RBCX procedure is performed since 2004 in our hospital and Spectra Optia (SO) system was introduced in 2010. In this study, we retrospectively compared the clinical features, technical efficacies, laboratory characteristics and side effects of RBCX in SCD of both systems.

Patients and Methods

Patients

This study was designed as a single-center, retrospective and cross-sectional study. The population of the study consisted of adult patients who underwent RBCX transfusion using the CS system (Terumo BCT; Lakewood, CO, USA) and the SO system (Terumo BCT) from January 2010 to March 2015. A total of 165 patients with SCD and who experienced prolonged painful crisis, ischemic cerebrovascular event, acute chest syndrome, continuous priapism, non-healing or recurrent skin ulcers, preoperative management, whose hydroxyurea treatment was interrupted due to request or presence of pregnancy were assessed. The clinical and laboratory data of the patients were collected from registry systems of hematology and therapeutic apheresis units (Nucleus version: 9.3.39 Monod Software Company; Ankara, Turkey). The age, sex, body weight, method of venous access (vein/temporary catheter), number of procedures, number of apheresis machines used, length of procedure, indication, number of RBC units used, pre- and post-procedure complete blood count and

HbS levels were recorded. Due to safety reasons heart rate, oxygen saturation and blood pressure were followed up during the RBCX transfusion. Forty patients were detected to have undergone at least two sessions on each apheresis system. These patients formed a control group for themselves.

Red Blood Cell Exchange

RBCX transfusions were performed using two different machines operating with a continuous flow apheresis system (Cobe Spectra Version 7 and Spectra Optia version 7, Terumo BCT). The flow rates per minute and centrifugation velocity of the inlet pump were automatically set before the procedure started according to the patients' characteristics (weight, height, sex and hematocrit [Hct] level). Accordingly, the maximum centrifugation velocity exposed by the cells was $930 \times g$ in line with the apheresis system guide (Cobe Spectra and Spectra Optia Apheresis System Essential guide, Terumo BCT). For some of the patients, the inlet pump flow rate per minute was manually set. The total blood volume was calculated according to the weight of the patients and the RBC volume was calculated according to their Hct levels. Acid citrate dextrose A (ACD-A) solution was used in all procedures and whole blood to ACD-A ratio was 15:1 [10]. The aim of the RBCX procedure was to exchange the erythrocytes of the patients with appropriate concentrates of erythrocyte at levels of 60–70%. Erythrocytes of compatible ABO, Rh D blood group antigens, cross-matched and stored for maximum 7 days were preferred. Hct values of the erythrocyte concentrate which is periodically checked at the transfusion centers as per the quality standards was $65 \pm 5\%$. As a general policy of our center, appropriate products were used after checking the Rh subgroups (C, c, E, e) and Kell blood group antigen types of the patients in whom the basic transfusion procedure and/or RBCX were performed. Before the RBCX procedure, auto-alloimmunization was analyzed through direct–indirect Coombs examination. Alloantibodies were determined if possible and a suitable product was found accordingly. Leucodepleted packed erythrocyte units were used and gamma radiation was applied for the patients who were candidates for allogeneic transplantation. The target post-RBCX Hct levels were determined as a maximum of 27–28% depending on the exchange indications of the patients. The RBCX procedures were performed through a computerized system in the two machines. The patient data before the procedure (height, weight, sex, pre Hct), target post-procedure Hct levels, donor erythrocyte concentrate used, Hct, and fraction of the subject's original RBCs remaining (FCR) were recorded and evaluated using special software and the exchange volume was calculated accordingly.

Safety

The patients were monitored during the procedure and at least 24 h post procedures for vital signs (blood pressure, pulse, temperature and pulse oximetry) and adverse events (AEs). AE severity was assessed based on the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

Statistical Analysis

Categorical measurements were expressed numerically as percentages, whereas continuous measurements were expressed as averages and standard deviation (if necessary as medians and the minimum–maximum). Chi squared test or Fisher's exact test was used for the comparison of categorical variables. Inter-rater reliability was applied using reliability test–correlations coefficient value. Correlations between FCR and ACD-A were tested by inter-rater correlation test. For the comparison of the continuous measurements of the machines, independent samples *t* test was used for the variables that met the assumption of the parametric distribution prerequisite, whereas the Mann–Whitney U-test was used for the variables that did not meet the assumption. Forty patients receiving the procedure with the two devices were analyzed with paired tests with regarding to pre and post procedure white blood cell, Hct, HbS and FCR. The SPSS 17.0 package program was used for the statistical analysis of the data. Statistical significance was considered < 0.05 for all tests.

Results

A total of 447 procedures were performed in 165 patients; 220 procedures were performed in 92 patients using the CS system and 227 procedures were performed in 113 patients using the SO system. The number of patients receiving the procedures using both machines was 40. A subgroup analyze of these patients is presented below.

The study group included patients with homozygous Hb S (79%) and Hb S- β^0 thalassemia (21%). The age, weight, sex, method of venous access (peripheral vein/catheter/fistula) according to the machines, and indications are summarized in Table 1. No statistically significant difference was observed in both groups in terms of age and weight distribution (0.945 and 0.233 respectively).

Most of the procedures were performed due to vasoocclusive crises, preoperative preparation and foot ulcers (49.6, 13 and 15.2% respectively). RBCX was urgently performed for 82 times (41 procedures in each system). The indications of the urgent cases are acute ischemic cerebrovascular event, priapism, intrahepatic cholestasis

Table 1 Patients' characteristics

	Cobe Spectra	Spectra Optia
Age (years) [†]	29.3 $\pm$ 9.00	29.71 $\pm$ 8.89
Body weight (kg) [†]	65.41 $\pm$ 14.18	63.59 $\pm$ 12.67
Gender (male/female)	59/33	63/51
Venous access (n)		
Peripheral	162	142
Catheter	58	82
Fistula	0	3
Indications (n)		
Painful crisis	98	124
Preoperation	26	34
Pregnancy	8	7
Priapism	12	6
Ischemic cerebrovascular event	12	11
Acute chest syndrome	10	4
Skin ulcers	47	21
Intrahepatic cholestasis	7	20

n Number of procedure

[†]Data reported as mean $\pm$ SD

and acute chest syndrome. 186 routine regular RBCX procedures were performed with SO and the remaining 179 with CS. In both groups, mainly peripheral venous access was used and three procedures were performed using the existing fistulas in patients with chronic kidney failure. Pre- and post-RBCX hematological parameters of the patients (HbS, Hct, thrombocyte, leukocyte levels) and technical data (total blood volume, replacement volume, FCR, ACD-A amount, operation duration) are summarized in Table 2.

The median number of erythrocyte units used in each group was seven (range: 4–9). The mean duration of the procedure, the mean ACD-A volume used, the mean replacement fluid volume were 104.45 $\pm$ 12.74 min, 325.40 $\pm$ 48.21 mL and 2092.53 $\pm$ 237.86 mL respectively for CS and 101.44 $\pm$ 15.26 min, 324.17 $\pm$ 49.78 mL and 2044.28 $\pm$ 264.29 mL respectively for SO (Table 2). The pre and post-RBCX HbS levels were 70.42 $\pm$ 20.78 and 22.64 $\pm$ 11.90 respectively for CS and 71.03 $\pm$ 19.55 and 25.57 $\pm$ 12.32 respectively for SO (Table 2).

Forty patients have undergone the procedure using both devices at different time points. While assessing the data of this subgroup, each patient formed a control group for himself/herself. The patients received 138 RBCX procedures using the CS system and 124 RBCX procedures using the SO system. The intragroup sub-analysis of exchange transfusions did not reveal a statistically significant difference regarding age, total blood volume transfused, replacement volume, amount of erythrocyte

Table 2 Laboratory tests and procedure parameters

Parameters	Cobe Spectra (n: 220)	Spectra Optia (n: 227)	<i>p</i> value
HbS pre (%)	70.42 ± 20.78	71.03 ± 19.55	.771
HbS post (%)	22.64 ± 11.9	25.57 ± 12.32	.018
WBC pre (× 10 ⁹ /L)	14.27 ± 5.57	15.62 ± 7.91	.072
WBC post (× 10 ⁹ /L)	11.75 ± 4.40	14.49 ± 22.17	.038
PLT pre (× 10 ⁹ /L)	481.77 ± 185.72	454.29 ± 201.17	.135
PLT post (× 10 ⁹ /L)	250.38 ± 87.04	224 ± 94.23	.003
Hct pre (%)	25.76 ± 5.14	26.06 ± 4.82	.512
Hct post (%)	27.87 ± 3.32	27.90 ± 3.46	.935
FCRa (%)	29.00 ± 7.65	30.93 ± 9.09	.016
Total ACD-A used (mL)	325.40 ± 48.21	324.17 ± 49.78	.791
Total blood volume (mL)	4394.34 ± 885.74	4287 ± 754.31	.171
Procedure duration (min)	104.45 ± 12.74	101.44 ± 15.26	.025
RBC replacement volume (mL)	2092.53 ± 237.86	2044.28 ± 264.29	.044

All data are reported as mean ± SD

Italic values indicate significance of *p* value (*p* < 0.05)

HbS hemoglobin S, *WBC* white blood cell, *PLT* platelet, *Hct* hematocrit, *FCRa* actual fraction of cells remaining, *ACD-A* acid citrate dextrose-A, *RBC* red blood cell

concentrate, pre- and post-RBCX number of white blood cells, Hct, HbS and FCR. Only the post-RBCX platelet levels were statistically significantly lower in the SO system. The data are presented in Table 3. The inter-rater correlation coefficient was calculated for post-RBCX HbS and actual fraction of cells remaining (FCRa) in the patient group and was 0.43 and 0.82 respectively.

No severe adverse events or unexpected events were observed during the RBCX procedure using both machines. The rate of adverse events was 4% with a grade of 1–2 in procedures with both machines. The patients suffered from mild nausea and dizziness. Difficulty in accessing the vein is another common issue in both machines. No technical

problems related to cell separators was noted in both machines.

The post-RBCX platelet count was < 100 × 10⁹/L in 15 of the patients (9%), but thrombocytopenia was detected in 2 before the RBCX. 9 patients had RBCX with CS and the remaining 6 with SO.

Discussion

Deterioration of the rheological properties of erythrocyte is not the only mechanism underlying organ damage in SCD. In addition to erythrocyte becoming rigid and sickle

Table 3 Laboratory tests and procedure parameters in forty patients who underwent RBCX procedure with both machines

Parameters	Cobe Spectra	Spectra Optia	<i>p</i> value
HbS pre (%)	77.57 ± 21.57	67.62 ± 21.8	.319
HbS post (%)	22.17 ± 10.8	23.88 ± 11.68	.251
WBC pre (× 10 ⁹ /L)	13.86 ± 5.39	15.53 ± 7.27	.035
WBC post (× 10 ⁹ /L)	11.71 ± 4.51	15.08 ± 29.17	.182
PLT pre (× 10 ⁹ /L)	503.85 ± 184.05	466.95 ± 162.05	.088
PLT post (× 10 ⁹ /L)	264.11 ± 81.04	226.68 ± 78.61	.000
Hct pre (%)	26.07 ± 5.22	26.90 ± 4.76	.187
Hct post (%)	28.37 ± 3.40	28.56 ± 3.85	.677
FCRa (%)	29.86 ± 7.81	31.60 ± 8.27	.080
Total ACD-A used (mL)	327.59 ± 39.74	331.26 ± 45.27	.485
Total blood volume (mL)	4503.70 ± 813.63	4391.85 ± 802.13	.264
Procedure duration (min)	103.39 ± 12.26	101.67 ± 13.57	.282
RBC replacement volume (mL)	2121 ± 215.94	2092.79 ± 208.77	.279

All data are reported as mean ± SD

Italic value indicates significance of *p* value (*p* < 0.05)

HbS hemoglobin S, *WBC* white blood cell, *PLT* platelet, *Hct* hematocrit, *FCRa* actual fraction of cells remaining, *ACD-A* acid citrate dextrose-A, *RBC* red blood cell

shaped, vascular endothelial dysfunction due to the low bioavailability of arginine and nitric oxide associated with particularly chronic hemolysis, elevated inflammatory cytokines and hypercoagulopathy are other known causes [11, 12]. Moreover the clinical manifestations of the disease are quite heterogeneous across races. However there remains a lack of a stand-alone treatment modality with proven efficacy against possible complications. The standard treatment commonly used in practice is blood transfusion to decrease the HbS concentration and increase the Hb level [13–17]. The prevalence of SCD in Çukurova region (Eastern Mediterranean part of Turkey) was found around 10% [5, 18].

RBCX is a treatment option for acute and chronic complications of SCD. It reduces the risk of hemosiderosis and organ damage associated with simple chronic transfusion. It also allows controlling the hypervolemia and high viscosity [10].

ASFA has determined the indications of RBCX in acute and non-acute states of SCD. These include acute stroke (category I); severe acute chest syndrome (category II); priapism, multi-organ failure, splenic sequestration, hepatic sequestration and intrahepatic cholestasis (category III) for acute indications. On the other hand the non-acute indications are stroke prophylaxis through the prevention of iron overload (category II); vaso-occlusive pain crisis (category III) and pre-operative preparation (category III) [9]. During the study interval, RBCX were mainly performed in the management of painful crisis. Other indications that we commonly performed RBCX are acute chest syndrome, acute stroke and refractory pain score despite the supportive treatment.

Although no special recording for pain scores was available for each patient in hospital electronic data management system, pain scores of the patients were monitored during daily visits. The pain score was observed to reduce more than 50% rapidly after RBCX procedure in most of the patients with prolonged vaso-occlusive crisis. The patients were also observed not to need further treatment with narcotic analgesic drugs and duration of hospital stay was observed to decrease.

In this study, the targeted HbS levels (mean level: < 30%) were achieved with both machines; however, statistical analysis revealed a significant difference in post-RBCX HbS and FCRA levels which were higher with SO than with CS. The length of the procedure and replacement volume was statistically significant lower with SO. This may have an influence over these results. No clinical implications of these results were observed. The subgroup analysis of the patients who underwent RBCX with both machines did not reveal any statistically significant differences between the pre- and post-RBCX HbS and FCRA levels. The only significant difference in this

subgroup was found in the post-RBCX platelet count. The fact that the coefficient was 0.82 according to the inter-rater correlation analysis between the two machines supports the interchangeability of these two machines. The few studies in the literature conducted with a lower number of procedures also demonstrated that SO was effective and safe [19–21]. SO and CS were compared in a study that revealed no significant difference regarding post-transfusion HbS and FCRA [20]. In that study, the authors performed a technical comparison between isovolemic hemodilution in CS and simplified automatic depletion in SO (23 patients and 46 procedures). The replacement volume used in SO was statistically significantly higher, but did not have any effect on the number of RBC units used. In our study, however, the replacement volume used in SO was statistically lower in the overall group comparison, while the subgroup analyses did not reveal any statistically significant difference. The median numbers of RBC units used were identical in both machines.

The advantage of CS and SO devices is having special software for RBCX. SO seems to be more preferred device because it is fully automated and its use is easy for RBCX.

Although a statistically significant decrease was found in the post-RBCX platelet count with SO in both groups, it was not clinically significant. Because of a lack of studies in the literature that included as many patients and procedures as in this study (including the group in which the same patients underwent a minimum of two procedures with both machines), a comparison could not be made.

Many patients with sickle cell disease are treated in our department and we have a considerable experience on exchange transfusion [4, 10, 18, 22–26]. This manuscript is also clinically important in that it highlights the difference between the technical and clinical properties. To our knowledge this is the largest study in fields.

Conclusions

We suggest that the SO apheresis system that has been used for 5 years can ensure that target post-transfusion HbS and FCRA levels are achieved through RBCX treatment in SCD patients in a safe and effective way and without any procedure-related severe adverse events.

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Compliance with Ethical Standards

Conflicts of interest The authors declare that they have no conflict of interest.

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