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Safety profile and predictors of procedural complications in automated erythrocytapheresis for sickle cell disease: a single-center retrospective cohort study

Sinan Mersin*[1], Pelin Aytan[1], Mahmut Bakır Koyuncu[1], Seher Yontar[2], Hamit Ünver[2], Aycan Erkenekli[1], Esin Oğuz Kocan[1], Enver Tekin[1], Eyüp Naci Tiftik[1]

[1]Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Mersin University, Mersin, Turkiye
[2]Department of Apheresis, Faculty of Medicine, Mersin University, Mersin, Turkiye

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***Corresponding Author:** Sinan Mersin, sinanmersin86@msn.com

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ABSTRACT

Aims: Automated erythrocytapheresis (red cell exchange; RCE) is an established therapeutic modality in sickle cell disease (SCD), yet procedural complication data from Turkiye and the Eastern Mediterranean region remain limited. This study evaluated the safety profile of RCE in adult SCD patients at a single tertiary center and identified clinical and procedural predictors of adverse events.

Methods: We conducted a retrospective cohort study of all automated RCE procedures performed in adult patients (≥18 years) with SCD between January 2015 and December 2020. Adverse events were graded according to the World Apheresis Association (WAA) classification (grades 1-4). Procedures with and without complications were compared using the Mann-Whitney U test for continuous variables and Fisher's exact or Chi-square tests for categorical variables.

Results: A total of 274 procedures in 83 patients were analyzed. The overall complication rate was 12.4% (n=34): grade 1 in 4.4%, grade 2 in 5.8%, and grade 3 in 2.2%; no grade 4 events were observed. Vascular and mechanical dysfunction accounted for 67.6% of complications. Complication rates declined from 31.2% in 2015 to 5.5% in 2018, with no severe events after 2016. Higher pre-procedure hemoglobin (9.4 vs. 8.9 g/dl; p=0.021) and hematocrit (27.0% vs. 25.9%; p=0.022) were significantly associated with complication occurrence. MCS® procedures had a substantially higher complication rate (42.9% vs. 10.8%; p=0.003) and severe event rate (28.6% vs. 0.8%; OR=51.4; p=0.0001) versus the Spectra Optia® system. Indication and hydroxyurea use were not significantly associated with outcomes.

Conclusion: Automated RCE is a safe procedure in adult SCD patients with a low rate of severe adverse events. Higher pre-procedure hemoglobin and hematocrit and use of the MCS® device were associated with increased complication risk. The marked temporal decline in complication rates reflects institutional learning and device transition to the Spectra Optia® platform.

Keywords: Hemoglobin S, vaso-occlusive crisis, transfusion medicine, adverse events, apheresis device, fetal hemoglobin

INTRODUCTION

Sickle cell disease (SCD) is one of the most prevalent monogenic disorders worldwide, affecting approximately 300.000 newborns annually and posing a significant public health burden particularly across sub-Saharan Africa, the Middle East, and the Mediterranean basin.[1,2] In Turkiye, SCD is endemic along the southern and southeastern coastal regions, where the carrier frequency reaches up to 10% in certain provinces of the Çukurova and Hatay regions.[3] Mersin province, situated within this high-prevalence belt, represents one of the largest SCD patient populations in the country, making it an important center for the longitudinal study of disease-related complications and treatment outcomes.

SCD is caused by a point mutation in the β-globin gene, resulting in the substitution of valine for glutamic acid at position 6 of the β-globin chain and the production of hemoglobin S (HbS). Under conditions of deoxygenation, HbS polymerizes, leading to erythrocyte sickling, chronic hemolysis, and progressive vaso-occlusion.[4] These pathophysiological processes underlie the broad spectrum of acute and chronic complications that characterize SCD, including painful vaso-occlusive crises, acute chest syndrome (ACS), stroke, pulmonary hypertension, and hepatic dysfunction.[5]

Red cell transfusion remains a cornerstone of SCD management. Among the available modalities, automated

erythrocytapheresis—also termed red cell exchange (RCE)—has emerged as the preferred approach in many centers given its ability to rapidly reduce the circulating HbS fraction while minimizing iron overload.[6,7] The American Society for Apheresis (ASFA) classifies RCE as a category I indication for stroke prevention in SCD, and its use has expanded to encompass additional indications including ACS, recurrent painful crises, preoperative preparation, and intrahepatic cholestasis.[8] The STOP and STOP 2 randomized trials established the efficacy of chronic RCE programs in reducing primary and recurrent stroke risk.[9,10]

Despite its clinical advantages, RCE is not without procedural risks. Complications include vascular access problems, catheter-related thrombosis, allergic reactions, hemodynamic instability, and—less frequently—hemolysis.[11,12] Adverse events are graded using standardized scales such as the World Apheresis Association (WAA) classification system.[13] Although several Western studies have described complication profiles of RCE in SCD, data from Turkiye and the Eastern Mediterranean region remain limited.[14,15] The present study aimed to evaluate the safety profile of automated erythrocytapheresis in adult SCD patients at a single tertiary center over a five-year period (2015–2020) and to identify clinical and procedural predictors of adverse events.

METHODS

Ethics

The study was approved by the Health Sciences Researches Ethics Committee of Mersin University Rectorate (Date: 28.04.2026, Decision No: 2026/248). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The requirement for individual informed consent was waived given the retrospective nature of data collection.

Study Design and Setting

This was a retrospective cohort study conducted at the Department of Hematology, Mersin University Faculty of Medicine, Mersin, Turkiye. All automated RCE procedures performed in adult patients with SCD between January 2015 and December 2020 were identified from the departmental apheresis registry and included in the analysis.

Patient Population

Adult patients (aged ≥18 years) with a confirmed diagnosis of SCD who underwent at least one automated RCE procedure during the study period were eligible for inclusion. Procedures were the primary unit of analysis; where a single patient underwent multiple procedures, each session was treated as a separate observation. As this approach does not account for potential within-patient clustering, the resulting limitation is addressed in the discussion.

Apheresis Procedure

All RCE procedures were performed using automated cell separators, predominantly the Spectra Optia® apheresis system (Terumo BCT, Lakewood, CO, USA) and, in a minority of early procedures, the MCS® device (Haemonetics, Boston, MA, USA). Anticoagulation was achieved with acid citrate dextrose solution A (ACD-A). Vascular access was established via peripheral venous catheterization in the majority of procedures; central venous catheterization was employed when peripheral access was inadequate.

Data Collection

Procedural and clinical data were extracted from the institutional apheresis registry and electronic medical records. Variables collected included patient demographics (age, gender, body weight), clinical characteristics (diagnosis, indication for RCE, referring department), pre- and post-procedure laboratory values (hemoglobin [Hb], hematocrit [Hct], white blood cell count [WBC], platelet count [PLT]), procedural parameters (device type, vascular access type, inlet flow rate, donor erythrocyte volume [DEV], total exchange volume [TEV], procedure duration), and concomitant hydroxyurea use. Where individual data fields were missing in the registry or medical records, the affected variable was recorded as missing for that procedure; the number of available observations is reported for each variable in the corresponding table.

Complication Classification

Adverse events were graded according to the WAA classification: grade 1 (mild, no intervention required), grade 2 (moderate, medical intervention required), grade 3 (severe), and grade 4 (life-threatening or fatal).[13] Three composite outcome variables were defined: (i) any complication (grade 1-4); (ii) severe complication (grade 3-4); and (iii) complication type, categorized as vascular/mechanical, allergic/systemic, hemodynamic, or other.

Statistical Analysis

Continuous variables are expressed as median and interquartile range (IQR). Categorical variables are presented as counts and percentages. Comparisons between groups were performed using the Mann–Whitney U test for continuous variables and Fisher's exact test or Pearson Chi-square for categorical variables. A two-tailed p value of less than 0.05 was considered statistically significant. No imputation was performed for missing data. All analyses were performed using Python (version 3.12; Python Software Foundation, Wilmington, DE, USA) with the SciPy and pandas libraries.

RESULTS

Study Population and Procedural Characteristics

A total of 274 RCE procedures performed in 83 adult patients with SCD were included. Three procedures were excluded due to patient age below 18 years. The median number of procedures per patient was 1 (IQR 1-2; range 1-38). Of the 274 procedures, 151 (55.1%) were performed in male patients. Median patient age was 31 years (IQR 23-44) and median body weight was 63 kg (IQR 54-72). Baseline and procedural characteristics are summarized in **Table 1**.

The most frequent indication was stroke prophylaxis/treatment (153 procedures, 55.8%), followed by painful vaso-occlusive crisis (40, 14.6%), hepatic or intrahepatic cholestasis (35, 12.8%), preoperative preparation or pregnancy-related indications (19, 6.9%), and ACS (18, 6.6%). The Spectra Optia® system was used in 259 procedures (94.5%), with the MCS® device employed in 14 (5.1%). Peripheral venous access was established in 236 procedures (86.1%) and central venous catheterization in 28 (10.2%).

Table 1. Baseline and procedural characteristics of the study population

Characteristic	Median (IQR) or n (%)	Available/range
General		
Total procedures	274	83 patients
Procedures per patient	1 (1–2)	range 1–38
Gender—male	151 (55.1%)	
Age (years)	31 (23–44)	range 18–87
Body weight (kg)	63 (54–72)	
Indication for RCE		
Stroke prophylaxis/treatment	153 (55.8%)	
Painful crisis	40 (14.6%)	
Hepatic/intrahepatic cholestasis	35 (12.8%)	
Preoperative/pregnancy-related	19 (6.9%)	
Acute chest syndrome	18 (6.6%)	
Other	9 (3.3%)	
Device and vascular access		
Spectra Optia® system	259 (94.5%)	
MCS® device	14 (5.1%)	
Peripheral venous access	236 (86.1%)	
Central venous access	28 (10.2%)	
Hydroxyurea use	206/227 (90.7%)	47 unknown
Pre-procedure laboratory values		
Hemoglobin (g/dl)	8.9 (7.8–9.9)	n=271
Hematocrit (%)	26.0 (22.0–29.0)	n=272
WBC ($\times 10^3/\mu L$)	10.8 (7.1–14.9)	n=269
Platelet ($\times 10^3/\mu L$)	359 (251–475)	n=272
Post-procedure laboratory values		
Hemoglobin (g/dl)	9.3 (8.8–9.9)	n=257
Hematocrit (%)	27.0 (26.0–29.0)	n=259
Procedural parameters		
Duration (min)	85 (68–102)	n=263
Inlet flow rate (ml/min)	40 (35–45)	n=260
Donor erythrocyte volume—DEV (ml)	902 (733–1067)	n=270
Total exchange volume—TEV (ml)	1057 (926–1272)	n=271

Data are presented as median (interquartile range) for continuous variables and n (%) for categorical variables. IQR: Interquartile range, RCE: Red cell exchange, WBC: White blood cell count, Min: Minute, DEV: Donor erythrocyte volume, TEV: Total exchange volume

Complication Incidence and Grade Distribution

Procedural complications were recorded in 34 of 274 procedures (12.4%). Of these, 12 events (4.4%) were grade 1, 16 (5.8%) were grade 2, and 6 (2.2%) were grade 3. No grade 4 events were observed. Annual complication rates declined from 31.2% in 2015 (10/32 procedures) to 5.5% in 2018 (3/55), with no severe events recorded after 2016.

Types of Complications

Among the 34 complicated procedures, vascular or mechanical dysfunction was the predominant category (23 events, 67.6%), comprising insufficient blood flow during the procedure (n=14), catheter-related thrombosis or fibrin formation (n=7), and circuit or set errors (n=2). Allergic or systemic reactions accounted for 6 events (17.6%), comprising urticaria (n=5) and chills or rigors (n=1); hemodynamic instability (hypotension) accounted for 2 events (5.9%); and the remaining 3 events (8.8%) comprised one patient-initiated discontinuation and two other or mixed events. Full grade and type distributions are presented in Table 2.

Table 2. Distribution of complication grades and types

Category	n	% of all procedures
Complication grade distribution (n=274 procedures)		
No complication	240	87.6%
Any complication	34	12.4%
Grade 1—mild	12	4.4%
Grade 2—moderate	16	5.8%
Grade 3—severe	6	2.2%
Grade 4—life-threatening	0	0.0%
Severe complications (grade 3–4)	6	2.2%
Complication type (among n=34 procedures with complications)		
Category	**n**	**% of all complications**
Vascular/mechanical	23	67.6%
Insufficient blood flow	14	41.2%
Circuit thrombosis/fibrin formation	7	20.6%
Circuit/set error	2	5.9%
Allergic/systemic reaction	6	17.6%
Urticaria	5	14.7%
Chills/rigors	1	2.9%
Hemodynamic (hypotension)	2	5.9%
Patient-initiated discontinuation	1	2.9%
Other/mixed	2	5.9%

WAA grades: Grade 1, mild; Grade 2, moderate; Grade 3, severe; Grade 4, life-threatening. Upper panel: % of all 274 procedures. Lower panel: % of the 34 complicated procedures

Factors Associated with Complications

Comparisons between procedures with and without complications are presented in Table 3. Pre-procedure Hb was significantly higher in the complication group (9.4 vs. 8.9 g/dl; p=0.021), as was pre-procedure Hct (27.0% vs. 25.9%; p=0.022) and post-procedure Hct (28.0% vs. 27.0%; p=0.039). No significant differences were observed for age, body weight, WBC, PLT, procedure duration, inlet flow rate, DEV, or TEV. Among categorical variables, gender (p=1.000), vascular access type (p=0.763), clinical indication (p=0.466), and hydroxyurea use (p=0.455) were not significantly associated with complication occurrence.

Severe vs. Mild Complications

Comparison of procedures with severe (grade 3, n=6) versus mild-to-moderate (grade 1-2, n=28) complications revealed no statistically significant differences for any variable examined, including age (40 vs. 31.5 years; p=0.331), DEV (700 vs. 973 ml; p=0.139), and pre-procedure Hb (9.3 vs. 9.4 g/dl; p=0.482). These analyses should be interpreted with caution given the small number of severe events (n=6).

Device Type, Indication, and Hydroxyurea Use

Device type was significantly associated with complication occurrence. MCS® procedures had a substantially higher complication rate compared with Spectra Optia® (42.9% vs. 10.8%; p=0.003). This difference was even more pronounced for severe events (28.6% vs. 0.8%; OR=51.4; p=0.0001). Clinical indication (p=0.466) and hydroxyurea use (p=0.455) were not significantly associated with complications. The high HU utilization rate (90.7% of procedures with available medication data) substantially limited statistical power to detect an HU-related effect.

Table 3. Comparison of clinical and procedural variables between procedures with and without complications

Variable	Complication+ (n=34)	Complication– (n=240)	p value	Test
	Median (IQR) or n (%)	Median (IQR) or n (%)		
Continuous variables				
Age (years)	37.0 (23.0–43.0)	30.0 (23.0–44.0)	0.877	MWU
Body weight (kg)	61.0 (55.0–73.5)	63.0 (54.0–72.0)	0.966	MWU
Pre-procedure Hb (g/dl)	9.4 (8.8–10.5)	8.9 (7.8–9.8)	**0.021**	MWU
Post-procedure Hb (g/dl)	9.5 (9.1–9.9)	9.3 (8.8–9.9)	0.133	MWU
Pre-procedure Hct (%)	27.0 (24.0–31.0)	25.9 (21.6–29.0)	**0.022**	MWU
Post-procedure Hct (%)	28.0 (27.0–29.0)	27.0 (26.0–29.0)	**0.039**	MWU
WBC ($\times 10^3/\mu L$)	9.5 (7.1–13.1)	10.9 (7.2–15.3)	0.389	MWU
Platelet ($\times 10^3/\mu L$)	336 (246–447)	361 (253–478)	0.474	MWU
Duration (min)	91 (78–100)	84 (67.5–103.5)	0.157	MWU
Inlet flow rate (ml/min)	40 (35–50)	40 (35–45)	0.604	MWU
DEV (ml)	911 (693–1274)	900 (762–1066)	0.655	MWU
TEV (ml)	1100 (904–1357)	1051 (932–1264)	0.548	MWU
Categorical variables				
Male gender	19 (55.9%)	132 (55.0%)	1.000	Fisher
Central vascular access	4 (11.8%)	24 (10.0%)	0.763	Fisher
MCS® device	6 (17.6%)	8 (3.3%)	**0.003**	Fisher
Stroke prophylaxis indication	17 (50.0%)	136 (56.7%)	0.466	χ^2
Hydroxyurea use[a]	20 (87.0%)	186 (91.2%)	0.455	Fisher

Bold p values indicate statistical significance ($p<0.05$). Continuous variables expressed as median (IQR), compared by Mann–Whitney U test (MWU). Categorical variables expressed as n (%), compared by Fisher's exact test or Pearson Chi-square (χ^2). Hb: Hemoglobin, Hct: Hematocrit, WBC: White blood cell count, Min: Minute, DEV: Donor erythrocyte volume, TEV: Total exchange volume. [a] Hydroxyurea analysis restricted to 227 procedures with available medication data.

DISCUSSION

In this retrospective cohort study of 274 RCE procedures in 83 adult SCD patients, the overall procedural complication rate was 12.4%, with severe adverse events occurring in 2.2% of procedures and no grade 4 events recorded. Vascular and mechanical complications predominated (67.6%). Higher pre-procedure Hb and Hct were significantly associated with complication occurrence, and device type was the categorical variable most strongly associated with both any complication and severe adverse events.

Overall Complication Rate in Context

The overall complication rate of 12.4% is broadly consistent with previously published series of therapeutic apheresis in SCD, where reported rates range from approximately 5% to over 20% depending on patient population, grading systems, and era of data collection.[11,12] Studies applying rigorous prospective adverse event capture tend to report higher rates than those relying on retrospective chart review alone.[13] The low rate of severe events (2.2%) and absence of grade 4 complications align with the generally favorable safety profile of modern automated apheresis.[11,12]

Predominance of Vascular and Mechanical Complications

Access-related problems consistently represent the most frequent adverse event category in therapeutic apheresis.[11,16] The high proportion of peripheral venous access use in our cohort (86.1%) is likely a contributing factor: peripheral veins are inherently more susceptible to flow insufficiency during extracorporeal circulation, particularly in SCD patients with compromised peripheral vasculature.[17] Allergic and systemic reactions (17.6%) are consistent with the known immunological burden of chronically transfused SCD patients.[18]

Declining Complication Rates Over Time

The marked temporal decline in complication rates—from 31.2% in 2015 to 5.5% in 2018—and the confinement of all severe complications to 2015–2016 are highly suggestive of a center-level learning curve effect. The early study period coincided with predominant use of the older MCS® device. Institutional factors including growing procedural experience, protocol refinement, and standardization of vascular access management likely also contributed.[19,20]

Pre-Procedure Hemoglobin and Hematocrit as Risk Factors

Higher pre-procedure Hb and Hct were significantly associated with complication occurrence. A plausible mechanistic explanation relates to blood rheology: higher Hct reflects greater red cell mass and increased whole-blood viscosity within the extracorporeal circuit, predisposing to slower flow rates, increased resistance, and circuit clotting—the dominant complication type in our series.[21] SCD patients with higher resting Hb levels may also carry a larger proportion of dense, dehydrated sickle erythrocytes prone to aggregation under shear stress.[21] These findings, if confirmed prospectively, may support individualized pre-procedure Hb targets or preemptive hydration strategies to reduce complication risk.

Device Type as a Major Determinant of Complication Risk

Among the categorical variables examined, device type showed the strongest association with complications. MCS® procedures had a four-fold higher rate of any complication

(42.9% vs. 10.8%; p=0.003) and a markedly higher rate of severe complications (OR=51.4; p=0.0001) compared with the Spectra Optia® system. These findings are consistent with the established technological advantages of the Spectra Optia®, which employs continuous real-time inlet and outlet Hct monitoring and automated flow optimization algorithms.[22,23] An important caveat is the temporal confounding between device type and study period: MCS® procedures were concentrated in 2015–2016, when overall complication rates were highest. Despite this limitation, the magnitude of the association supports a genuine contribution of device technology to patient safety.

Hydroxyurea Use and Indication

Neither clinical indication nor hydroxyurea use was significantly associated with complication rates. Hydroxyurea reduces sickling by increasing fetal Hb levels and has anti-inflammatory and rheological effects that might theoretically influence blood handling in the extracorporeal circuit.[24] However, given that 90.7% of medication-documented procedures were performed in HU-treated patients, our study was severely underpowered to detect any meaningful difference. The null finding should be interpreted accordingly rather than as evidence of absence of effect.

Limitations

This study represents one of the largest single-center adult SCD apheresis series from Turkiye, a high-prevalence region with limited published data. Standardized WAA grading, a five-year observation window, and comprehensive procedural data collection are notable strengths. Several limitations should nonetheless be acknowledged. First, the analytical unit was the individual procedure, and multiple procedures performed in the same patient were treated as separate observations. Because repeated measurements from the same individual are not statistically independent, this approach may introduce a within-patient clustering effect that could influence the observed associations; the results should therefore be interpreted with this potential dependency in mind, and future studies should employ clustered or mixed-effects models to account for it. Second, all comparisons were univariate, and no multivariable analysis was performed to adjust for potential confounders; consequently, the reported associations cannot be considered independent of one another, and the relationship between device type and study period in particular remains confounded. Third, the retrospective design carries a risk of incomplete or inconsistent complication documentation, especially for milder events in the earlier study years. Fourth, the small number of severe adverse events (n=6) markedly limited statistical power for analyses of severe complications. Fifth, hydroxyurea data were missing for 47 procedures (17.2%), which further reduced power for the medication-related analysis. Finally, the single-center design may limit the generalizability of the findings to other settings.

CONCLUSION

Automated RCE is a safe modality for the management of adult patients with SCD, with an overall procedural complication rate of 12.4% and a severe adverse event rate of 2.2%. No life-threatening complications were recorded. Higher pre-procedure Hb and Hct values were significantly associated with increased complication risk—a novel finding warranting prospective validation. The Spectra Optia® apheresis system demonstrated a markedly superior safety profile compared with the MCS® device. The substantial improvement in complication rates over the study period reflects the combined impact of institutional learning, protocol maturation, and device modernization. These findings may support protocol development and quality improvement at centers establishing or expanding erythrocytapheresis programs for patients with SCD.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the Health Sciences Researches Ethics Committee of Mersin University Rectorate (Date: 28.04.2026, Decision No: 2026/248).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

Concept: SM, PA, SY, HÜ, MBK, AE, EOK, ET, ENT; Design: SM; Control: ENT; Data Collection and/or Processing: PA, MBK, AE, EOK, ET; Analysis and/or Interpretation: SM; Literature Review: SM; Article Writing: SM; Critical Review: ENT.

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