Received: 6 July 2023 | Revised: 3 August 2023 | Accepted: 3 August 2023

DOI: 10.1111/ejh.14083

ORIGINAL ARTICLE

European Journal of Haematology

WILEY

Feasibility of peripheral blood stem cell collection from sickle cell trait donors with an intensified G-CSF regimen

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Funding information
Deutsche Forschungsgemeinschaft; EuduraCT No: 2018-002652-33

Abstract

Objectives: Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative treatment for SCD and bone marrow from an HLA-matched sibling is currently the standard of care. Haploidentical HSCT from a family donor with a TCR αβ/CD19 depleted graft (T-haplo) is an increasingly successful alternative, which requires the generation of G-CSF stimulated peripheral stem cell (PBSC) from haploidentical relatives. These sickle cell trait (SCT) donors reported to develop SCD-related complications in conditions of severe stress.

Methods: In this retrospective analysis, we compared the safety and efficacy of PBSC mobilization with a G-CSF intensified mobilization regimen in SCT donors with a conventional G-CSF mobilization regimen in healthy donors.

Results: The reported adverse events were similar during intensified G-CSF mobilization, apheresis, and shortly after stem cell apheresis in SCT and control donors. In SCT and control donors, we were able to mobilize high yields of $CD34^+$ stem cells and the harvested $CD34^+$ cell count was comparable with control donors.

Conclusions: Peripheral stem cell mobilization using an intensified G-CSF regimen is safe, and well tolerated among SCT donors. SCT donors are a valid alternative for collection of peripheral $CD34^+$ stem cells for T-cell-depleted haploidentical stem cell transplantation.

KEYWORDS
sickle cell trait, sickle cell disease, stem cell mobilization, stem cell transplantation, stem cell harvest

Novelty Statements

What is the new aspect of the work?

In SCT and control donors, we were able to mobilize high yields of $CD34^+$ stem cells and the harvested $CD34^+$ cell count was comparable with control donors.

Morad Mohrez and Anja Troeger contributed equally as first authors. Juergen Foell and Norbert Ahrens contributed equally as last authors.

What is the central findings of your work?

Peripheral stem cell mobilization using an intensified G-CSF regimen is highly efficient, and well tolerated among SCT donors.

What is (or could be) the specific clinical relevance of your work?

SCT donors are valid alternative donors for collection of peripheral blood $CD34^{+}$ stem cells for T-cell depleted haploidentical stem cell transplantation procedures.

1 | INTRODUCTION

Sickle cell disease (SCD) is one of the most prevalent monogenic disorders worldwide, caused by a single point mutation in the ß-globin chain.[1] Homozygous or compound heterozygous hemoglobin S forms insoluble polymers when deoxygenated leading to vaso-occlusion (VOC) and hemolytic anemia in homozygous individuals, responsible for all related complications of SCD.[2] Heterozygosity leads to sickle cell trait (SCT), usually considered a benign carrier state with approximately 35% HbS, near normal hematological parameters, and no impact on life expectancy.[3,4] However, several case reports report on SCD-like complications in oxidative stress with hyposthenuria or venous thromboembolism, hemolysis, pulmonary and splenic infarctions, and increased sudden fatalities during extensive physical exertion and extreme conditions such as high altitudes.[4,5]

To date, allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative treatment for SCD currently offered to patients with serious SCD-related complications. HSCT with bone marrow from a HLA-matched sibling (MSD) is currently standard of care with a reported overall and event-free survival in children exceeding 90% and 80%, respectively.[6,7] The availability of MSD and matched unrelated donors (MUD) is less well below 20%, in particular in patients from African descent.[8,9]

This unmet need can be covered increasingly successfully with an HSCT from partially HLA-matched first-degree related donors (haplo-HSCT) with T cell-depleted grafts, either via in-vitro αßT/CD19 cell depletion[10,11] or an in vivo depletion using the post-transplant cyclophosphamide approach (Post-Cy).[12] Post-Cy-haplo-HSCT seems very intriguing due to its simplicity, ubiquitous availability, and fast immune recovery after the infusion of a non-manipulated bone marrow graft. Despite possible differences in the incidence of graft versus host disease (GvHD), graft failure, or development of macrophage activation syndrome (MAS), Post-Cy-haplo-HSCT may be a good option for younger patients with severe SCD due to rapid immune recovery and reduction of complications from infections.[13,14] For haplo HSCTs with in vitro T cell depletion, G-CFS mobilized peripheral blood stem cells (PBSC) from relatives are the standard of care. For SCD patients, these donors, in particular the parents, are invariably SCT.

It is postulated that by using G-CSF for PBSC mobilization the sudden increase of white blood cells, granulocytes, neutrophil activation, and cytokine release may lead to VOC in donors with SCD, triggering VOC in SCD.[15–19] In two case reports, fatalities were reported due to VOC with multiorgan failure after G-CSF mobilization in SCD patients.[20,21] Although there are various reports of successful stem cell mobilizations from SCT donors,[22–25] G-CSF represents a major safety concern and is not recommended for mobilization in several countries. This restriction can impact significantly curative approaches using PBSCs, in particular in haploidentical T cell-depleted HSCT.

Within our in-vitro T-depleted haplo-identical HSCT trial (T-Haplo-HSCT; NCT04201210) for patients with high-risk SCD and no available sibling donor, we compared in this retrospective analysis the safety and efficacy of PBSC mobilization with a G-CSF intensified mobilization regimen in healthy and SCT donors.

2 | MATERIALS AND METHODS

2.1 | Study subjects

We conducted a retrospective comparative analysis of the safety and efficacy of stem cell mobilization with G-CSF and apheresis outcomes between healthy and haploidentical HSCT SCT donors. Thirteen healthy allogeneic peripheral stem cell donors (nine matched sibling donors, MSD, four MMRD, haploidentical donors, mean age 46, range 16–60) and 19 SCT donors (miss matched related donors, MMRD, haploidentical donors, mean age 43, range 15–57) from our haplo-HSCT program for SCD patients were enrolled in this analysis. Informed consent was obtained in accordance with the Helsinki Declaration and our Institutional Review Board. All donors were screened for SCT status via hemoglobin electrophoresis. Potential stem cell donors who did not meet the general criteria for healthy donors were excluded from donation (e.g., signs of infections or unstable physical conditions). All donors were carefully monitored for potential adverse events during and following the apheresis process, graded by the common terminology criteria for adverse events (CTCAE). For this reason, we used a standardized questionnaire for self-reporting adverse events and asked specifically about symptoms during the mobilization regimen and the stem cell harvesting process.

2.2 | PBSC mobilization and apheresis

Stem cell mobilization was performed using G-CSF [Neupogen; Filgrastim (Amgen, Mississauga, Canada/USA) or Granocyte;

Lenograstim (Chugai-Rhone-Poulenc, Paris, France)] for 5 days. The control group received 10 μg/kg G-CSF subcutaneously for at least 5 days. The SCT donor mobilization regimen is based on previous studies, mainly with African American SCT donors.[19,22] The donors received, 10 μg/kg G-CSF, for the first 3 days, a dosing that was increased to 15 μg/kg 1 day before apheresis. On the day of apheresis (fifth day), the last dose (10 μg/kg) was given about 3 h prior to stem cell collection (intensified mobilization schema). Stem cell apheresis was performed via a double-lumen catheter (Shaldon) or peripheral veins by using the IDL set with a Spectra Optia cell separator (Terumo BCT, Lakewood, CO, USA) with cMNC software (version 1.3) for continuous collection of mononuclear cells. ACD-A was used as an anticoagulant at a standard ratio of 1:12. Calcium gluconate was administered intravenously as clinically required. In general, four times the patient's total blood volume was processed in 300 min for cell collection. In case of low yield, a second collection day was performed. It is worth mentioning that the critical points of apheresis (i.e., duration and processed blood volume) adapted here as standard represents the maximum permissible parameters defined by local German guidelines.

According to our routine documentation protocol, reporting and documenting of any observed side effects during or resulting from the apheresis is mandatory. This strategy allowed us to evaluate all the data from healthy and SCT donors retrospectively.

2.3 | Laboratory data

$CD34^+$ cell counts in donor peripheral blood prior to the harvest and from the harvested stem cell products were measured using a Navios flow cytometer (Beckman Coulter, USA). For haplo-HSCT, the collection target was $\geq 5 \times 10^6$/kg $CD34^+$ cells, and for the controls $\geq 2 \times 10^6$/kg $CD34^+$ cells of recipient weight to allow safe engraftment. Similarly, complete blood counts were monitored for leukocyte increment from all donors before and after apheresis on a XN-550 hematology analyser (Sysmex, Germany) in order to identify poor mobilizers.

2.4 | Statistical analysis

Data were extracted from the hospital's central laboratory information system (Swisslab, Berlin, Germany) and electronic data system (SAP) and exported to R® software for statistical analysis and graph creation. Collection efficiencies were calculated using the formula: $CD34^+$ cell count in harvest product multiplied with 100 divided through $CD34^+$ count donor (mean of pre- and post-apheresis) multiplied with processed Volume. Two-tailed unpaired student *t*-tests were used to compare groups of two with equal variance and in case of no equal variance, the data were tested for significance using the Mann–Whitney-U test. *p*-values below .05 were considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

Table 1 summarize the baseline characteristics of the 32 HSCT donors in this retrospective study. Of the 32 HSCT donors, 19 donors were SCT (SCT group), confirmed by hemoglobin electrophoresis and 13 donors were healthy participants without SCT donating for allogeneic HSCT (9 MSD and 4 MMRD, control group). No significant difference was found between the two groups with regard to age, gender, and weight (Table 1). In the control group, 4 donors (4/13) and in the SCT group 12 donors (12/19) had second apheresis, difference based on higher target stem cell amount for haploidentical HSCT. Baseline laboratory results did not differ between both groups before and after apheresis, with the exception of nearly significant hemoglobin count before apheresis, and significantly higher hemoglobin count after apheresis in the SCT group (median, 11.2 mg/dL vs. 13.2 mg/dL, $p = .05$). It should be noted that there were differences in the ethical origins of the donors. In the SCT group 6 African donors and 13 Caucasian donors and in the control group 2 African (both MMRD) and 11 Caucasian donors.[22]

3.2 | Mobilization and collection

The stem cell collecting procedure was successful in both groups and mobilization failure or poor mobilization did not occur. The higher hemoglobin levels in the SCT group before and after apheresis did not affect the apheresis (Table 1). In both groups, comparably high yields of $CD34^+$ stem cells were mobilized. Taking into account the intensified mobilization regimens and higher $CD34^+$ stem cell target volume (for haploidentical stem cell transplantation), the total harvested $CD34^+$ cell count (Table 1) was comparable in the SCT group and in the control group (median, 55.27×10^7 $CD34^+$ cells versus 47.44×10^7 $CD34^+$ cells, $p = .706$). Due to the lower body weight of the recipients in the SCT group (median 56 kg, 17–77 kg) compared to the control group (median 80 kg, 51–124 kg), the $CD34^+$ cells per kg recipient body weight (BW, Table 1) was significantly higher in the SCT group (median, 10.2×10^6 $CD34^+$ cells/kg BW) compared to the control group (5.9×10^6 $CD34^+$ cells/kg BW) ($p = .036$). Furthermore, we found no statistical difference in the $CD34^+$ cells per 70 kg BW (Table 1) in the SCT group (median, 7.9×10^6 $CD34^+$ cells/70 kg BW) compared to the control group (6.8×10^6 $CD34^+$ cells/70 kg BW). Because of the required higher target $CD34^+$ counts, multiple-day collections in the SCT group (12 SCT group versus 4 control group patients) were necessary (Table 1).

In spite of the slightly higher hemoglobin levels in the SCT group compared to the control group, we found a similar collection efficacy for white blood cells, lymphocytes, monocytes, mononuclear and $CD34^+$ cells in SCT and healthy donors (Figure 1). In the collection

TABLE 1 Patient characteristics and collection parameters.

Characteristic	Control ($n = 13$)	SCT ($n = 19$)	*p*-value
Age [years]	46 (16–60)	43 (15–57)	0.294
Gender (m/f)	6/7	12/7	
Weight [kg]	67 (53–123)	79 (64–118)	0.267
HbS [%]	n.p.	38 (25–41)	
HbA [%]	n.p.	60 (56–72)	
Collection parameters			
Apheresis	**$n = 17$**	**$n = 31$**	
Number of collection procedures per donor	1.3 (1–2)	1.6 (1–2)	
Apheresis volume	395 (267–489)	357 (155–466)	0.223
Processing volume	15 344 [10 499–22 295]	14 946 [7655–21 917]	0.240
Hb (before apheresis) [mg/dL]	12.5 (11.1–15.8)	14.1 (10.2–17.5)	0.062
Hb (after apheresis) [mg/dL]	11.2 (9.8–14.8)	13.2 (8.9–16.5)	0.053
Reticulocytes before apheresis [%]	18.1 (7.4–33.1)	17.9 (9.5–32.3)	0.724
HCT (before apheresis) [%]	37.5 (33.6–46.1)	39.9 [31.2–49.1]	0.145
White blood cells, before [$\times 10^3/\mu L$]	52.7 (34.9–95.1)	54.4 (30.66–81.04)	0.991
White blood cells, after [$\times 10^3/\mu L$]	52.8 (26.2–75.9)	47.7 (31.81–81.45)	0.871
Platelets, before [$\times 10^3/\mu L$]	198 (98–295)	153 (85–270)	0.065
Platelets, after [$\times 10^3/\mu L$]	111 (58–227)	91 (52–180)	0.151
$CD34^+$ blood count before apheresis ($/\mu L$]	67 (16–309)	87 [21–363]	0.207
$CD34^+$ count (complete collected) [$\times 10^6$]	474.4 (96.3–2262.7)	552.7 (41–1567.9)	0.706
$CD34^+$/kg body weight recipient [$\times 10^6$]	5.9 [1.7–34.8]	10.2 [0.8–82.5]	**0.036**
$CD34^+$/70 kg body weight [$\times 10^6$]	6.8 (1.4–32.3)	7.9 (0.69–22.4)	0.706

Note: Baseline characteristics of study subjects with (SCT group) and without (healthy donors, control group) heterozygous sickle cell trait. Data shown as median with min. and max. range in parenthesis. Bold value indicates the significance between groups.
Abbreviation: n.p. = no parameters.

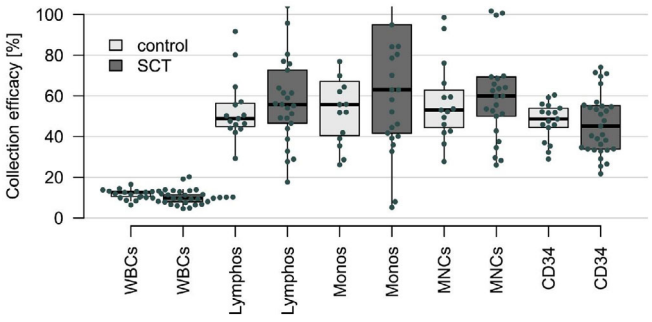

FIGURE 1 Cell collection efficacy after stem cell apheresis. Collection efficacy of white blood cells (WBCs), lymphocytes (Lymphos), monocytes (Monos), mononuclear cells (MNCs) and $CD34^+$ positive stem cells after apheresis for the control (white bars) and SCT group (gray bars). Values shown in box plots. The box plot contains the middle 25 to 75% of the data, with median shown by the line inside the box, and top and bottom lines outside the box demarcating the lowest 10% and highest 90% of the data.

efficacy prediction analyses, it seemed that higher reticulocyte counts before apheresis have a positive effect and the white blood cell count a negative effect on the $CD34^+$ collection efficiency (Figure 2A, F).

The predicted $CD34^+$ collection efficiencies were more comparable between the SCT and control group in case of the $CD34^+$ cell count, hemoglobin, hematocrit, and monuclear cells before apheresis (Figure 2B–E).

3.3 | Adverse events

Adverse events were similar and statistically not different during intensified G-CSF mobilization, apheresis, and short-after stem cell apheresis in SCT and control donors. There was no significant difference with regard to incidence or severity of reported symptoms; specifically bone pain, headache, and paresthesia (grade 1 by CTCAE). In the SCT group, 14 donors had bone pain (74%), 2 donors had headache (10%), and 1 donor paresthesia. In the control group, 9 donors had bone pain (69%), 1 donor headache (8%), and 1 donor paresthesia. Most of the donors with bone pain in both groups required limited analgesia. None of our donors developed infection, seizure, bleeding, nausea, and splenic rupture.

In particular, no SC-related complications such as thrombosis, chest pain, or any signs of VOC were observed in the SCT group.

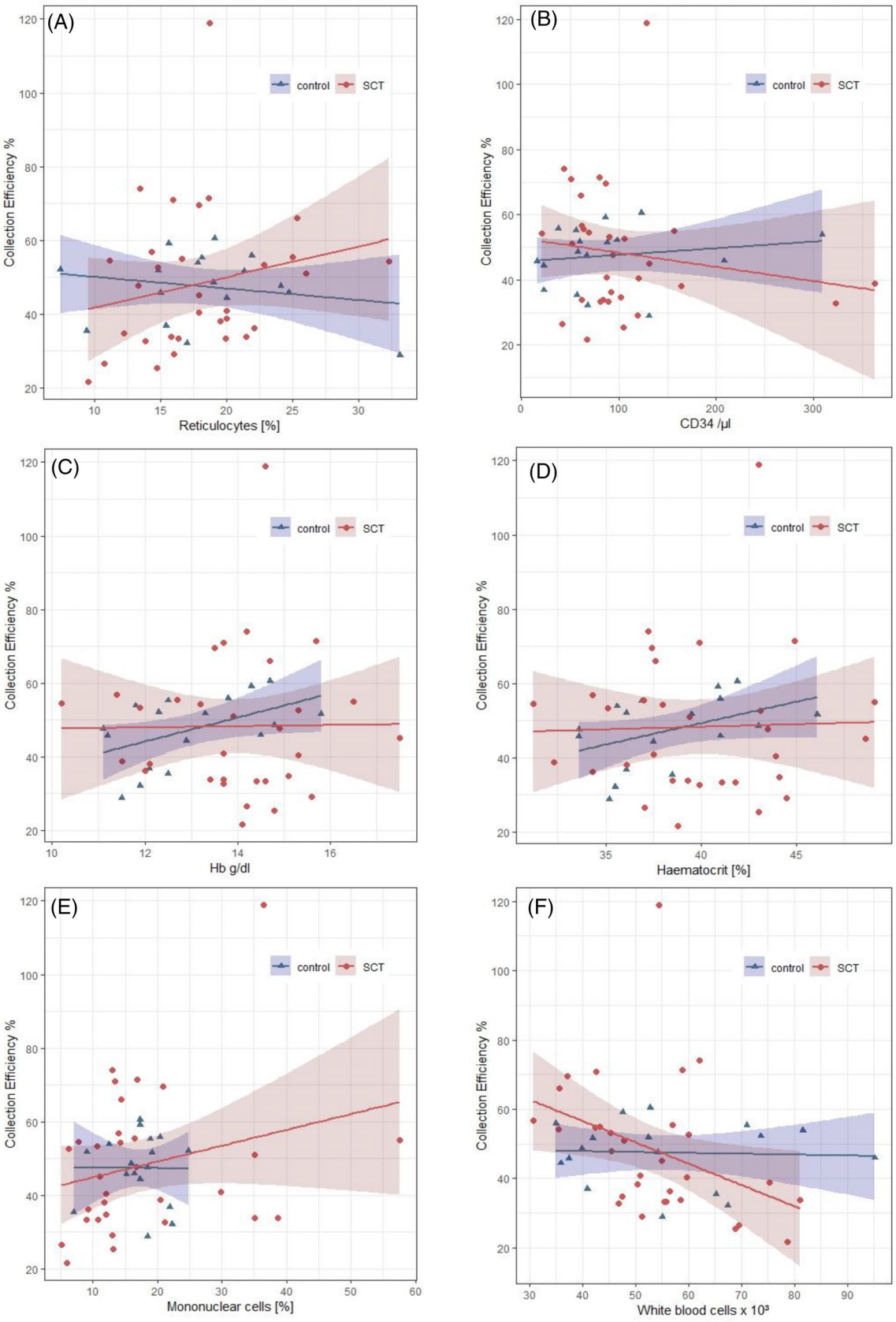

FIGURE 2 Collection efficacy prediction intervals for $CD34^+$ stem cells. Shown are $CD34^+$ collection efficiency linear regression, prediction and 95% confidence intervals depends on peripheral reticulocytes (A), $CD34^+$ cell count (B), hemoglobin levels (C), hematocrit (D), mononuclear cells (E), and white blood cells (F) before apheresis.

4 | DISCUSSION

An in vitro αßT cell depleted haploidentical HSCT allows a curative and safe approach for the majority of patients with no available matched donor with the advantage of a fast hematologic recovery and low incidence of acute and chronic GvHD.[10,26,27] However, it is postulated that by using G-CSF for PBSC mobilization the sudden increase of white blood cells, granulocytes, neutrophil activation, and cytokine release may lead to VOC in donors with SCD and presumably in donors with SCT.[15,16,20,22,23] Therefore, we compared in a retrospective analysis the safety and efficacy of an intensified G-CSF mobilization regimen for SCT donors with healthy PBSC donors for allogenic HSCT (MSD, MMRD). We show in this study that the PBSC mobilization with a G-CSF slightly intensified mobilization regimen in SCT donors is as safe and efficient as in healthy donors.

Several studies with a limited number of patients reported from sickle cell pain crisis like VOC, acute chest syndrome, disseminated intravascular coagulation and in one case with life threatening multiorgan failure after G-CSF mobilization in SCD patients.[16,18–21,28,29] At present, exist no study of severe SCD like complications in SCT patients after G-CSF mobilization. However, there are various reports of successful G-CSF stem cell mobilizations from SCT individuals with no significant SCD-like complications.[23–25,30] Only in the prospective study of Kang et al., it was reported that after G-CSF mobilization in eight SCT donors, the cumulative symptom score was significantly higher with a trend toward higher use of analgesia as compared to healthy donors.[24] The intensified G-CSF regimen with increased G-CSF dosage at the end of the mobilization regimen that was used in our SCT donors is based on previous studies mostly with African American SCT donors.[19,22] In the present study, the intensified G-CSF PBSC mobilization was well tolerated and none of the SCT donor has experienced unexpected adverse events compared to healthy donors, including symptoms resembling SC-related complications. The observed findings do not differ with regard to adverse effects and use of analgesics under G-CSF mobilization compared to various previously reported studies in healthy donors.[22,24,30,31]

Although there are no guidelines or recommendations, there are suggestions to avoid G-CSF based mobilization of peripheral stem cells in SCT donors with HbS levels over 30% or a leukocytosis over 80×10^9/L.[19,23,25] We observed in our SCT patient cohort with a median HbS of 38% (range 25%–41%) and leukocyte counts of up to 80×10^9/L no symptoms resembling sickle cell crisis.

With our intensified G-CSF mobilization regimen, we found a statistically not significant trend to a higher number of circulating $CD34^+$ cells before apheresis, and comparable $CD34^+$ count (total and per 70 kg BW) after apheresis in the SCT group and the control group. We found only a significantly higher $CD34^+$ cell count related to the BW of the recipient in the SCT group compared to the control group, because of the lower BW of the recipients in these group. Panch et al. found in African Americans with SCT who received a similarly high dose of G-CSF for PBSC mobilization (12 µg/kg BW/day) a not significant difference in $CD34^+$ counts and the $CD34^+$ cell collection efficiency, but a significant higher $CD34^+$ count before apheresis in African Americans compare to Caucasians.[22] We found a not significant, more slightly increased, $CD34^+$ count berfore apheresis in the SCT group compared to the control group. These differences may be explained through a higher number of donors with African origin in the SCT group.[22] Furthermore, Kang et al. reported on 8 SCT patients a not statistically significant trend to a higher $CD34^+$ cell count post-apheresis in the SCT subjects (median 7.1 ± 4 vs. 4.9 ± 2.3 $CD34^+/70\ kg \times 10^6$) using a standard G-CSF dose (10 µg/kg BW/day). But, the $CD34^+$ collection efficiency was significantly better in the subjects without SCT.[24] This trend to higher $CD34^+$ counts and better $CD34^+$ collection efficiency with regular G-CSF dose used in the control subjects compared to SCT subjects is confirmed in two other newer publications.[31,32] We found in our analysis a similar trend to higher $CD34^+$ counts before apheresis, but no differences in collection efficiencies in both groups of donors. In context of the trend to higher hemoglobin levels before apheresis in the SCT donors compared to normal donors, one explanation could be that patients with SCT have a constitutively more activated bone marrow resulting in an increase in hematopoietic drive and therefore in higher hemoglobin levels. But, SCT red cells seem to have a normal life span, and comparable Reticulocytes levels suggest no increase in hematopoietic drive.[33] However, the trend to higher hemoglobin and lower platelets in our series suggests a more active or reactive hematopoietic system, at least in adult SCT donors, and could also explain the expected increase of $CD34^+$stem cell collection efficiency with an increase of reticulocytes, but not with increase of $CD34^+$ counts before apheresis.

In conclusion, peripheral stem cell mobilization and apheresis using an intensified G-CSF regimen among SCT donors is safe and highly effective. SCT donors are valid alternative as donors for collection of peripheral blood $CD34^+$ stem cells for T-cell depleted haploidentical stem cell transplantation procedures (T-haplo HSCT) for relatives with SCD.

AUTHOR CONTRIBUTIONS

Morad Mohrez, Anja Troeger, Norbert Ahrens, Selim Corbacioglu, and Juergen Foell designed the study and prepared the manuscript. Morad Mohrez, Anja Troeger, Katharina Kleinschmidt, Tarek Hanafee Alali, Andreas Brosig, Viola Hähnel, Silke Kietz, Robert Offner, Ralph Burkhardt, Selim Corbacioglu, Norbert Ahrens, Juergen Foell managed the donors. Morad Mohrez, Anja Troeger, and Juergen Foell collected and organized the data. Norbert Ahrens and Juergen Foell performed the statistical analysis. Norbert Ahrens, Ralph Burkhardt, Selim Corbacioglu, and Juergen Foell critically revised the draft of the paper and gave important intellectual contributions. All authors critically reviewed and approved the paper.

ACKNOWLEDGEMENTS

The help and support of the apheresis operators and physicians who conducted the apheresis procedures at the Institute of Clinical Chemistry and Laboratory Medicine and of the Department of Pediatric Hematology, Oncology and Stem Cell Transplantation of the University Hospital Regensburg are very much appreciated. Open Access funding enabled and organized by Projekt DEAL.

FUNDING INFORMATION

These study was funded by Deutsche Forschungsgemeinschaft (DFG; T-Haplo-HSCT; EuduraCT No: 2018-002652-33).

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Mohrez M, Troeger A, Kleinschmidt K, et al. Feasibility of peripheral blood stem cell collection from sickle cell trait donors with an intensified G-CSF regimen. *Eur J Haematol*. 2023;1-7. doi:10.1111/ejh.14083