Erythrocytapheresis versus phlebotomy in the initial treatment of HFE hemochromatosis patients: results from a randomized trial

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BACKGROUND: Standard treatment of newly diagnosed HFE hemochromatosis patients is phlebotomy. Erythrocytapheresis provides a new therapeutic modality that can remove up to three times more red blood cells per single procedure and could thus have a clinical and economic benefit.

STUDY DESIGN AND METHODS: To compare the number of treatment procedures between erythrocytapheresis and phlebotomy needed to reach the serum ferritin (SF) target level of 50 μg/L, a two-treatment-arms, randomized trial was conducted in which 38 newly diagnosed patients homozygous for C282Y were randomly assigned in a 1:1 ratio to undergo either erythrocytapheresis or phlebotomy. A 50% decrease in the number of treatment procedures for erythrocytapheresis compared to phlebotomy was chosen as the relevant difference to detect.

RESULTS: Univariate analysis showed a significantly lower mean number of treatment procedures in the erythrocytapheresis group (9 vs. 27; ratio, 0.33; 95% confidence interval [CI], 0.25-0.45; Mann-Whitney $p < 0.001$). After adjustments for the two important influential factors initial SF level and body weight, the reduction ratio was still significant (0.43; 95% CI, 0.35-0.52; $p < 0.001$). Cost analysis showed no significant difference in treatment costs between both procedures. The costs resulting from productivity loss were significantly lower for the erythrocytapheresis group.

CONCLUSION: Erythrocytapheresis is highly effective treatment to reduce iron overload and from a societal perspective might potentially also be a cost-saving therapy.

Standard treatment for HFE hemochromatosis (HFE-HC) is removal of an excess in body iron by phlebotomy. Serum ferritin (SF) level is used as a marker for the amount of iron overload and to monitor the effectiveness of phlebotomy. The advised target SF level is 50 μg/L or less.[1-4] Phlebotomy is inexpensive and easy to perform but in patients with high initial SF concentrations up to 100 procedures are required.[5,6] In a large survey in hemochromatosis patients, 15% of patients treated with phlebotomy expressed a negative opinion about this therapy. The primary negative aspects were venous access problems, traveling time, waiting

ABBREVIATIONS: HFE-HC = HFE hemochromatosis; SF = serum ferritin.

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time, and duration of the procedure.[7,8] In an online survey performed in the United States, France, Ireland, and the United Kingdom, 16% of the patients would definitely decide not to receive phlebotomy, if alternative options were available and 52% of induction treatment patients experienced side effects always or most of the time after phlebotomy.[9]

The past 15 years erythrocytapheresis has also been used as a therapeutic modality and has been evaluated in nonrandomized studies.[10-20] With erythrocytapheresis up to 800 mL of red blood cells (RBCs) per single procedure can be removed compared to 200 to 250 mL of RBCs per phlebotomy, which means that erythrocytapheresis potentially offers a more efficient method to remove iron overload with fewer procedures in less time. Up to now, however, no randomized trials have been performed to evaluate the effectiveness of erythrocytapheresis compared to phlebotomy. Therefore, the aim of this study was to compare in a randomized, prospective way erythrocytapheresis with the standard of care phlebotomy and to test the hypothesis that erythrocytapheresis significantly reduces the number of treatment procedures.

MATERIALS AND METHODS

Study design

We conducted a two-treatment-arms, randomized, clinical trial, involving 38 newly diagnosed patients with HFE-HC, homozygous for C282Y. Participants were randomly assigned in a 1:1 ratio to erythrocytapheresis or phlebotomy treatment. The primary outcome measure was the number of treatment procedures to reach the SF target level of 50 μg/L or less. Secondary outcomes were the total duration of treatment, the occurrence of side effects, change in iron status and liver function, health-related quality of life, and costs. A 50% decrease in the number of treatment procedures for erythrocytapheresis compared to phlebotomy was chosen as the relevant difference to detect. The ethics committee of each participating hospital approved of the study.

Participants

Between December 2005 and November 2008 all newly diagnosed HFE-HC patients were referred from four hospitals in the region of Sanquin Blood Bank South East Division (the Netherlands). Inclusion criteria were as follows: Homozygous for C282Y mutation, age between 18 and 80 years, weight 50 kg or more, transferrin saturation greater than 50%, SF greater than 450 μg/L, and hemoglobin (Hb) concentration 7.5 mmol/L or more (120 g/L) in women and 8.0 mmol/L or more (128 g/L) in men. Exclusion criteria were as follows: malignancy, serious cardiac arrhythmias, heart failure, and epilepsy.

All participants gave written informed consent and were randomized to erythrocytapheresis or phlebotomy treatment by an independent person working as quality assurance manager at Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht. He was contacted by phone upon enrollment of each new patient.

Treatment procedures

Phlebotomy

Per single treatment procedure 500 mL of whole blood (equals 200-250 mL of RBCs) was withdrawn once weekly, after puncturing a superficial vein of the forearm with a 16-gauge (1.6 mm) straight needle, using a mixing device and a collection bag (Compo Guard and Compo Select T 3941, respectively, Fresenius SE, Bad Homburg, Germany). Under the assumption that each milliliter of RBCs equals 1 mg of iron[21] the absolute amount of iron removed in this group was estimated by the formula:

$Fe_{removed}$ = blood volume withdrawn × mean preprocedure hematocrit (Hct) of each individual patient.

Therapeutic erythrocytapheresis

Per single treatment procedure 350 to 800 mL of RBCs was withdrawn once every 2 weeks, after puncturing a superficial vein of the forearm with a 16-gauge (1.6 mm) straight needle. We used an erythrocytapheresis collection device (Model 944 and MCS+ equipment, Haemonetics Corporation, Braintree, MA). The removed RBC volume was determined by the total estimated blood volume (based on sex, weight, and height) and Hct of each individual patient and the minimal targeted postprocedure Hct set at 30%. The total blood volume was calculated according:

Men

$$2740\times\sqrt{\frac{height(cm)\times weight(kg)}{3600}},$$

Women

$$2370\times\sqrt{\frac{height(cm)\times weight(kg)}{3600}}$$

A 2-week interval was in agreement with results from our pilot study[13] indicating an optimal return of Hb values within those 2 weeks. During first treatment 30% of the estimated removed RBC volume was replaced with isotonic saline. Depending on how well the patient tolerated the first treatment procedure, 0% to 50% of the estimated removed RBC volume was replaced by saline in all subsequent treatment sessions. The absolute amount of iron removed in this group was calculated according to

$$Fe_{removed} = \text{RBCs volume withdrawn} \times 0.80.$$

The correction factor 0.80 was based on the actual Hct of removed RBCs.

All phlebotomy and erythrocytapheresis procedures were performed in one blood donor center of Sanquin

Blood Supply, by two certified research nurses experienced in therapeutic procedures, using standard equipment available in blood donor centers.

Monitoring of treatment

In blood samples taken before and immediately after each procedure, the values of Hb, Hct, MCV, white blood cells (WBCs), platelets (PLTs), serum iron, SF, transferrin, and transferrin saturation were assessed. Treatment was discontinued when a SF level of 50 µg/L or less, as measured in a blood sample taken at least 1 week after any treatment, was reached. Health-related quality of life was assessed at baseline, halftime, and at end of treatment by means of the EQ-VAS or "feeling thermometer," which is a 20-cm 100-point visual vertical analog scale, portrayed as similar to a thermometer, on which the respondent rates his or her health state at the visit between 0 (worst imaginable health) to 100 (best imaginable health).[22]

Statistical analysis

Sample size calculation

From earlier phlebotomy studies it was clear that the number of treatment procedures in newly diagnosed HFE-HC patients could vary between 10 and 60 with a median between 30 and 40. In a restricted, earlier conducted erythrocytapheresis study[13] the median for a much more homogeneous population was approximately 10 with a range between 5 and 20. With a two-sided α level of 0.05 and a $1 - \beta$ power of 0.95, the number of patients needed for each arm is 18. To allow for possible nonadherence numbers needed have been set at 19 for each arm and thus 38 patients had to be included in the study.

Data analysis

The main outcomes of this study were the number of treatment procedures the patient must undergo as well as the treatment duration in weeks. Interval and ratio variables are tested for normality of distribution by the Wilk-Shapiro test. If normally distributed, means and standard deviations (SDs) are presented; if not, the score range is provided. Univariate analysis on baseline differences in metric, normally distributed (clinical) data between both groups (phlebotomy and erythrocytapheresis) is done with the t test or Fisher's exact test, in nonnormally distributed data with the Mann-Whitney test. Multiple analysis is done with logistic regression analysis using both classes in preferential numbers of treatment as a dichotomous outcome variable.

Despite randomization of the participants the univariate analysis showed a significant difference of the mean initial SF level between both treatment arms. Based on this knowledge we corrected for the initial SF level by multiple linear regression analysis to analyze differences in means between standard phlebotomy and erythrocytapheresis. A p value of less than 0.05 was considered significant. All data analysis was done with computer software (SPSS-pc Version 16.0, SPSS, Inc., Chicago, IL).

Cost analysis

The cost analysis included treatment costs and costs related to the loss of productivity. A cost price calculation of both treatment procedures was performed by Sanquin Blood Supply's financial department based on the actual personnel time and use of material per single procedure. Productivity loss was measured by asking patients to report the hours they were absent from work. The costs related to the hours of work lost were valued based on the friction cost method which calculates the hours of work lost until another employee can take over.[23,24] Since there was no information available about full-time or part-time characteristics of the patient's job, we calculated productivity costs as follows: the number of working hours absent multiplied by the gross national wage per hour multiplied by 0.8 elasticity factor. This elasticity factor reflects the fact that the decrease in productivity is not proportional to the reduction in annual labor.[23] Uncertainty intervals (2.5th and 97.5th percentiles) for the mean differential costs were calculated by the bootstrap method.[25] All costs are presented in euros (1€ = $1.30) for the year 2009.

RESULTS

A total of 38 patients were randomly assigned to one of the two treatment arms. There were no dropouts. Baseline patient characteristics are summarized in Table 1. The demographics, hematologic, and biochemical variables as well as perceived health status, assessed by means of the EQ-VAS visual analog scale, were not significantly different between groups. However, the initial SF concentrations were significantly lower in the erythrocytapheresis group.

In two patients treated with phlebotomy the volume of blood withdrawn per treatment procedure was reduced to 300 to 400 mL because of dizziness during or immediately after the procedure. In two other patients, who complained about fatigue in the days after treatment, the time interval was extended by 1 week. In the erythrocytapheresis group two female patients needed extension of the 2-week interval by 1 week due to slowly restored Hb values after treatment procedure.

Hematologic and biochemical variables

After the treatment period no significant differences in hematologic and biochemical variables were observed between both treatment groups (Table 1). The aspartate aminotransferase (AST) levels at the end of treatment showed complete recovery in 18 of 19 patients (95%). The alanine aminotransferase (ALT) levels at the end of treat-

ment showed complete recovery in 20 of 23 (87%) patients. In four patients the levels were almost normalized (one) or substantially decreased (three).

Health-related quality of life

As shown in Table 1, no significant difference in perceived health status assessed by means of the EQ-VAS visual analog scale between both treatment groups was observed at the end of the treatment period.

Iron variables

The estimated mean total amount of removed iron (Table 2) was lower in the erythrocytapheresis group (3759 mg vs. 5369 mg, Mann-Whitney $p < 0.001$). This corresponds with the lower initial SF levels in the erythrocytapheresis group. However, the mean amount of iron removed per treatment procedure was significantly higher in the erythrocytapheresis group than in the phlebotomy group (427 mg vs. 205 mg, $p < 0.001$).

TABLE 1. Baseline and end of treatment characteristics*

	Phlebotomy, n = 19 (5♀, 14♂)		Erythrocytapheresis, n = 19 (5♀, 14♂)		p value	
Patient characteristics	Start	End	Start	End	Start	End
Age (years)	52 (12)		52 (10)		0.96	
Height (cm)	176 (9)		176 (10)		0.81	
Weight (kg)	82 (17)		84 (16)		0.74	
Blood volume (L)	5153 (939)		5178 (912)		0.93	
SF (♂: 16-250 µg/L) (♀: 6-125 µg/L)	1676 (612-3418)	41.7 (28-50)	1103 (454-3279)	40.2 (23-50)	0.04†	0.62†
Transferrin (♂♀: 1.5-3.5 g/L)	1.75 (0.26)‡	2.34 (0.26)§	1.69 (0.26)‡	2.31 (0.28)‡	0.53	0.81
Transferrin saturation (♂♀: 20%-45%)	87.9 (52.5-105.6)	25.3 (11.9-52.0)	89.9 (68.7-102.0)	29.5 (7.6-75.9)	0.91†	0.91†
Serum iron (♂: 14-27 µmol/L) (♀: 11-25 µmol/L)	35.1 (8.2)	13.2 (8.0-24.9)	36.3 (6.8)	14.9 (4.7-37.4)	0.60	0.95†
Hct (♂: 0.41%-0.52%) (♀: 0.36%-0.48%)	44 (4)	39 (3)	44 (4)	40 (4)	0.76	0.75
Hb (♂: 8.2-11.0 mmol/L) (♀: 7.3-9.7 mmol/L)	9.7 (1.0)	8.2 (0.8)	9.5 (0.8)	8.1 (0.7)	0.36	0.72
MCV (♂♀: 87-98 f/L)	95.9 (4.6)	95.6 (3.8)	94.9 (3.7)	94.8 (6.1)	0.49	0.64
AST (♂: 0-35 U/L) (♀: 0-30 U/L)	42 (16-79)	23.5 (7.2)‡	33 (6-69)	19.1 (7.9)	0.25†	0.09
ALT (♂: 0-45 U/L) (♀: 0-35 U/L)	73.6 (18-161)	26.2 (12.0-60.0)‡	50.4 (12-125)	23.2 (8.0-77.0)	0.17†	0.58†
Perceived health thermometer‖	71 (16)	68 (17)	68 (19)	69 (20)	0.56	0.56

* Data are reported as mean (SD) or mean (range).
† Using Mann-Whitney test.
‡ One missing value.
§ Three missing values.
‖ Assessed by means of the EQ-VAS visual analog scale.

TABLE 2. Results of the univariate comparisons between phlebotomy and erythrocytapheresis groups*

Variables	Phlebotomy, n = 19 (5♀, 14♂)	Erythrocytapheresis, n = 19 (5♀, 14♂)	Reduction factor	p value
No procedures	27 (11-58)	9 (4-20)	0.33	<0.001†
Treatment duration (weeks)	33.7 (12-79)	19.6 (7-37)	0.58	0.002†
Treatment Interval (days)	9 (7-14)	16 (11-26)	1.77	<0.001†
Total volume removed (mL)	13,016 (5,500-21,000)	4699 (1,839-11,655)	0.36	<0.001†
Estimated total removal of iron (mg)	5369 (2,310-8,820)	3759 (1,471-9,324)	0.70	0.008†
Estimated removal of iron per procedure (mg)	205 (136-230)	427 (294-545)	2.08	<0.001†

* Data are reported as mean (range).
† Using Mann-Whitney test.

Number of treatment procedures and treatment duration

Univariate comparisons of outcome variables between the phlebotomy and erythrocytapheresis groups are depicted in Table 2. Because none of the six outcome variables were normally distributed, means and score ranges are given, the Mann-Whitney test was performed, and the observed reduction factors of erythrocytapheresis versus phlebotomy are given as rates. In number of procedures the reduction rate of erythrocytapheresis versus phlebotomy is 0.33. In treatment duration in weeks it is 0.58 and both outcomes are significantly different between the treatment groups (Mann-Whitney $p < 0.001$ and $p = 0.002$, respectively).

To meet the assumptions of normality to facilitate the analysis of the number of treatment procedures and the treatment duration in weeks, both have been log transformed. Linear unadjusted regression analysis on the transformed number of procedures (Table 3, left side) using only treatment groups as a (0-1) predicting factor also shows significantly lower numbers for erythrocytapheresis over phlebotomy. Calculating the antilog of the unadjusted regression coefficient provides the same observed reduction factor as in Table 2 (0.33), but also its confidence interval (95% CI, 0.25-0.45), which is well in line with the hypothetically expected reduction factor of 0.50 or less (Table 3, left-side RF). For the number of weeks the reduction factor was 0.58 (95% CI, 0.43-0.79).

The multiple regression analysis was performed to adjust for the initial SF level and patient weight. After this adjustment there is still a significant regression effect between both treatment arms (Table 3, right-side RF). The estimated reduction factor of the mean number of treatment procedures of erythrocytapheresis over phlebotomy was 0.43 (95% CI, 0.33-0.52), which just exceeds the 0.50 target in the expected upper 95% CI. For treatment duration in weeks, the same adjustment gave a reduction factor of 0.70 (95% CI, 0.52-0.95).

Adverse events

All adverse events appeared to be mild or very mild in both groups. In the erythrocytapheresis group, 3 of 19 patients (15.8%) reported eight events (one case of very mild citrate reaction, one vasovagal collapse and six cases of mild dizziness) at a total of 171 procedures. In the phlebotomy group, 5 of 19 patients (26.3%) reported 10 events (one short-lasting collapse and nine cases of mild dizziness) at a total of 513 procedures. This difference was not significant when expressed by number of patients ($p = 0.12$) nor when expressed as adverse events per number of required procedures (Fisher's exact $p = 0.09$).

Cost analysis

Table 4 gives an overview of the separate items of the cost price calculation per single procedure. The cost price for erythrocytapheresis was 3.5-fold greater compared with the cost price for phlebotomy. These higher costs are a consequence of longer personnel time of the blood bank assistant and higher costs of the collection bag and collecting equipment.

There was no significant difference in total treatment costs between the erythrocytapheresis group and the phlebotomy group (Table 5). The costs resulting from the number of hours absence at work are significantly lower for the erythrocytapheresis group.

DISCUSSION

This is, to the best of our knowledge, the first randomized trial comparing phlebotomy, the standard of care, with erythrocytapheresis in the initial treatment of newly diagnosed HFE-HC patients homozygous for C282Y. Results from the univariate analysis support our hypothesis that erythrocytapheresis treatment reduced the total number of procedures with at least 50%. The observed reduction factor of 0.33 is in agreement with the results of our pilot study.[13] In addition the mean treatment duration in the erythrocytapheresis group is reduced with a factor of 0.58 ($p < 0.001$).

Despite an imbalance in initial SF between both treatment arms after randomization, multivariate analysis with correction for confounders like patient weight and initial SF confirmed the conclusions from the univariate analysis. For number of treatment procedures the ratio of 0.43 as found in the multiple regression analysis was still below the ratio of 0.50, which was set in the protocol as

TABLE 3. Results of the (multiple) linear regression analysis

	Unadjusted		Adjusted for initial SF and patient weight	
Variables	RF*	95.0% CI for RF*	RF†	95.0% CI for RF†
Number of treatment procedures	0.33	0.25-0.45	0.43	0.33-0.52
Treatment duration in weeks	0.58	0.43-0.79	0.70	0.52-0.95

* Unadjusted reduction factor (RF) of the number of treatment procedures needed or treatment duration between both treatment arms. Treatment arm was defined as "0" for phlebotomy and "1" for erythrocytapheresis.
† Estimated reduction factor adjusted for both initial SF and patient weight.

TABLE 4. Cost prices for a single treatment procedure in euros (€) for 2009

	Phlebotomy			Erythrocytapheresis		
Items	Resource use	Unit costs	Costs per procedure	Resource use	Unit costs	Costs per procedure
Personal costs						
Blood bank assistant	0.67 (hr)	31.90 (€/hr)	21,37	1.25 (hr)	31.90 (€/hr)	39.88
Blood bank physician	0.19 (hr)	65.25 (€/hr)	12.40	0.25 (hr)	65.25 (€/hr)	16.31
Material costs						
Collection bag	1	8.30*	8.30	1	90†	90
Equipment costs‡‡						
Collecting equipment	1/1500‡	2070 (€/year)§	1.38	1/800‖	13,110 (€/year)¶	16.39
Collecting bed	1/1500**	1150 (€/year)	0.77	1/800††	1,150 (€/year)	1.44
Tests costs	2	1.68	3.36	2	1.68	3.36
Destroy costs	1	0.08	0.08	1	0.08	0.08
Indirect costs (building, IT, overhead)	50% of costs	47.66	23.83	50% of costs	167.46	83.73
Total costs			71.49			251.18

* Whole blood collection bag Compo Select T 3941 (Fresenius).
† Apheresis collection device 944 (Haemonetics).
‡ 1500 procedures/equipment/year.
§ Mixing device Compo Guard (Fresenius).
‖ 800 procedures/equipment/year.
¶ MCS + equipment (Haemonetics).
** 1500 procedures/bed/year.
†† 800 procedures/bed/year.
‡‡ Depreciation costs/year (23%), maintenance costs/year (23%).

TABLE 5. Total mean costs of phlebotomy and erythrocytapheresis treatment in euros (€)*

Items	Phlebotomy n = 19 (5♀, 14♂)	Erythrocytapheresis n = 19 (5♀, 14♂)	Difference in mean	UI (2.5-97.5)
Treatment costs (€)	1898 (186)	2263 (233)	+358	(–250 to + 927)
Costs of lost production (€)	2669 (465)	775 (280)	–1983	(–2927 to –857)
Total costs (€)	4438 (599)	3005 (444)	–1433	(–2834 to +114)

* Data are reported as mean (SD).
UI = uncertainty interval.

endpoint, but just exceeds the estimated upper 95% confidence limit of 0.50. In hindsight, we assume that a somewhat higher power and/or a by baseline SF stratified randomization design might have led to an upper confidence level within the 0.50 or less range.

A lower mean amount of total removed iron in the erythrocytapheresis group (Table 2) was also a consequence of the difference in the initial SF levels between both groups. However, per single treatment procedure significantly more iron was removed in erythrocytapheresis group, suggesting that erythrocytapheresis is a much more effective treatment.

Erythrocytapheresis in symptomatic patients with initial SF levels above 1000 µg/L in whom phlebotomy usually takes 2 years with up to 100 or more procedures will substantially reduce the number of procedures as well as the treatment duration. The biweekly treatment regimen used by erythrocytapheresis may be easier to endure knowing that only one-third of HFE-HC patients can tolerate and adhere to weekly phlebotomy.[26]

The use of apheresis equipment generally leads to a reduction of adverse events.[27] This is most likely related to the saline compensation and the longer collection time during apheresis procedures, facilitating transcapillary refilling of the intravascular compartment.[28,29] However, our study showed no differences in adverse events between both therapies, although the number of patients was limited and the study was not powered to show a difference in adverse events.

Erythrocytapheresis did remove more than two times the amount of RBCs per single procedure without inducing anemia. This reflects the individual fine tuning adapted to sex, weight, the total blood volume, and actual Hct in which erythrocytapheresis allows for a much more sophisticated and accurate adjustment. In addition, erythrocytapheresis has the potential to selectively reduce the iron source and preserve valuable blood components of the patient such as plasma proteins, PLTs, clotting factors, and WBCs, which make this approach also attractive for patients with hypoproteinemia or thrombocytopenia.

An advantage of phlebotomy is that it is a simple procedure that can be performed in various situations. In contrast, erythrocytapheresis needs specialized equipment and adequately trained staff. This can be overcome by using blood donor centers as treatment locations. Blood centers with apheresis equipment and trained staff are readily available in Europe, the United States, and Canada. We performed our study with MCS+ equipment (Haemonetics), which uses a one-needle system and is standard available in most blood donor centers. Nevertheless it is also possible to perform these procedures with Spectra equipment (CaridianBCT, Lakewood, CO), which uses a two-needle system.

Published data suggest that erythrocytapheresis is expensive.[16,18] However, our study throws another light on this important issue. In the Netherlands, in Sanquin blood donor centers, the cost price of a single erythrocytapheresis is 3.5 times higher compared to phlebotomy. This cost difference is probably much smaller compared to other countries and health care settings. However, comparing our results with costs from other studies or countries is difficult, since mostly reimbursement charges are reported. These reimbursement charges are generally higher than costs and do not reflect real resource use. For that reason we performed a cost price calculation. This approach is also known as microcosting, which has the advantage of allowing others to see how well the analysis matches their own situation where patterns of care may differ.[30] Hence, it becomes possible to compare volumes of use between different countries or settings and to examine whether a large cost difference between erythrocytapheresis and phlebotomy is in fact related to real differences in resource use.

Furthermore, it should be noted that the costs in our study are based on a status quo assumption. If erythrocytapheresis is more widely used the costs per single procedure will be even lower due to a more efficient use of equipment. In addition, another potential factor of decreasing erythrocytapheresis costs is the option to use the collected blood for transfusion purposes as has already been done in some parts of the United States, Canada, and more recently in France. In that case 2 units of RBCs can be produced during one erythrocytapheresis procedure.

The cost price for a single treatment procedure might also depend on the location. In our trial, both treatment procedures are performed in Sanquin blood donor centers, which have lower costs for beds, equipment, and personnel compared to the hospitals.

Although the costs of a single erythrocytapheresis are higher, the total treatment costs are not significantly higher because fewer treatment procedures in the erythrocytapheresis group are needed to reach the recommended target. The costs resulting from the loss of hours absent from work are significantly lower in the erythrocytapheresis group because again fewer procedures are needed to reach an SF level of 50 μg/L or less. This means that patients in the erythrocytapheresis group report less hours absent from work compared to the phlebotomy group. Still, further research in a larger group is necessary to confirm these results.

A post hoc analysis of our data (results not shown) on preferable number of treatment procedures showed that heavier patients (>76 kg) had a larger benefit of the erythrocytapheresis treatment. However, this needs further confirmation in future studies with higher number of patients.

In conclusion, erythrocytapheresis significantly reduces the number of treatment procedures as well as treatment duration in weeks compared to phlebotomy and from a societal perspective might also be a cost-saving therapy. Studies in a larger population must be performed to confirm these findings.

AUTHORSHIP

ERS designed the study, collected and analyzed data and wrote the manuscript; FHMN, PAHN, and FR performed the statistical analysis; BABE and RB performed the cost analysis; MCHJ CThBMD, and LPB collected data; and GHK and PWL edited the manuscript and contributed invaluable expertise.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest relevant to the manuscript submitted to **TRANSFUSION**.

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