The role of cell savers and filters in cardiac surgery

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Chapter 2

Effects of cell saving devices and filters on transfusion in cardiac surgery: a multicenter randomized study

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Abstract

Background: Cell-saving devices (CS) are frequently used in cardiac surgery to reduce transfusion requirements, but convincing evidence from randomized clinical trials is missing. Filtration of salvaged blood in combination with the CS is widely used to improve the quality of retransfused blood, but there are no data to justify this approach.

Methods: To determine the contribution of CS and filters on transfusion requirements, we performed a multicenter factorial randomized clinical trial in two academic and four non-academic hospitals. Patients undergoing elective coronary, valve or combined surgical procedures were included. The primary end point was the number of allogeneic blood products transfused in each group during hospital admission.

Results: From 738 included patients, 716 patients completed the study (CS + filter: 175, CS: 189, filter: 175, neither CS nor filter: 177). There was no significant effect of CS or filter on the total number of blood products (fraction [95% confidence interval]: CS: 0.96 [0.79, 1.18]; filter: 1.17 [0.96, 1.43]). Use of a CS significantly reduced red blood cell transfusions within 24 hours (0.75 [0.61,0.92]), but not during hospital stay (0.86 [0.71, 1.05]). CS was significantly associated with increased transfusions of fresh frozen plasma (1.39 [1.04; 1.86]), but not with platelets (1.25 [0.93; 1.68]). Use of a CS significantly reduced the percentage of patients who received any transfusion (odds ratio [95%CI): 0.67 [0.49; 0.91]), whereas filters did not (0.92 [0.68, 1.25]).

Conclusion: Use of a CS, with or without filter, does not reduce the total number of allogeneic blood products, but reduces the percentage of patients who need blood products during cardiac surgery.

Introduction

There is some evidence that cell-saving devices (CS) reduce red blood cell (RBC) transfusion during cardiac surgery, but that extensive use of a CS may lead to a bleeding diathesis [1,2]. Two recent meta-analyses [3,4] suggest that fewer patients receive allogeneic blood transfusions when a CS is used. However there was substantial heterogeneity due to different blood conservation concepts of the included studies, and most studies were underpowered with methodological shortcomings. Furthermore, transfusion of higher volumes of cell saver blood is associated with increased transfusion requirements of fresh frozen plasma (FFP) [2,5]. For a valid comparison of transfusion requirements it is therefore important to consider all administered blood products and the percentage of patients transfused during hospital admission. Currently, there are no randomized clinical trials with sufficient statistical power to justify the routine use of a CS in cardiac surgery.

Many institutions nowadays use an additional filter for transfusion of CS to improve the quality of the retransfused blood. Although this is recommended by several authors and manufacturers [6-8] this practise is not supported by clinical data.

Retransfusion of cardiotomy suction blood to the cardiopulmonary bypass (CPB) circuit is usually the first step in blood conservation during cardiac surgery. Cardiotomy blood is highly inflammatory and associated with increased transfusion requirements and organ injury [9,10]. It can be processed either by washing with a CS [2] or by passing through a leukocyte depletion (LD) filter [8]. This latter approach may improve coagulation as the plasma fraction of the blood is retained. This may decrease transfusion requirements. We previously demonstrated that retransfusion of residual blood from the CPB circuit through a LD filter resulted in improved post-operative lung function [7]. Thus, transfusion of both cardiotomy suction blood and residual blood from the CPB circuit through a LD filter could have a similar clinical effect as processing this blood with a CS.

Considering the possible positive and negative effects of CS and filters on the use of allogeneic blood products during cardiac surgery and the lack of sufficient clinical evidence we conducted a multicenter factorial randomized clinical trial to investigate the effect of CS, LD filters, and their combination on transfusion requirements in cardiac surgical patients.

Methods

This study was a partially blinded randomized 2x2 factorial multicenter trial with CS and LD filter as the two factors. Adult patients scheduled for elective coronary artery bypass grafting, valve surgery or combined procedures were included. Patients scheduled for off-pump surgery and patients with known coagulation disorders except after the use of aspirin, clopidogrel or low molecular-weight heparin were excluded. Aspirin and clopidogrel were stopped according to local protocol. Each institutional review board approved the study (2 academic and 4 non-academic centers), covering the whole country (fig 1) and informed consent was obtained from all patients included in the study. Only morning scheduled patients were included.

In groups 1 (CS), 2 (CS + filter) and 3 (filter) cardiotomy suction blood, blood from the surgical field, and residual heart lung machine blood, was collected. This blood was washed with a CS in groups 1 and 2 and retransfused through a standard blood giving set in group 1, and through a LD filter in group 2 and 3. In group 4 (control) neither CS nor filters were used. Instead, conventional cardiotomy suction was used and blood from the surgical field was discarded after reversal of heparin. Residual heart lung machine blood was retransfused through a standard blood giving set.

Anaesthesia, surgery and CPB were performed according to institutional practice. Protease inhibitors were not used. The CPB circuit was primed with 1000mL lactated Ringer's solution and 500mL hydroxyethylstarch 10% (Fresenius, Bad Homburg, Germany). Pump flow was 2.4 L/m2/min and temperature was allowed to drift to 34°C. Heparin was given to obtain activated clotting time >400 seconds and was reversed with protamine in a 1:1 ratio after CPB. Hemoconcentrators were not used. The centers used their own CS with standard washing program (CATS (Fresenius, Bad Homburg, Germany), Brat 5 (Haemonetics, Braintree, MA, USA), or Dideco-electa (Sorin, Milan, Italy)). Suction pressure was minimized to prevent haemolysis. Biofil 2 LD filters (Fresenius, Bad Homburg, Germany) were used and changed after 1000 ml of blood and after 250 ml of CS-processed blood [11].

Based on Dutch transfusion guidelines RBC's were transfused when the post-operative hemoglobin level was <5 mmol/L. Transfusion of RBC's during CPB was guided by clinical judgment of the attending anaesthesiologist and perfusionist. Transfusion

of FFP occured in case of excessive bleeding (>150 ml/h for 2 consecutive hours and prothrombin time >1.5 times normal). Platelets were transfused when platelet counts were $<100x10^9$/L in combination with excessive bleeding. The decision for surgical reexploration was made on the usual clinical grounds.

Patients were extubated when normothermic, haemodynamically stable with an arterial partial pressure of oxygen of greater than 9 kPa on minimal ventilatory support. It is standard policy in the Netherlands to transfer patients after cardiac surgery to the ward in the morning.

The primary endpoint was the number of allogeneic blood products used in each group during hospital admission. Secondary end points were percentage of patients who received any allogeneic blood products, number of reexplorations, myocardial infarction, stroke, post-operative ventilation time, length of stay in the intensive care unit and in the hospital, and 1-year mortality.

Preliminary data from the institutional database of the investigational leading center (Groningen) was used to calculate sample sizes with the two-sample Student's *t*-test using PASS software, version 6.0 (NCSS, LLC, Kaysville, UT). A difference in the average value of 466 ml (control) and 274 ml (CS + filter) blood products per patient requires 150 patients in each group (α= 0.05, β= 0.80), and an overly conservative standard deviation of 593 ml. Because of the multicenter character of the study we chose to include at least 180 patients per treatment group.

For each center a computer-generated randomization table was made with four groups. Allocation was done with sealed sequentially numbered envelopes. The study was not blinded for the intra-operative part, because the CS could not be concealed by its size, noise and special suction tube. However, all other caregivers were blinded to the intervention.

The analysis was based on the intention-to-treat principle. Logistic regression was used for binary outcomes and Poisson regression for count variables. Overdispersion was estimated with the deviance statistic. Linear regression was used for concentrations and for the logarithmic transformed blood loss. These analyses included an effect of CS, of filter, and an interaction effect and they were corrected for centers, except for the outcomes mortality, myocardial infarction, and stroke. The effects of CS and filter, with their 95% confidence intervals, and the p-value for the interaction effect are

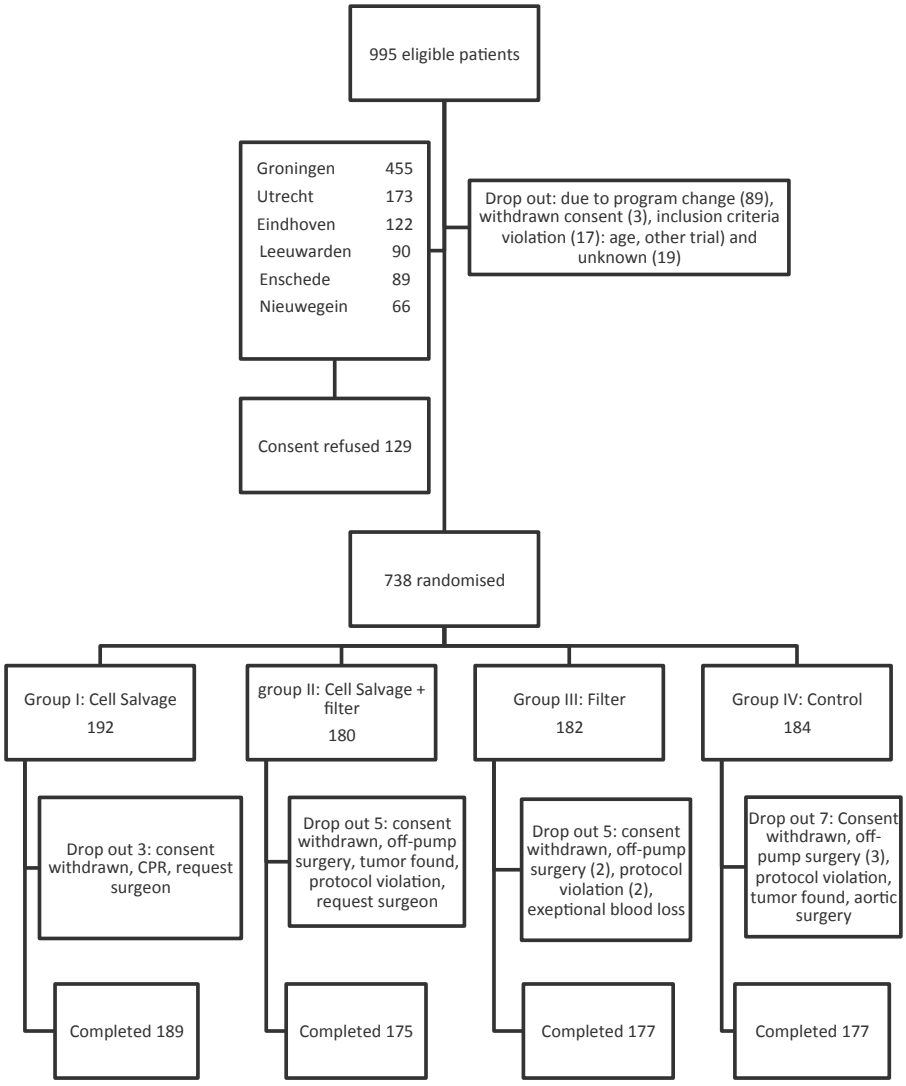
reported. For binary outcomes the odds ratio was used, for count data and blood loss the ratio of average blood products between treatment groups and for concentrations the mean difference was used. A p-value below 0.05 was considered significant. All statistical analyses were performed with SAS, version 9.3 (SAS institute Inc, Cary, NC).

Results

Participants were recruited from January 2005 to January 2009. The flowchart through the trial is shown in fig 1.

Seven hundred sixteen patients completed the study. All transfusion data were not available from 6 patients (3 in the filter group and 3 in the control group). As a result of the implementation of new Dutch transfusion guidelines during the study period tranexamic acid (2g) was used in 156 patients, equally divided over the four groups. The demographic data are shown in table 1, and the intra-operative data in table 2.

Fig 1. Flow chart of patients through the trial



CPR, cardiopulmonary resuscitation

Table 1: Demographic Data

Characteristics	CS (n= 189)	CS + Filter (n=175)	Filter (n=175)	Control (n=177)
Age (y)	66 ± 9.5	65 ± 9.7	66 ± 10.5	66 ± 9.7
Height (cm)	173 ± 8	174 ± 8	174 ± 9	172 ± 9
Weight (kg)	81 ± 13	84 ± 13	84 ± 14	81 ± 14
Male, n (%)	134 (71)	140 (80)	132 (75)	127 (71)
Euro SCORE	4.2 ± 3.0	4.3 ± 3.0	4.7 ± 3.3	4.7 ± 3.4
Myocardial infarction (%)	23	21	28	27
Hypertension (%)	46	46	39	46
Stroke (%)	4	6	7	6
Atrial fibrillation (%)	13	11	12	12
Diabetes (%)	24	22	15	21
Pulmonary disease (%)	11	14	15	10
Aspirin < 3 days (%)	37	45	42	44
Clopidogrel < 3 days (%)	7	5	4	6
Beta-blocker (%)	68	68	69	70
Calcium antagonist (%)	31	22	24	32
ACE inhibitor (%)	43	46	38	36
Haemoglobin (mmol/l)	7.6 ± 0.9	7.6 ± 0.9	7.6 ± 0.9	7.5 ± 0.9
Creatinine (mmol/l)	84 ± 19	87 ± 23	88 ± 21	90 ± 35

ACE, angiotensin-converting enzyme; CS = cell-saving device; Euro SCORE = European System for Cardiac Operative Risk Evaluation

Table 2: Intra-operative Data: Procedures and Cardiopulmonary Bypass Management[a]

Variable	CS	CS + Filter	Filter	Control
CABG, n (%)	116 (61)	106 (61)	110 (63)	115 (65)
Valve, n (%)	54 (29)	44 (25)	33 (19)	37 (21)
CABG + valve, n (%)	19 (10)	25 (14)	32 (18)	25 (14)
CPB time (min)	103 ± 41	104 ± 43	105 ± 35	104 ± 45
Cross-clamp time (min)	65 ± 27	67 ± 29	68 ± 26	68 ± 30
Hemoglobine CPB (mmol/L)	4.8 ± 0.70	4.9 ± 0.76	4.9 ± 0.79	4.8 ± 0.75
Residual CPB blood (mL)	784 ± 490	774 ± 421	815 ± 461	951 ± 472
Blood collected (mL)	1,310 ± 1,186	1,537 ± 1,541	1,463 ± 971	NA
CS processed (mL)[b]	658 ± 390	684 ± 514	NA	NA

[a] Data are presented as mean ± SD unless otherwise stated. [b] Residual CPB blood plus blood collected. CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; CS, cell-saving device; NA, not applicable.

The overall transfusion data are shown in table 3. This table also contains the effect size with the 95% confidence interval for the treatment comparisons: "use of a CS versus no use of a CS" and "use of a filter versus no use of a filter".

Table 3: Transfusion Data Overall

Variable	CS (n=189)	CS + Filter (n=175)	Filter (n=175)	Control (n=177)	Effect of CS[a]	Effect of Filter[a]	p value[b]
Total units RBC in first 24 h	205	186	255	244	0.75 (0.61-0.92)	1.02 (0.83-1.25)	0.84
Patients transfused RBC in first 24 h, n (%)	76 (40)	61 (35)	90 (52)	86 (49)	0.57 (0.42-0.78)	0.95 (0.70-1.29)	0.35
Total units RBC during hospital admission	358	355	429	357	0.86 (0.71-1.04)	1.13 (0.93-1.38)	0.63
Patients transfused with RBC during hospital admission, n (%)	94 (50)	79 (45)	103 (59)	104 (59)	0.58 (0.42-0.79)	0.92 (0.67-1.25)	0.73
Total units FFP	97	109	78	64	1.39 (1.04-1.85)	1.22 (0.91-1.62)	0.95
Patients transfused with FFP, n (%)	30 (16)	30 (17)	24 (14)	29 (16)	1.12 (0.74-1.70)	0.94 (0.62-1.43)	0.43
Total units platelets	32	51	32	30	1.24 (0.92-1.67)	1.33 (0.99-1.79)	0.09
Patients transfused with platelets, n (%)	25 (13)	33 (19)	24 (14)	22 (13)	1.25 (0.82-1.91)	1.30 (0.85-1.99)	0.43
Total units RBC, FFP, and platelets	487	515	539	451	0.96 (0.78-1.17)	1.16 (0.96-1.42)	0.92
Patients transfused with any RBC, FFP, and platelets, n (%)	98 (52)	83 (47)	103 (59)	108 (61)	0.67 (0.49-0.91)	0.91 (0.67-1.24)	0.92

[a] Effects are ratio and 95% confidence intervals. A ratio larger than 1 indicates a higher risk for blood products in the control group. [b] The p value indicates the interaction effect of the CS in combination with the filter.
CS, cell-saving device; FFP, fresh frozen plasma; RBC, red blood cells.

Use of a CS resulted in a significant reduction of 25% (95% confidence interval [CI], 8% to 39%) in the number of RBC's that were transfused within the first 24 hours. This effect decreased to 14% (95% CI,-5% to 29%) in the further post-operative period. However, there was only a 4% (95% CI, -18% to 21%) reduction in the total number of blood products that were transfused during hospital admission (table 3). In the groups with CS, 56.1% (95% CI, 49.5% to 62.4%) patients used blood products versus 65.6% (95% CI, 59.2% to

71.4%) in the groups without CS. In contrast, use of a filter was associated with higher transfusion requirements, although none of the effects were statistically significant (table 3). Transfusion data of the individual patients are presented in table 4. When a CS was used 22% of the platelets were transfused without concurrent administration of FFP and 35% when a CS was not used.

Table 4: Transfusion Data by Patient Level

Variable	CS (n=189)	CS + Filter (n=175)	Filter (n=175)	Control (n=177)
Units RBC transfused in first 24 h to patients (n)				
0	113	114	84	91
1-2	48	32	50	48
3+	28	29	40	38
Units RBC/patient in first 24h	1.1	1.1	1.4	1.4
Units RBC/transfused patient in first 24h	2.1	3.0	2.8	2.8
Units RBC transfused to patients during hospital admission (n)				
0	95	96	72	73
1-2	48	36	41	51
3+	46	43	62	53
Units RBC/patient during hospital admission	1.9	2.0	2.5	2.0
Units RBC/transfused patient during hospital admission	3.8	4.5	4.2	3.4
Units FFP transfused to patients (n)				
0	159	145	151	148
1-2	15	16	12	24
3+	15	14	12	5
Units FFP/patient	0.5	0.6	0.4	0.4
Units FFP/transfused patient	3.2	3.6	3.2	0.6
Units platelets transfused to patients (n)				
0	164	142	150	153
1	20	24	18	17
2+	5	9	6	5
Units platelets/patient	0.2	0.3	0.2	0.2
Units platelets/transfused patient	1.3	1.5	1.3	1.4

CS, cell-saving device; FFP, fresh frozen plasma; RBC, red blood cell concentrate

Post-operative data are presented in table 5 in a similar way as in table 3. For post-operative blood loss we observed an interaction effect. When the filter was applied an effect of the CS was detected (0.81; 95% CI, 0.71 to 0.94) and when no CS was used, an

effect of the filter was almost significant (1.13; 95% CI, 0.98 to 1.31). The lowest average blood loss was obtained with the use of a filter and a CS. Although all groups had similar pre-operative hemoglobin levels (table 1), and during CPB (table 2), use of a CS resulted in higher post-operative hemoglobin levels on the first post-operative day, although fewer patients received RBC transfusion (tables 3-5).

Table 5: Post-operative Data[a]

Characteristics	CS	CS + Filter	Filter	Control	Effect of CS[b]	Effect of Filter[b]	p value[c]
12-h blood loss chest tube (mL)	728 ± 726	646 ± 487	772 ± 597	670 ± 444	0.90 (0.82-0.98)	1.02 (0.92-1.13)	0.04
Haemoglobin day 1 (mmol/L)	6.6 ± 0.9	6.6 ± 0.8	6.3 ± 0.8	6.1 ± 0.7	0.38 (0.26-0.49)	0.05 (-0.06-0.17)	0.15
Reexploration, n (%)	15 (8)	14 (8)	17 (10)	12 (7)	1.00 (0.56-1.80)	1.17 (0.65-2.11)	0.91
Myocardial infarction, n (%)	7 (4)	1 (1)	5 (3)	5 (3)	0.50 (0.14-1.73)	0.38 (0.11-1.32)	0.09
Stroke, n (%)	1 (1)	5 (3)	7 (4)	5 (3)	0.36 (0.10-1.22)	2.82 (0.82-9.62)	0.24
Ventilation time (h)	16.0 ± 23.9	14.9 ± 16.4	23.2 ± 43.5	21.3 ± 42.7	0.69 (0.55-0.86)	1.00 (0.80-1.26)	0.47
LOS intensive care unit (days)	1.9 ± 5.6	1.7 ± 2.4	2.4 ± 4.7	1.5 ± 1.7	0.95 (0.79-1.12)	1.18 (0.99-1.39)	<0.001
LOS hospital (days)	11.5 ±10.5	10.3 ± 7.8	12.7 ± 15.0	11.8 ± 9.6	0.89 (0.80-0.98)	0.98 (0.87–1.08)	0.08
One-year mortality, n (%)	1 (1)	6 (3)	8 (5)	5 (3)	0.36 (0.11–1.23)	3.32 (0.99–11.0)	0.21

[a] Data are presented as mean ± standard deviation, unless indicated otherwise. [b] Effects are ratio and 95% confidence intervals. A ratio larger than 1 indicates a higher risk in the control group. [c] The p value indicates the interaction effect of the CS in combination with the filter. CS, cell saver device; LOS, length of stay

Reexplorations were equally divided between the four groups (table 5). These 58 patients comprised 8% of the total study population, but consumed 30% of total RBC, 46% of total FFP, and 41% of total platelet concentrates. Exclusion of patients with a re-exploration did not change the result of the primary outcome.

Use of the CS resulted in a 31% (95% CI, 14% to 45%) shorter post-operative ventilation time. For the length of stay in the intensive care an interaction effect between CS and filter was significant. Without the CS, the use of a filter increased the length of stay by 60% (P<0.001). The length of hospital stay was reduced when the cell saver was used with a filter by 30% (P=0.002), but, when the filter was not used the cell saver increased the length of stay by 28% (p=0.048).

Discussion

This study demonstrates that during cardiac surgery, intra-operative use of a CS, with or without a filter, does not reduce the total number of allogeneic blood products that are transfused during hospital admission. However, the lower percentage of patients who received any transfusion when a CS was used is, from a clinical standpoint, equally important because transfusion with allogeneic blood products is associated with reduced long-term survival, increased morbidity and costs [12,13]. It is important to realize that this study had approximately 80% power to detect a 10% reduction in patients who required any allogeneic blood products and to detect an approximately 22% reduction in the number of blood products.

An explanation for these seemingly contradictory findings is that patients who were bleeding required more FFP's and platelets when a CS was used, which minimized the effect of the intervention in the overall population. The meta-analyses [3,4] did not show an association between CS use and FFP's, but the reported amounts of processed CS blood were small which may have obscured these effects. We processed all intra-operative wound blood, including cardiotomy suction and residual blood from the CPB circuit. This is reflected in the amount of retransfused blood, which was higher than in any of the published studies [2,5,14-17]. Unfortunately, we did not separately measure the blood collected before and after CPB and the cardiotomy blood. This would have given the opportunity to better characterize the effects of cell saving versus surgical bleeding on transfusion of haemostatic products.

Several differences with these previous investigations exist. We not only included coronary but also valve and combined procedures to reflect the usual clinical spectrum, which very few studies do [15]. Another difference is that this is a multicenter study

in which all centers used the same transfusion trigger. Cell-salvage procedures are usually tailored to local customs. This may explain why we found that the treatment effects were not consistent across the centers for all outcome measures. Another explanation is that protocol violations occurred. Violations were virtually absent for RBC transfusion (although clinical judgment was sometimes used to modify the transfusion threshold) but occurred in about 10% of FFP and platelet transfusions. In certain cases these violations were inevitable, for example in case of a large blood loss requiring immediate action, whereas in other cases intervention could wait until laboratory data were present.

We noticed also that a substantial amount of late RBC transfusions occurred, some of which fell outside the transfusion protocol. The majority occurred in patients with prolonged intensive care stay. Due to the blinding of the study, and hemoglobin levels between 4.5 (intensive care) and 5 mmol/L (ward) as transfusion trigger, a major effect on the results is unlikely. We did not exclude these cases from analysis as this reflects common clinical practice in the Netherlands. We believe therefore that our study provides a representative overall effect. This is supported by the fact that exclusion of the reexplorations, in which the highest number of platelets and FFP was used, did not change the results on the primary outcome.

We did not use point-of-care testing to guide transfusion decisions, as this was not state of the art when we conceived the study. Therefore, our transfusion protocol may have resulted in a too aggressive administration of FFP as the trigger was persistent blood loss combined with an increased prothrombin time (which most patients have already after CPB). This approach may not have produced the expected improvement in haemostasis. Point-of-care testing could better have guided transfusion of platelets or FFP as first haemostatic component, although already a substantial percentage of the platelets was transfused without concurrent administration of FFP.

Post-operative ventilation times were shorter when a CS was used. We also found higher post-operative haemoglobin levels, although fewer patients received RBC transfusion. Because of the washing process of a CS, approximately 1.4L of fluid was removed from the circulation in this study. Thus, a CS may act as haemoconcentrator by removing excess fluid and thus explain the shorter ventilation times.

There was no clinical relevant effect of the additional filtration of CS blood. Cell-saving device blood contains activated leukocytes with increased expression of integrins on both neutrophils and monocytes [18]. Furthermore fat and cytokines are incompletely removed by the washing process [19]. Leukocyte depletion filters can remove activated leukocytes microparticles and fat [6,8,19].

We included group 3 (filter) as part of the factorial study design to test the hypothesis that it is not mandatory to wash the blood with a CS when leukocyte depletion filters are extensively used. Kaza et al. [20] demonstrated that a 21-µm filter placed after the cardiotomy reservoir of the CPB circuit was able to remove fat micro-emboli completely. This approach was more effective than the use of a CS. Leukocyte depletion filters have an even finer mesh and also bind cells and particles through adhesion. Although the plasma fraction of the blood was preserved with this approach, transfusion requirements were higher and the post-operative ventilation time and length of stay in the intensive care and the hospital were longer. Using these filters alone cannot replace a CS and is not indicated as a routine technique in cardiac surgical patients.

In conclusion, this study shows that intra-operative use of a CS during cardiac surgery did not reduce the total number of allogeneic blood products, but its use reduced the percentage of patients who received allogeneic blood products. This finding has clinical implications, as transfusion of allogeneic blood products is associated with reduced long-term survival and increased morbidity. An additional filter did not result in a clinical relevant advantage. Finally, the novel approach to retransfuse all wound blood through a LD filter did not reduce allogeneic blood products and is not indicated in this setting. Our findings therefore support the routine use of a CS during cardiac surgery.

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