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Additional filtering of blood from a cell salvage device is not likely to show important additional benefits in outcome in cardiac surgery

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BACKGROUND: Several authors and manufacturers of cell salvage devices recommend additional filtering of processed blood before transfusion. There is no evidence to support this practice. Therefore, we compared the clinical outcome and biochemical effects of cell salvage with or without additional filtering.

STUDY DESIGN AND METHODS: The patients, scheduled for coronary artery bypass grafting, valve replacement, or combined procedures were part of our randomized multicenter factorial study of cell salvage and filter use on transfusion requirements (ISRCTN 58333401). They were randomized to intraoperative cell salvage or cell salvage plus additional WBC depletion filter. We compared the occurrence of major adverse events (combined death/stroke/myocardial infarction) as primary outcome and minor adverse events (renal function disturbances, infections, delirium), ventilation time, and length of stay in the intensive care unit and hospital. We also measured biochemical markers of organ injury and inflammation.

RESULTS: One hundred eighty-nine patients had cell salvage, and 175 patients had cell salvage plus filter and completed the study. Demographic data, surgical procedures, and amount of salvaged blood were not different between the groups. There was no difference in the primary outcome with a risk of 6.3% (95% confidence interval [CI], 3.34–11.25) in the cell salvage plus filter group versus 5.8% (95% CI, 3.09–10.45) in the cell salvage group, a relative risk of 1.08 (95% CI, 0.48– 2.43]. There were no differences in minor adverse events and biochemical markers between the groups.

CONCLUSION: The routine use of an additional filter for transfusion of salvaged blood is unlikely to show important additional benefits.

Intraoperative cell salvage is widely used in cardiac surgery to reduce blood transfusion requirements. Blood from the surgical wounds is usually contaminated with fat particles and other debris that may produce emboli if this blood is transfused unprocessed, as is the case when pericardial suction blood is transferred directly into the venous reservoir of the heart-lung machine. Cell salvaging devices reduce the microembolic load by separating fat particles and debris from the RBCs.[1,2] Figure 1 illustrates this separation. The RBC fraction can be transfused without the contaminating particles. Thus, the incidence of neurologic complications after cardiac surgery and other signs of organ damage may be reduced.[2,3]

There are no universally accepted guidelines on how to transfuse salvaged blood. The AABB suggests "a filter designed to retain particles that are potentially harmful to the patient,"[4] and when fat particles are suspected in this blood, a WBC depletion filter is recommended. The guidelines of the Association of Anesthetists of Great Britain and Ireland state that "a standard blood administration set is usually adequate."[5]

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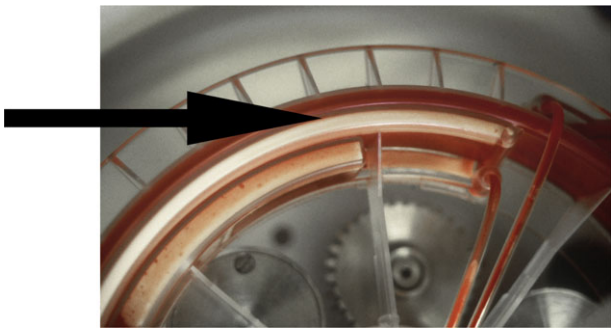

Fig. 1. Effect of cell salvage on salvaged blood. Photo of a continuous cell salvage device after use in cardiac surgery. The arrow points at a white rim, which reflects fat and particles that are separated and removed from the RBCs during cell salvage ("washing").

In an effort to further reduce the potential detrimental effects of microemboli, several authors use[6,7] or advocate the use[8] of an additional filter before salvaged blood cells are transfused into the patient. Several manufacturers of cell salvage devices recommend the use of an additional microfilter with a pore size of 40 μm or a WBC depletion filter, which has a pore size of around 15 μm to reduce the risk of end-organ damage.

Because there is currently no evidence to support these recommendations, we analyzed the effects of an additional filter on clinical outcome and on biochemical markers of brain, heart, and kidney injury and inflammation after cardiac surgery.

METHODS

After written informed consent was obtained, adult patients scheduled for on-pump coronary artery bypass grafting, valve replacement, or combined procedures were randomized to either intraoperative cell salvage alone or cell salvage plus additional filtration. These patients were part of our randomized factorial multicenter trial (ISRCTN 58333401) on cell salvage and filter use. The primary endpoint for that trial was the number of allogeneic blood products transfused in each group during hospital admission, and its main conclusion was that cell salvage, with or without a filter, does not significantly reduce the total number of allogeneic blood products, but reduces the percentage of patients who need blood products during cardiac surgery.[9]

During the operation, blood from the surgical field, cardiotomy suction blood, and residual heart-lung machine blood was collected in the cell salvage device. This blood was washed and transfused into the patient. In one group we used a standard blood administration set with a filter pore size of 200 μm (Codan). In the other group we used, in addition to the filter in this standard blood administration set, an additional WBC depletion filter (Biofil 2, Fresenius). We changed the filter after each 250-mL aliquot of processed blood.

Anesthesia, surgery, and cardiopulmonary bypass were performed according to local institutional practice. The bypass circuit was primed with 1000 mL of Ringer's lactate solution in 500 mL of hydroxyethyl starch 10% (Fresenius). Target pump flow was 2.4 L/m^2/min, and temperature was allowed to drift to 34°C. Heparin was given to reach an activated clotting time greater than 400 seconds. The six participating centers used their own cell salvage devices with standard washing program (CATS, Fresenius, n = 276; Brat 5, Haemonetics, n = 19; or Dideco-electa, Sorin, n = 69). Postoperative caregivers were blinded to the intervention.

After the operation, we measured the occurrence of major clinical adverse events (combined death/stroke/myocardial infarction), renal function disturbances according to the criteria of the Acute Kidney Injury Network, infections, delirium, postoperative ventilation time, and length of stay in the intensive care unit and hospital.

In addition, we measured biochemical markers of organ injury on the first and second postoperative days. Blood samples were taken from the radial artery catheter on the first postoperative day, and from the antecubital vein or the central venous line on the second postoperative day. For the heart, we measured creatinine kinase and its myocardial band and cardiac troponin-T; for the kidney, we measured serum creatinine, urinary albumin, and N-acetyl-β-D-glucosaminidase; and for the brain, we measured S-100β, neuroketal, and brain-type fatty acid binding protein. As markers of inflammation, we measured circulating WBCs, interleukin-6, myeloperoxidase, elastase, and C-reactive protein.

TABLE 1. Demographic and intraoperative data

	Cell salvage (n = 189)	Cell salvage + filter (n = 175)
Age (y)	66 ± 9.5	65 ± 9.7
Male (%)	71	80
EuroSCORE	4.2 ± 3.0	4.3 ± 3.0
Previous MI (%)	32	21
Previous PCI (%)	12	12
Hypertension (%)	46	46
Diabetes (%)	24	22
COPD (%)	11	14
CABG, n (%)	116 (61)	106 (61)
Valve, n (%)	54 (29)	44 (25)
CABG + valve, n (%)	19 (10)	25 (14)
Cross-clamp time (min)	65 ± 27	67 ± 29
Preoperative hemoglobin (mmol/L)	7.6 ± 0.9	7.6 ± 0.9
Postoperative hemoglobin (mmol/L)	5.3 ± 0.7	5.3 ± 0.9
Blood collected for salvage (mL)	2127 ± 1246	2306 ± 1551
Cell salvage processed blood (mL)	658 ± 390	684 ± 514

Values are given as mean ± standard deviation unless otherwise stated.
CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; PCI = percutaneous coronary intervention.

TABLE 2. Postoperative clinical data

	Cell salvage (n = 189)	Cell salvage + filter (n = 175)	p value
Death/stroke/myocardial infarction, n (%)	11 (6)	11 (6)	0.99
Creatinine increase >50% baseline, n (%)	11 (6)	10 (6)	0.99
Dialysis, n (%)	1 (1)	1 (1)	0.99
Infection, n (%)	30 (16)	28 (16)	0.99
Delirium, n (%)	8 (4)	8 (4)	0.99
Atrial fibrillation, n (%)	60 (32)	55 (31)	0.99
Postoperative mechanical ventilation (h, mean ± SD)	16.0 ± 23.9	14.9 ± 16.4	0.70
In intensive care unit stay (days ± SD)	1.9 ± 5.6	1.7 ± 2.4	0.61
Hospital stay	11.5 ± 10.5	10.3 ± 7.8	0.20

Creatinine kinase and its myocardial band, cardiac troponin-T, serum creatinine, WBC counts, and C-reactive protein were measured with standard laboratory tests. Plasma for determination of the other markers was obtained by centrifuging the blood samples at 1000 rpm for 10 minutes. The supernatant plasma was stored in −80°C until analysis. Urinary albumin was determined by the bromcresol green method, and N-acetyl-β-D-glucosaminidase by a substrate assay. For S100-β, we used a noninvasive system for capture (Abnova) capture and detection antibodies (Hytest); for neuroketal, we used an in-house–developed immunoassay (antibodies from Biogenes), and for brain-type fatty acid binding protein we also used an inhouse–developed immunoassay (antibodies from Biogenes). Standard immunoassay techniques were used to determine concentrations of interleukin-6 (Sanguin), elastase (Affinity Biologicals), and myeloperoxidase (Hytest).

To assess the removal of microemboli by the cell salvage device with and without additional filter, we performed a standard blood cell count on an automated hematology analyzer (XN10, Sysmex).

STATISTICAL ANALYSIS

For continuous data, we used the Student t test and for categorical variables the Fisher exact test. We considered a p value less than 0.05 as significant. As the primary endpoint we used the composite occurrence of in-hospital death, stroke, or myocardial infarction. If we estimate the occurrence of this primary endpoint at 7%, and we would be able to reduce this to 4% using an additional filter, about 900 patients would be required to detect a difference with the usual assumptions of $\beta = 0.8$ and $\alpha = 0.05$.

RESULTS

All 189 patients in the cell salvage group and 175 patients in the cell salvage plus filter group who completed the original study were included in this study. Demographic data, surgical procedures, and aortic cross-clamp times were not different between the two groups (Table 1). In 276 patients (76%) a continuous cell salvage system was used, and in the remainder a bowl system was used. There was no difference between the two groups (p = 0.71). In both groups, a similar amount of processed blood was transfused (Table 1). The blood recovery rate (the processed blood as percentage of the blood collected in the reservoir) was 31% in the cell salvage group and 30% in the cell salvage plus filter group.

The clinical outcomes are presented in Table 2. There was no difference in the occurrence of combined hospital death/stroke/myocardial infarction. The risk on this combined endpoint was 6.3% (95% confidence interval [CI], 3.34–11.25) in the cell salvage plus filter group versus 5.8% (95% CI, 3.09–10.45) in the cell salvage group. This resulted in a relative risk of 1.08 (95% CI, 0.48–2.43]. There were no differences in renal function disturbances, infections, delirium, atrial fibrillation, duration of postoperative ventilation, and length of stay in the intensive care unit and hospital between the two groups. There were no differences in

TABLE 3. Postoperative biochemical markers

	Postop day 1			Postop day 2		
	Cell salvage	Cell salvage + filter	p value	Cell salvage	Cell salvage + filter	p value
Leukocytes (× 10^9/L)	14.7 ± 4.5	14.6 ± 4.4	0.84	16.0 ± 4.7	15.4 ± 4.8	0.22
Interleukin-6 (pg/mL)	32 ± 34	31 ± 30	0.82	42 ± 49	44 ± 50	0.65
Myeloperoxidase (ng/mL)	204 ± 145	242 ± 160	0.08	222 ± 142	253 ± 160	0.15
Elastase (ng/mL)	1.55 ± 0.81	1.76 ± 1.15	0.11	1.69 ± 0.94	1.84 ± 0.99	0.28
C-reactive protein (μg/mL)	24 ± 32	25 ± 25	0.81	30 ± 27	30 ± 17	0.96
CK-total (U/L)	444 ± 453	477 ± 439	0.48	409 ± 363	499 ± 707	0.14
CK-MB (U/L)	28 ± 31	28 ± 30	0.82	19 ± 30	17 ± 30	0.48
Troponin T (ng/L)	3.6 ± 11.2	2.4 ± 3.7	0.19	2.2 ± 8.5	1.8 ± 2.7	0.53
Urinary albumin (mg/mL)	23 ± 46	16 ± 41	0.34	34 ± 76	42 ± 98	0.58
NAG (U/L)	13 ± 11	14 ± 9	0.47	27 ± 17	28 ± 16	0.51
S100-β (pg/mL)	442 ± 310	443 ± 327	0.91	408 ± 290	383 ± 265	0.63
BFABP (pg/mL)	815 ± 637	788 ± 638	0.69	749 ± 612	794 ± 639	0.51
Neuroketal (pg/mL)	201 ± 212	232 ± 264	0.97	352 ± 504	357 ± 504	0.78

P-values were assessed with the Student t test.
BFABP = brain-type fatty acid binding protein; CK = creatinine kinase; MB = myocardial band; NAG = N-acetyl-β-D-glucosaminidase.

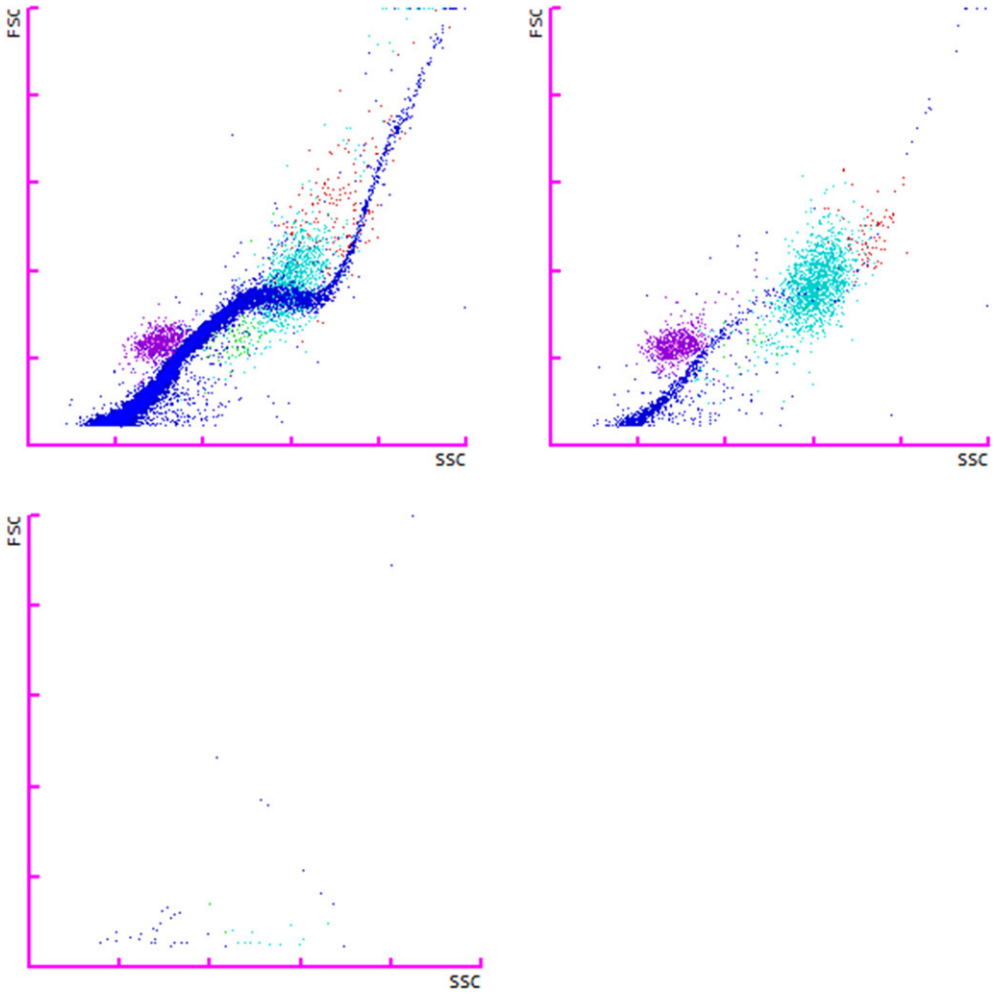

Fig. 2. Effect of washing salvaged wound blood with a cell salvage device and additional filtration. Left upper panel: Unprocessed salvaged wound blood with a hematocrit of 0.28. A blue S-shaped curve is present, representing particles. The size of these particles increases with the forward scatter (FSC; y-axis). The blue/gray cloud represents granulocytes. Their count was 1.4×10^9/L. The purple cloud represents lymphocytes. Their count was 0.5×10^9/L. The platelet count was 70×10^9/L. Right panel: Salvaged wound blood after processing and washing with a hematocrit of 0.64. The contaminating particles, and especially the larger ones, are almost completely removed during the process, but granulocytes (1.7×10^9/L) and lymphocytes (0.9×10^9/L) are still present. The platelet count was 10×10^9/L. Left lower panel: The same processed salvaged wound blood, but now after passage through an additional WBC depletion filter. No particles are present and all WBCs and platelets have been removed.

any of the measured biochemical variables on the first and second postoperative days (Table 3).

In Fig. 2, we show the effects of processing of the salvaged blood with or without additional filtration on removal of particles. Although washing of the salvaged blood reduced the quantity of small (fat) particles considerably, only passage through a WBC depletion filter removed them almost completely.

DISCUSSION

We found that additional filtration of processed salvaged blood did not improve the clinical outcome in patients after cardiac surgery. We also found no indication for subtle differences in biochemical markers of end-organ damage on the first and second postoperative days. As such, the results of the present study do not support the use of an additional filter for organ protection.

However, our study did not have sufficient power to detect a difference in the primary endpoint, although none of the clinical or biochemical measurements suggested a trend in favor of the use of an additional filter. The observed relative risk on the combined endpoint was even slightly higher in the filter group, and this makes it unlikely that the risk on major adverse events with a filter is better than half the risk without a filter. In addition, serious adverse events observed in fixed time intervals, as combined in our endpoint, may

typically be Poisson distributed, which makes clustering of these events over time unlikely. Indeed, we observed in both groups a gradual increase in adverse events over time and did not detect clustering (data not shown), supporting the Poisson hypothesis. Given all this information, we believe that it is unlikely that a larger study of the same design would lead to important different findings.

Worldwide, different protocols are in use for intraoperative cell salvage during cardiac surgery, resulting in a large heterogeneity in the reported studies.[10] In a number of studies, cell salvage of pericardial suction blood was compared with direct reinfusion of this blood into the heart-lung machine with the aim of reducing brain injury or the postoperative inflammatory response.[3,11,12] Pericardial suction blood contains a substantial amount of particles, hemolyzed RBCs, activated platelets, and proinflammatory cytokines. Unprocessed transfusion of this blood impairs hemostasis and increases the postoperative inflammatory response.[13,14]

In our study, we processed both blood that was lost before and after cardiopulmonary bypass and pericardial suction blood. This had two major effects. First, we processed and transfused more salvaged blood than other authors did. The mean reported quantity of processed blood in cardiac surgery is about 350 mL.[10] In our study, we transfused almost twice that amount. Therefore, we can exclude that we did not find an effect of additional filtering because too little blood was transfused. Second, we reduced the number of particles in the patient's circulation, and, as a consequence, increased the number of particles in the salvaged blood. Given the constant efficacy of the salvage system, this would result in more particles in the processed blood. Thus, any effects of an additional filter would be clearer.

We used a WBC depletion filter because we hypothesized that such a filter would result in the best possible removal of (fat) particles. These filters have a gradually tapering fine mesh resulting in a pore size of around 15 μm, and work not only by sieving but also by adhesion of cells and particles.[15] We previously demonstrated that WBC removal filters are superior to fat removal filters in the removal of fat particles and that they have a satisfactory blood passage time.[16] The filters were also changed frequently to obtain a maximal effect. It has been shown that additional filters may reduce the blood recovery rate.[17] This was not the case in our study. We used a filter with a small air valve by which we could drain all the contents and had no loss of blood with a high hematocrit. Filters require 30 to 50 mL of blood, which is usually lost when a filter is changed.

Both continuous and bowl-type salvage devices were used, as each participating center used its own device. Currently, little is known about the effects of the various processing methods on the quality of the blood. It has been shown that the efficacy for fat removal is less in bowl systems,[8,17] but in these studies reconstituted blood with an added fat emulsion was used. We performed a separate analysis for the bowl-type salvage device and found similar results. Moreover, it is likely that the differences between the two systems will become smaller. Currently, special fat removal programs are already available on certain bowl systems.

We did not assess postoperative neurocognitive dysfunction, which occurs after cardiac surgery but is difficult to assess properly. As we demonstrated, most of the particles are removed by the washing procedure. Even so, the reported effects of cell salvage on neurocognitive function are inconclusive.[3,12] We measured biochemical markers of brain injury and found similar results in both groups. Although very unlikely, we cannot exclude an effect of the filter on neurocognitive dysfunction.

Given the similarities in clinical outcome and biochemical measurements, we conclude that the routine use of an additional filter before transfusion of salvaged blood is unlikely to show important additional benefits.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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