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Published in:
Journal of cardiothoracic and vascular anesthesia

DOI:
10.1053/j.jvca.2020.01.023

Publication date:
2020

Journal of Cardiothoracic and Vascular Anesthesia 34 (2020) 1457–1463

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Original Article

Does Intraoperative Cell Salvage Reduce Postoperative Infection Rates in Cardiac Surgery?

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Objective: Primary outcome was the risk for infections after cell salvage in cardiac surgery.
Design: Data of a randomized controlled trial on cell salvage and filter use (ISRCTN58333401).
Setting: Six cardiac surgery centers in the Netherlands.
Participants: All 716 patients undergoing elective coronary artery bypass grafting, valve surgery, or combined procedures over a 4-year period who completed the trial.
Interventions: Postoperative infection data were assessed according to Centre of Disease Control and Prevention/National Healthcare Safety Network surveillance definitions.
Measurements and Main Results: Fifty-eight (15.9%) patients with cell salvage had infections, compared with 46 (13.1%) control patients. Mediation analysis was performed to estimate the direct effect of cell salvage on infections (OR 2.291 [1.177;4.460], p = 0.015) and the indirect effects of allogeneic transfusion and processed cell salvage blood on infections. Correction for confounders, including age, seks and body mass index was performed. Allogeneic transfusion had a direct effect on infections (OR = 2.082 [1.133;3.828], p = 0.018), but processed cell salvage blood did not (OR = 0.999 [0.999; 1.001], p = 0.089). There was a positive direct effect of cell salvage on allogeneic transfusion (OR = 0.275 [0.176;0.432], p < 0.001), but a negative direct effect of processed cell salvage blood (1.001 [1.001;1.002], p < 0.001) on allogeneic transfusion. Finally, there was a positive direct effect of cell salvage on the amount of processed blood.
Conclusions: Cell salvage was directly associated with higher infection rates, but this direct effect was almost completely eliminated by its indirect protective effect through reduced allogeneic blood transfusion.

Key Words: cell saver; infection; transfusion

INFECTIONS AFTER CARDIAC surgery have an incidence of 11% to 14% and affect outcome, length of hospital stay, and costs.[1-3] Several patient- and procedure-related risk factors are associated with the development of these postoperative infections, and red blood cell (RBC) transfusion appears to be one of the most important factors.[4,5] These RBC transfusions increase the incidence of postoperative infections in a dose dependent way.[5]

Cell salvage (CS) reduces the number of patients receiving allogeneic blood transfusions and it also reduces the number of transfused RBCs.[6-8] This suggests that CS could reduce the incidence of postoperative infections. Indeed, it was shown in a meta-analysis of CS use in cardiac, orthopedic, and vascular surgery that patients who were treated with CS had a lower

The Netherlands Organization for Health Research and Development (ZonMw) funded this study.

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https://doi.org/10.1053/j.jvca.2020.01.023

infection rate.[9] However, in another meta-analysis investigating the effects of CS during cardiac surgery, CS was not associated with less postoperative infections.[8] How CS is used during surgery varies, and that resulted in a considerable statistical heterogeneity in the meta-analyses. In addition, most patients do not receive RBC transfusion, regardless of the use of CS, which may mask the effects of CS on infections. It is therefore necessary to explore the effects of CS on infection more in depth. In this study the authors will conduct a mediation analysis using the dataset of their previously published study on CS and filters in cardiac surgery.[7] Mediation analysis is appropriate when an independent variable (in this study CS) not only has a direct effect on a dependent variable (in this study infection), but also has an effect on a mediator variable (in this study RBC transfusion), which has in turn its effect on the dependent variable.[10] This is shown in Figure 1. For a mediator it is necessary to demonstrate a significant effect for paths A and B in Figure 1. However, a significant direct effect between exposure and outcome as in path C is not necessary.

In this way, we assessed the connection between CS and postoperative infections was assessed.

Materials and Methods

The authors used the data of all 716 patients who completed the multifactorial multicenter randomized trial on CS and leucocyte depletion filter use conducted in the Netherlands (ISRCTN58333401).[7] The original primary end point for that trial was the number of allogeneic blood products that were transfused in each group during hospital admission, and the main conclusion was that use of CS, with or without a filter, did not significantly reduce the total number of allogeneic blood products but reduced the percentage of patients who needed blood products during cardiac surgery.

Briefly, adult patients scheduled for elective coronary artery bypass grafting (CABG), valve surgery, or combined procedures were included. In CABG the left internal mammary artery and the saphenous vein were used as bypass conduits in almost all patients. Saphenous vein harvesting was done by conventional incision and not by a scopic technique. In a few patients the radial artery was used. Written informed consent was obtained from all patients. Upon arrival in the operating room patients were randomized to CS or no CS using sealed, sequentially numbered envelopes.

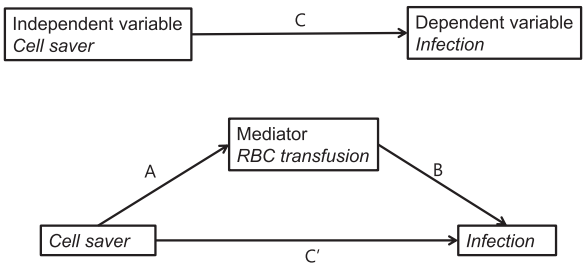

Fig 1. A mediation model explaining the mechanism that underlies a relationship between an independent variable (cell saver) and a depending variable (infection) (upper part), via the inclusion of a third variable, the mediator RBC transfusion (lower part). This model proposes that the independent variable influences the mediator, which in turn influences the dependent variable. The mediator serves to clarify the nature of the relationship between the independent and dependent variables. Arrows point in the direction of the effect. C is the total effect. The direct effects on infection are indicated with symbol C. The indirect effects on RBC transfusion are indicated with symbol A, and the effects of RBC transfusion on infection with symbol B.

In the CS group (n = 364), blood from the surgical field, cardiotomy suction blood, and residual heart lung machine blood were collected (collected blood). This blood was washed with a CS and subsequently retransfused (processed blood). In the group without CS (n = 352), the blood was either collected and filtered during cardiopulmonary bypass (CPB) and retransfused, or conventional cardiotomy suction was used and blood from the surgical field was discarded before and after heparinization. Residual heart-lung machine blood was retransfused without processing. A Biofil 2 leucodepletion filter was used (Fresenius, Germany) in the retransfusion system in the filter group.

Anesthesia, surgery, and CPB were performed according to local institutional practice following (inter)national guidelines. All patients received cefazolin (2 g) during induction of anesthesia and this dose was repeated every 6 hours for the first 24 hours after surgery. The CPB circuit was primed with 1000 mL of Ringer's lactate solution and 500 mL of hydroxyethyl starch 10% (Fresenius, Bad Homburg, Germany). Target pump flow was 2.4 L/min/m^2, and temperature was allowed to drift to 34°C.

Transfusion of RBCs during CPB was guided by clinical judgment of the responsible anesthesiologist and perfusionist. According to transfusion guidelines in the Netherlands, RBCs were transfused when the postoperative hemoglobin level was less than 8 g/dL. Transfusion of fresh frozen plasma and platelets was given in case of excessive bleeding. The decision for surgical re-exploration was based on the usual clinical criteria.

Postoperative infection data were prospectively collected and assessed according to Centre of Disease Control and Prevention/National Healthcare Safety Network (CDC/NHSN) surveillance definition.[11] If more than one infection occurred in a patient, this patient was counted just once. For pneumonia, positive X-ray signs need to be present in combination with at least 1 of the following: fever (> 38 °C), leucocyte count <4000 or >12.000 WBC/mm3, or, for adults ≥70 years old, altered mental status. This is in combination with 1 of the following: new onset or change in character of sputum production or new onset or worsening cough, dyspnea or tachypnea, rales or bronchial breath sounds, or worsening of gas exchange (O_2 desaturations or increased oxygen requirements). In a surgical site infection (SSI), superficial or deep, infection occurs within 30 days after the operative procedure, and at least 1 of the following are present: purulent drainage from the incision site, organisms isolated from the incision site, the presence of clinical signs of infection, or the diagnosis of SSI by the surgeon or an attending physician. These criteria also count for organ/space SSI infection and mediastinitis. For a urinary tract infection criteria are fever (>38°C), positive clinical signs and proof of bacterial growth or a physician diagnosis or instituted proper therapy for a urinary tract infection.

Statistical Analysis

For continuous variables means and standard deviations were used, and for categorical variables numbers and percentages were used. Differences in descriptive statistics between treatment groups were analyzed with Student *t* test for numerical variables and with Pearson's chi-square test for categorical variables. Several statistical analyses were conducted to understand the effects of CS on infections.

To begin, the total effect of CS on infections was determined with a logistic regression analysis on infections, corrected for age, seks and body mass index (BMI). This analysis simply compared the 2 randomized groups and corresponds to path C in Figure 1.

Then a mediation analysis was performed because it is likely that the effect of C on postoperative infections is mediated by RBC transfusions, given that the postoperative infection rate increases with the number of RBCs that are transfused and that CS is associated with a reduction in transfusion of RBCs.[4,6,7] This consisted of 3 statistical analyses, and they now refer to the directed acyclic graph in Figure 2 to understand the direct and indirect effects of CS on infections. This is a more elaborate version of Figure 1 and includes all effects with the addition of the confounders age, sex, and BMI. Confounders should be taken into account in mediation analysis when they have an effect on both the mediator and the outcome. The first analysis was a binary logistic regression analysis of infection with independent variables age, sex, BMI, CS, RBC transfusion, and quantity of processed blood (mL). This analysis provides the direct effects of CS (α_{CS}), blood transfusion (α_{RBC}), and processed blood (α_{PB}) on infections, corrected for the confounders of age, sex, and BMI (Fig 2). The second analysis was an ordinal logistic regression analysis (proportional odds model) of blood transfusion with the independent variables age, sex, BMI, CS, and quantity of processed blood. In this analysis the authors obtain the direct effects of cell saver (β_{CS}) and processed blood (β_{PB}) on blood transfusion, corrected for confounders of age, sex, and BMI. The third and final analysis is a linear regression analysis of processed blood with independent variables of age, sex, BMI, and CS. This analysis provides the direct effect of CS (γ_{CS}) on processed blood, corrected for confounders age, sex, and BMI.

To complete the mediation analysis of Figure 2, we must test 5 null hypotheses (H_0). First, $H_0 : \alpha_{CS} = 0$ to understand the direct effect of CS on infections. Then $H_0 : \alpha_{RBC} = 0$ and $H\alpha_{PB} = 0$ to understand direct effects of blood transfusion and processed blood on infections, in combination with the direct effect of CS on blood transfusion ($H_0 : \beta_{CS} = 0$) and on processed blood ($H_0 : \gamma_{CS} = 0$). If all these last 4 null hypotheses are rejected, CS has an indirect effect through blood transfusion and through processed blood, ie, both blood transfusion and processed blood are mediators for an effect of CS on infections. These mediated effects may also pass through the direct effect of processed blood on blood transfusion ($H_0 : \beta_{PB} = 0$). This would indicate that the effect of cell saver is not just mediated through 2 separate processes, but the 2 mediators also influence each other, making it a complex mediation process. It should be noted that when there is no direct effect of processed blood on the risk of infections ($\alpha_{PB} = 0$), the directed acyclic graph in Figure 2 reduces to the directed acyclic graph in Figure 1 with path B as the total effect of cell savers on blood transfusion (either directly or through processed blood).

These analyses were all performed with SAS Institute version 9.4 software, and associations were considered significant at the level of 0.05.

Results

Seven hundred and sixteen patients completed the study, 364 in the CS group and 352 in the control group. The complete flowchart of this study has been published previously.[7] Patient data are summarized in Table 1. Postoperative infections occurred 112 times in 104 patients (14.5%) during their hospital stay: 58 (15.9%) patients in the CS group and 46 (13.1%) patients in the control group (Table 2). Patients without transfusion had an infection rate of 8.4%, regardless of the use of CS (Fig 3). The total effect of CS on infections, corrected for age, sex, and BMI, is equal to an odds ratio of 1.290 (0.846; 1.969 [95% confidence interval]). There seems to exist

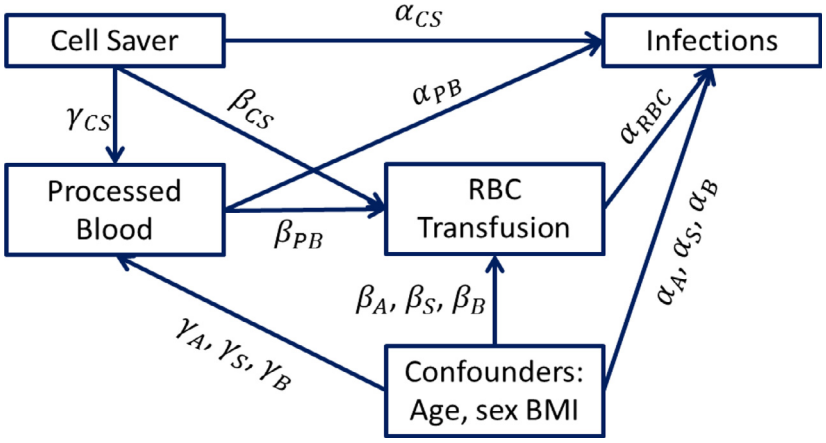

Fig 2. Directed acyclic graph for the effect of cell saver on infections. Arrows point in the direction of effect. The direct effects on infection are indicated with symbol α. The indirect effects on RBC transfusion are indicated with symbol β and the effects on processed blood with symbol γ.

Table 1
Baseline Characteristics and Perioperative Data of Patients Treated with Cell Salvage or No Cell Salvage.

Variable	Cell Salvage (n = 364)	No Cell Salvage (n = 352)	p Value
Age (years)	65 ± 9.6	66 ± 10	
Sex (male) n (%)	276 (76)	256 (73)	
EuroSCORE	4.3 ± 3.0	4.7 ± 3.4	
Previous MI n (%)	76 (21)	95 (27)	
Hypertension n (%)	170 (46)	155 (44)	
Diabetes n (%)	82 (23)	63 (18)	
Pulmonary disease n (%)	46 (13)	43 (12)	
Beta-blocker n (%)	248 (68)	244 (69)	
Calcium antagonist n (%)	98 (27)	98 (28)	
ACE inhibitor n (%)	160 (44)	133 (38)	
Hemoglobin (g/dL)	12.3 ± 1.5	12.3 ± 1.5	
Creatinine (mmol/L)	85 ± 21	89 ± 29	
CABG n (%)	222 (61)	225 (64)	0.418
Valve n (%)	98 (27)	70 (20)	0.026
CABG + valve n (%)	44 (12)	57 (16)	0.114
CPB time (min)	103 ± 41	104 ± 40	0.737
Cross-clamp time (min)	65 ± 27	68 ± 28	0.301
Residual CPB blood (mL)	795 ± 575	883 ± 471	0.028
Collected blood (mL)	2214 ± 1403	NA	
Processed blood (mL)	671 ± 453	NA	
12-h blood loss (mL)	688 ± 623	721 ± 528	0.451
Re-exploration n (%)	25 (7)	24 (8)	0.987
RBC (units)	2.0 ± 3.5	2.3 ± 3.0	0.246
FFP (units)	0.6 ± 1.5	0.4 ± 1.1	0.110
Platelets(units)	0.2 ± 0.6	0.2 ± 0.5	0.243
Intensive care unit stay (days)	1.8 ± 4.3	1.9 ± 3.5	0.664
Hospital stay (days)	10.9 ± 9.3	12.2 ± 12.5	0.121

NOTE. Data are expressed as mean (SD) or number (%).
Abbreviations: CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; CS, cell salvage; FFP, fresh frozen plasma; MI, myocardial infarction; RBC, red blood cells.

Table 2
Rate and Location of Infections in Patients Treated with Cell Salvage or No Cell Salvage

Postoperative Infections	Cell Salvage	No Cell Salvage
None n (%)	304 (84.0)	305 (86.9)
Lung n (%)	30 (8.3)	23 (6.6)
Saphenous vein wound n (%)	8 (2.2)	8 (2.3)
Urinary n (%)	13 (3.6)	9 (2.6)
Lung and wound n (%)	4 (1.1)	4 (1.1)
Unknown n (%)	3 (0.8)	2 (0.6)

NOTE. Data expressed as numbers (%).

an increased observed effect, but this is not significant (p = 0.237).

The results for the 3 statistical analyses for the mediation analysis in Figure 1 are provided in Tables 3 through 5. This includes the parameter estimates, their 95% confidence intervals, and the Wald-type p values for testing the null hypotheses. The binary logistic regression analysis of infections in Table 3 shows that the direct effect of CS increases the risk of infection. This effect with an odds ratio of 2.291 is slightly stronger than the direct effect of 1-2 RBCs, which has an odds ratio of 2.082. More RBCs rapidly increase the risk of infections as shown in Figure 3, but this increase seemed to be more when CS was used. The direct effect of processed blood does not seem to be significant. From the ordinal logistic regression analysis of blood transfusion presented in Table 4, it follows that CS reduces the risk of blood transfusion, but the amount of processed blood seems to increase the risk of blood transfusion. To understand the total effect of cell saver on RBC transfusion (directly and indirectly through processed blood), we performed the same ordinal logistic regression analysis was performed, but now without processed blood. The effect of cell saver reduced to an odds ratio of to 0.664 [0.501; 0.881], but it was still protective for blood transfusion. The linear regression analysis of processed blood (Table 5) clearly shows that CS has a strong effect on processed blood, which is expected of course.

Discussion

In a direct comparison of CS versus no CS on the occurrence of postoperative infections, the authors found that CS had no impact on postoperative infection rate after cardiac surgery. However, the results of the mediation analysis suggest that CS directly contributes to an increased risk of postoperative infections, but that its indirect effect through a reduction in blood transfusion almost completely compensates for this direct effect. In a meta-analysis of CS use in cardiac surgery, no significant difference in infection rate was found whether CS was used or not, although slightly more infections were reported with CS use (OR = 1.25 [0.75;2.10], p = 0.39).[8] This result is in accordance with the authors' findings. However, this meta-analysis suffered from a considerable statistical heterogeneity owing to the variation of cell saver use in the included studies. When the analysis was limited to studies with a similar approach as this study, the odds ratio on infection increased to 1.36 with a p-value of 0.06.[6,7,12-15] Together with the mediation analysis, this suggests that the total effect of CS on infections is small, but real. It is difficult to reveal because many patients do not require RBC transfusion. In addition, most of these studies were limited to patients who had CABG surgery. It is known that valve surgery and combined procedures are associated with a higher infection risk.[1]

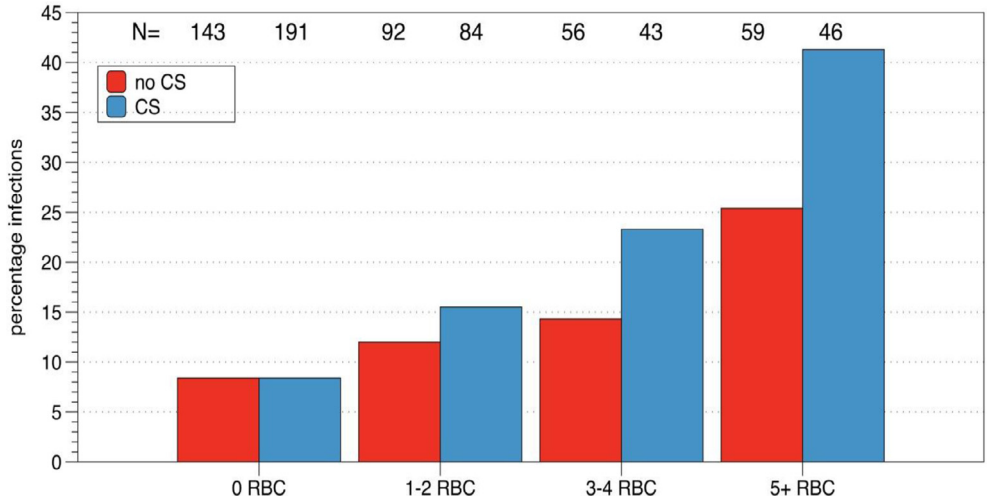

Fig 3. Percentage of patients with postoperative infections stratified by units of red blood cell transfusion and cell saver use. Abbreviations: CS, cell salvage; N, number of patients in each group; RBC, units of red blood cells.

Table 3
Binary Logistic Regression Analysis of Infections

Variable		Odds Ratio	95% CI	p Value
Age (years)		1.022	(0.997-1.048)	0.090
Female sex		1.814	(1.062-3.101)	0.029
Body mass index		1.073	(1.014-1.136)	0.015
Cell saver		2.291	(1.177-4.460)	0.015
Blood transfusion:				
	1-2 products vs none	2.082	(1.133-3.828)	0.018
	3-4 products vs none	3.091	(1.538-6.210)	0.002
	More than 4 vs none	7.024	(3.728-13.23)	<0.001
Processed blood (ml)		0.999	(0.999-1.001)	0.089

NOTE. Odds ratios are presented with 95% confidence interval. A p value < 0.05 is considered significant.
Abbreviation: CI, confidence interval.

Table 4
Ordinal Logistic Regression Analysis of Red Blood Cell Transfusion

Variable	Odds Ratio	95% CI	p Value
Age (years)	1.051	(1.081-1.067)	<0.001
Female sex	0.378	(0.275-0.519)	<0.001
Body mass index	0.905	(0.871-0.940)	<0.001
Cell saver	0.275	(0.176-0.432)	<0.001
Processed blood (mL)	1.001	(1.001-1.002)	<0.001

NOTE. Odds ratios are presented with 95% confidence interval. A p value < 0.05 is considered significant.
Abbreviation: CI, confidence interval.

As confounders in the mediation analysis, the authors used age, sex, and BMI. Confounders have an effect on both the mediators processed blood and transfusion and on the outcome infection. In general, older patients are more likely to receive a transfusion,[16] but they also suffer more often from postoperative infection.[17] The same is true for gender. Women suffer more often from infection and receive transfusions more often.[17,18] Not all studies agree that a low BMI is associated with a higher infection rate,[1,17] but a low BMI is associated with a higher transfusion requirement.[19] Similarly, these 3 confounders are likely to result in less processed CS blood through a lower circulating blood volume.

Table 5
Linear Regression Analysis of Processed Blood

Variable	Effect	95% CI	p Value
Age (years)	0.67	(−1.85 to 3.20)	0.601
Female sex	24.5	(−32.2 to 81.2)	0.397
Body mass index	5.20	(−0.99 to 11.38)	0.100
Cell saver	659.5	(611.1-707.9)	<0.001

NOTE. A p value < 0.05 is considered significant.
Abbreviation: CI, confidence interval.

The amount of processed blood was associated with more transfusions. This is not surprising because a higher amount of processed blood is associated with a higher intraoperative blood loss, which may ultimately lead to RBC transfusions. This observation supports the statistical approach.

Although it is clear that it is unlikely that patients without CS would receive processed blood, the authors also analyzed the effect of CS on processed blood for a complete mediation analysis.

In the interpretation of these data it is important that major infection after cardiac surgery is a relative rare complication, with a rate around 3% to 5%, but the occurrence of any infection is more common and may be as high as 13% to 18%.[1,2,3] This is in accordance with the overall 14.5% infection rate that the authors observed.

Based on a large cohort of 331,429 patients from the Society of Thoracic Surgeons National Cardiac Database, 12 clinical predictors of major infection were identified, but no data on blood transfusion were provided.[20] In another study of 5,158 patients, the incidence of major infection was nearly 5%. In that study, 48% of the patients received RBCs. The transfusion-associated risk of infection was dose dependent, with a 13% increase for each additional unit of RBC.[1]

There was no direct effect of processed blood on infections. This is supported by the similar infection rate in both groups when no RBC transfusion was given. Therefore, Figure 1 may be sufficient.

A direct effect of CS on postoperative infection rates has not been demonstrated before, and several mechanisms may be considered.

Plasma from the patient is effectively removed during the processing of blood with CS.[21] Plasma contains platelets with direct antimicrobial activity, as they are activated to release peptides in response to trauma or mediators of inflammation,[22] for this reason pure platelet rich plasma is applied topically, for instance in oral surgery.[23] Plasma of cardiac surgical patients contains, as a result of the inflammatory response caused by surgery and CPB, pro- and anti-inflammatory enzymes and cytokines, such as interleukines, tumor necrosis factor, myeloperoxidase, elastase and complement factors.[24-26] Use of CS may, depending on the amount of collected blood, result in a temporary imbalance in the defense mechanisms of the patient and thus explain the authors' results. This imbalance in defense mechanism may be more pronounced in cardiac surgical patients than in other patients as a result of CPB use and therefore explain why in the general meta-analysis of cell salvage a positive effect of cell salvage on infections was found,[9] whereas this was not the case in the meta-analysis of cell salvage during cardiac surgery.[8] It should be noted that during cardiac surgery the amount of processed blood is usually about a third of the amount of collected blood and is generally higher than in other fields.

Another possible mechanism is that processed CS blood is already contaminated. This has been demonstrated in several studies, but was not considered to be of clinical importance because the number of postoperative infections was very low.[27,28] However, these studies were done in small patient populations and more extensive research on this topic is necessary to make this more clear. Still the authors consider this as a less likely mechanism based on the current available knowledge and because they used 24-hour full antibiotic prophylaxis in all patients.

The authors did not take into account the storage time of CS blood. Theoretically, longer storage times may promote the development of infection. However, this blood was processed and retransfused already during the surgery in order to reduce allogeneic transfusions as much as possible.

A point of criticism may be that RBC transfusion could mask a more severe clinical situation in the CS group because these patients received their own processed blood and in addition RBC transfusion. This is however not supported by increased length of stay in the ICU or hospital in this group, nor in more postoperative complications. Another limitation is the fact that the CS group had more patients with simple valve surgery.

The authors believe that their results are valid because all data were prospectively collected in a large, well-conducted randomized trial, with excellent comparable patient groups, which lowers the risk of bias and confounding. The authors conclude that intraoperative CS was associated with higher infection rates through a direct effect, but that this direct effect was almost completely eliminated by its indirect protective effect through reduction in blood transfusion alone. Intraoperative CS is therefore not associated with lower infection rates in cardiac surgery.

Conflict of Interest

The authors declare that they have no conflicts of interest relevant to this manuscript.

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