The role of cell savers and filters in cardiac surgery

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Chapter 4

Additional post-operative cell salvage of shed mediastinal blood in cardiac surgery does not reduce allogeneic blood transfusions: a cohort study

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Accepted by Perfusion in revised form 2015

Abstract

Background: Does additional post-operative collection and processing of mediastinal shed blood with a cell salvage device reduce the number of allogeneic blood transfusions compared to intra-operative cell salvage alone.

Methods: Single centre cohort study in which 99 adult patients with coronary artery bypass grafting or aortic valve replacement were allocated to either a C.A.T.S® group with intra-operative blood processing only or a CardioPat® group with both intra- and post-operative blood processing. The primary endpoint was the number of allogeneic blood transfusions during hospital admission.

Results: The study included 99 patients, 50 in the C.A.T.S® and 49 in the CardioPat® group. There was no difference between groups in the number of RBC (C.AT.S® group 43 units versus CardioPat® 50 units, p= 0.74), number of FFP (C.A.T.S® 8 units versus CardioPat® 8 units, p=1.00) or platelets (C.A.T.S® 5 units versus CardioPat® 4 units, p=1.00) transfused during hospital stay. Creatinine kinase (CK) levels were not different between groups three hours after arrival in the ICU (CardioPat® group versus CATS® group, p= 0.17)). But compared to the CATS® group on the first (CK 416 IU/L ± 355 IU/L) and second post-operative day (CK 418 IU/L ± 380 IU/L) the increase in CK levels was more in the CardioPat group on the first (CK 640 IU/L ± 668 IU/L, p=0.02) and second post-operative day (CK 658 IU/L ± 723 IU/L, p=0.05). There was no difference over time in the levels of Troponin T (p=0.67) or CK-MB (p=0.43).

Conclusions: Post-operative cell salvage does not reduce transfusion requirements compared to intra-operative cell salvage alone but results in elevated total CK levels that indicates haemolysis.

Introduction

Intra-operative salvage of shed autologous blood with a mechanical device (cell saver) is a well-established blood conservation strategy to reduce allogeneic blood transfusion during cardiac surgery [1]. Blood conservation strategies are also expanded beyond the intra-operative period. Post-operative auto transfusion of unwashed shed mediastinal blood (SMB) has been studied before, but was largely abandoned for fear of inducing coagulopathy with the retransfusion of the activated and inflammatory blood and is not recommended by the current guidelines [2]. However, recent studies suggest that there is no impairment of haemostasis or an increase in blood loss with the retransfusion of unwashed SMB and that this procedure is an effective way to reduce allogeneic blood transfusions [3, 4], although SMB contains a substantial amount of potential embolic substances, activated platelets and pro-inflammatory substances [5]. Several studies have been undertaken to investigate the (additional) efficacy and safety of washing and processing post-operative SMB with a cell saver device before retransfusion [6-10]. Current guidelines now advocate this method, but only with a class III recommendation [2].

Recently a new type of cell saver (CardioPat®, Haemonetics) has become available. By its novel design, using a small collapsible processing disk and well-regulated level of suction, this cell saver is particularly suitable for continuous intra-operative and post-operative use [10].

This cohort study investigates whether additional post-operative collection and processing of mediastinal shed blood with a cell salvage device that was also used intra-operatively would reduce the number of allogeneic blood transfusions in patients undergoing cardiac surgery compared to intra-operative cell salvage alone.

Methods

This retrospective single centre cohort study comprised 99 adult patients scheduled for either non-emergent coronary artery bypass grafting (CABG) or first time aortic valve replacement (AVR). Excluded were patients with off-pump CABG, patients with known coagulation disorders except for the use of aspirin, and patients with

pre-existing liver disease or renal dysfunction. The institutional review board of the University Medical Centre Groningen approved the study. Patients gave signed informed consent.

Fifty patients were operated using the continuous auto-transfusion system (C.A.T.S®, Fresenius, Bad Homburg, Germany) for intra-operative blood processing. To minimize time effects, these patients were the last 50 patients from a previous study (ISRCTN 58333401), which studied the effects of cell saver, leukocyte depletion filters and their combination [11]. 49 consecutive patients were operated using the CardioPat® (Haemonetics, Braintree, USA) as part of a clinical evaluation for this device in our hospital. The study period was from 2009 to 2010. Patients were followed up until hospital discharge, without loss to follow up.

All patients received standard anaesthesia, consisting of propofol, and sufentanil (1-3 µg/kg). Ventilation was performed with an inspiratory oxygen fraction of 0.4, a tidal volume of 6-8ml/kg and a respiratory rate adjusted to maintain normocapnia. Protease inhibitors were not used. The CPB circuit consisted of roller pumps and an open venous reservoir and was primed with 1000 ml lactated Ringer's solution and 500 mL hydroxyethylstarch 10% (Fresenius, Bad Homburg Germany). Pump flow was set at 2.4 L/m^2/min and temperature was allowed to drift to 34°C. Anticoagulation was performed with heparin (3 mg/kg) and additional doses if required to maintain an activated clotting time (ACT), greater than 400 sec. Cardioplegia was performed with either blood or crystalloid solution.

In both groups, all blood suctioned from the wound and pleural space from incision until wound closure was processed with the cell saver and retransfused. Thus, conventional cardiotomy suction was not used during CPB. Residual blood in the heart lung machine circuit after the end of CPB was also processed with the cell saver and retransfused into the patient. Both cell savers were set-up according to the manufacturers instructions. The reservoir of the cell saver was primed with 100 ml of normal saline with 30.000 IU/L of heparin. During the operation there was a continuous flush of heparinised saline through the cell salvage suction tube. In the CATS® group the cell salvage was not used in the post-operative period. In the CardioPat® group however, cell salvage was continued during the first 6 post-operative hours. During that time all SMB was collected, processed and returned to the patient. After the first 6 hours

the shed blood was no longer processed or returned. This is in accordance with the manufacturer's instructions and the guidelines of the American Association of Blood Banks [12]. In contrast to the intra-operative period, there was no anticoagulation added to the reservoir of the CardioPat® in the post-operative period as per manufacturer's instructions.

The transfusion protocol prescribed that RBC's were to be transfused when the post-operative haemoglobin level was <8 g/dl. FFP was transfused in case of excessive bleeding (>150 ml/h for 2 consecutive hours and International Normalized Ratio (INR) or Prothrombin Time (PT) >1.5 normal). Platelets were transfused when platelet counts were $<100x10^9$/l in combination with excessive bleeding. The decision for surgical re-exploration was made on the usual clinical grounds.

The primary endpoint of this study was the number of allogeneic blood transfusions during hospital admission. Secondary endpoints were the percentage of patients that received allogeneic blood products, amount of post-operative blood loss (defined as the total amount of blood loss from closure of the sternum until 12 hours post-operatively), myocardial damage and renal dysfunction, number of re-explorations, length of stay in the ICU and hospital, the number of post-operative complications (myocardial infarction, atrial fibrillations and stroke). Myocardial damage was assessed by EKG changes and routine enzymatic measurements (creatine kinase (CK), myocardial band (MB) isoenzymes of CK and troponin T). Renal function was assessed by measuring serum creatinine. Routine coagulation test (PT, APTT and fibrinogen) were used to assess the coagulation profile. Blood samples were taken pre-operatively, after end of CPB, after admission in the ICU, the morning of the first post-operative day and the morning of the second post-operative day and at hospital discharge.

Statistical analysis

Continuous data were analysed using Student's t test or the Mann-Whitney U-test as appropriate. Blood transfusion data were analysed using Poisson regression for count variables and logistic regression for binary variables. Categorical variables were analysed using the chi-square test or Fisher's exact test as appropriate. To achieve

an approximately normal distribution of the biochemical markers we applied log conversion. We then used repeated measurements analysis of variance for serial data. A p value of < 0,05 was considered statistically significant. We calculated the sample size for this study as follows. Preliminary data based on the first results of our trial (ISRCTN 58333401) showed a mean transfusion rate of two units RBC and a standard deviation of two units. Mean post-operative chest tube lost was about 700 ml. This corresponded to a processed volume of at least 1 unit of RBC. Therefore to reach a reduction by 33% in RBC about 50 patients would be necessary in each group with the usual assumptions of an alpha 0.05 and a beta 0.8.

Results

The study included 99 patients, 50 in the CATS® group, and 49 in the CardioPat® group. Data of the post-operative blood collection of one patient in the CardioPat® group was missing; all other data from this patient were used.
Patient demographics revealed no differences between the groups (table 1).

The residual volume of CPB blood was higher in the CATS® group, whereas more intra-operative blood was collected in the CardioPat® group (table 1). Post-operative blood loss in the first 12 hours was 482 ± 339 mL in the CATS® group and 654 ± 523 mL in the CardioPat® group (p=0.55). From this blood, 474±363 mL was processed with the CardioPat® after 6 hours which resulted in 141 ± 122 mL of blood that was retransfused.The haemoglobin level of the processed blood from the CardioPat® was 25.3 ± 3.0 g/dL corresponding to a haematocrit of 70 ± 5 % (n=12). However, the extraction ratio (i.e. the amount of processed blood divided by the amount of collected blood) of the CardioPat® was lower than the extraction ratio of the CATS® (table 1).
Table 2 shows the transfusion data with confidence intervals. There were no differences between the groups in the number of units of red blood cells (RBC) that were transfused or in the number of patients who received RBC transfusions (table 2).

Table 1: Patient demographics and intra-operative data

	CATS® (n=50)	CardioPat® (n=49)	p-value
Age (years)	66.8 ± 9.7	65.5 ± 9.3	0.48
Sex (m/f)	36/14	42/7	0.09
Euro SCORE	4.8 ± 3.2	4.5 ± 3.0	0.67
CABG/AVR (n)	37/13	38/11	0.68
Previous myocardial infarction (n (%))	12 (24%)	7 (14%)	0.22
Pulmonary disease (n (%))	5 (10%)	7 (14%)	0.51
Hypertension (n (%))	24 (48%)	26 (54%)	0.61
Diabetes (n (%))	12 (24%)	13 (27%)	0.77
Previous Cerebrovascular accident (n (%))	0 (0%)	1 (2%)	0.31
Aspirin (n (%))	28 (56%)	35 (72%)	0.11
Haemoglobin (g/dL)	12.2 ± 1.3	12.3 ± 1.3	0.35
Creatinine (umol/L)	76 ± 15	82 ± 24	0.15
Aortic clamp time (min)	62 ± 27	63 ± 20	0.94
Perfusion time (min)	104 ± 41	102 ± 27	0.75
Haemoglobin at end of operation (g/dL)	8.2 ± 0.8	8.3 ± 1.1	0.30
Residual volume CPB (mL)	922 ± 352	752 ± 149	< 0.01
Intra-operative collected blood (mL)	1929 ± 766	2470 ± 895	< 0.01
Processed blood (mL)	605 ± 247	600 ± 207	0.9
Extraction ratio cell saver device	0.32 ± 0.09	0.25 ± 0.05	< 0.01

Results are presented as number of patients (n) and percentage (%) or mean ± standard deviation (SD), as indicated. Euro Score, European System for Cardiac Operative Risk Evaluation; CABG, coronary artery bypass grafting; AVR, aortic valve replacement; CPB, cardiopulmonary bypass

Table 2: Transfusion Data

	CATS® (n=50)	CardioPat® (n=49)	p value	Odds Ratio [95% confidence interval]
Units RBC transfused first 24 hrs (n)	31	26	0.80	0.99 [0.87-1.12]
Patients transfused first 24 hrs (n (%))	11 (22%)	11 (22%)	0.96	1.02 [0.39-2.64]
Units RBC transfused during hospital stay (n)	43	50	0.74	1.00 [0.80-1.24]
Patients transfused (n (%))	14 (28%)	12 (25%)	0.69	0.83 [0.34-1.04]
Units FFP transfused (n)	8	8	1.00	1.00 [0.80-1.24]
Patients transfused FFP (n (%))	2 (4%)	3 (6%)	0.68	1.56 [0.25-9.80]
Units platelets transfused (n)	5	4	1.00	0.97 [0.58-1.68]
Patients transfused platelets (n (%))	4 (8%)	4 (8%)	1.00	1.02 [0.24-4.33]
Total allogeneic transfusion (n)	56	62	0.61	1.00 [0.94-1.06]

Results are presented as number of patients (n) and percentage (%) or mean ± standard deviation (SD), as indicated.

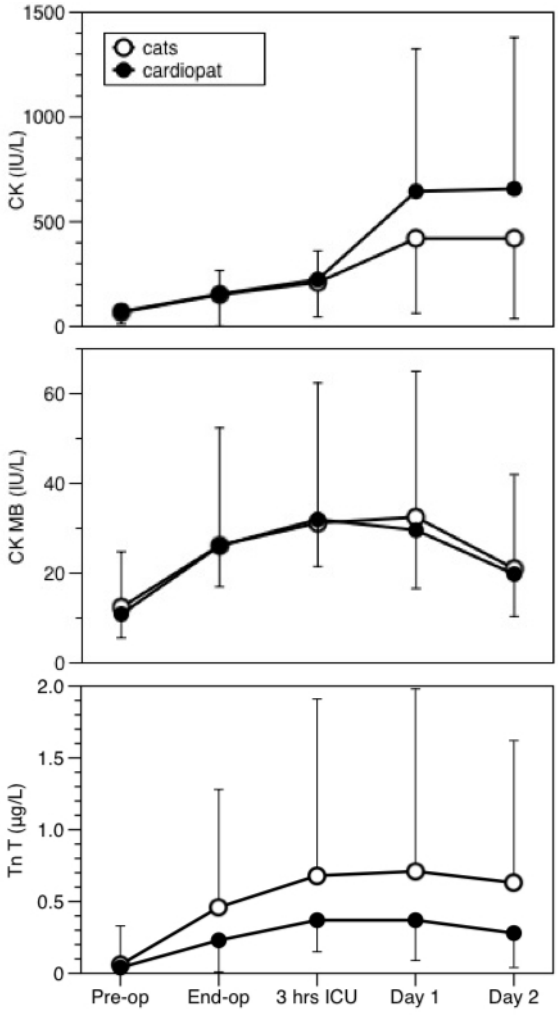
The transfusion load of the RBC's in the first 24 hours therefore equalled 0.6 U per patient in the CATS® group and 0.5 U per patient in the CardioPat® group (p=0.74). This amounted to 2.8 U per transfused patient in the CATS® group and 2.4 U per transfused patient in the CardioPat® group (p= 0.54). There was also no difference between the groups in the number of units of FFP or platelets that were transfused (table 2). There was no difference in post-operative blood loss between cell savers, although there was a trend towards more blood loss in the CardioPat® group.
In table 3 the results of the routine coagulation tests are shown. There was no clinical relevant difference between the groups.

Table 3: Coagulation test

	Time point	CATS® (n=50)	CardioPat® (n=49)	p-value
Prothrombin Time (sec)	Pre-operative	11.6 ± 1.5	11.0 ± 0.5	0.01
	ICU	13.4 ± 2.5	12.6 ± 1.0	0.03
	Day1	11.7 ± 1.5	11.3 ± 0.7	0.04
Activated Partial Thromboplastin Time (sec)	Pre-operative	30.9 ± 24.9	26.6 ± 2.2	0.24
	ICU	32.7 ± 5.9	30.2 ± 3.9	0.02
	Day1	26.8 ± 2.6	27.4 ± 2.6	0.25
Fibrogen (g/l)	Pre-operative	3.2 ± 0.7	3.4 ± 0.8	0.31
	ICU	2.0 ± 0.6	1.9 ± 0.5	0.32
	Day1	2.8 ± 0.8	3.0 ± 0.9	0.23

Creatinine kinase levels were not different between groups 3 hours after arrival in the ICU (CardioPat® group (226 IU/L ± 135 IU/L) and CATS® group (210 IU/L ± 165 IU/L, p= 0.17)), but increased more in the CardioPat® group on the first (640 IU/L ± 668 IU/L) and second post-operative day (658 IU/L ± 723 IU/L) compared to the CATS® group on the first (416 IU/L ± 355 IU/L, p=0.02) and second post-operative day (418 IU/L ± 380 IU/L, p=0.05) figure 1). There was no difference between the groups at the time points in the levels of Troponin T (p=0.67) or CK-MB (p=0.43, figure 1).

Figure 1: Perioperative course of biochemical markers



Results are presented as mean ± standard deviation (SD). Pre-op, before operation; end-op, end of operation; ICU, intensive care unit; Day 1 and 2, post-operative day 1 and 2; CK, Creatine kinase; CK MB: Creatine kinase myocardial band; TnT, Troponin T.

There were no differences in the post-operative data as shown in table 4.

Table 4: Post-operative data

	CATS® (n=50)	CardioPat® (n=49)	p value
Post-operative collected blood over 12hrs (mL)	482 ± 339	654 ± 523	0.55
Post-operative processed blood (mL)	Na	474 ± 363	Na
Retransfused post-operative blood volume (mL)	Na	141 ± 122	Na
Extraction ratio	Na	0.29 ± 0.11	Na
Re-explorations (n (%))	2 (4%)	2 (4%)	1.00
Myocardial infarction (n (%))	1 (2%)	0 (0%)	1.00
New atrial fibrillation (n (%))	12 (24%)	10 (21%)	0.81
Stroke (n (%))	0 (0%)	0 (0%)	1.00
Length of stay intensive care (days)	1.2 ± 1.0	1.3 ± 1.4	0.76
Length of stay hospital (days)	9.3 ± 4.7	10.8 ± 16.2	0.70

Results are presented as patients (n)/percentage (%) or mean ± standard deviation (SD), as indicated.
NA, not applicable

Discussion

We found that additional post-operative salvage and washing of the shed mediastinal blood after intra-operative cell salvage neither reduced the number of allogeneic RBC transfusions nor the number of patients transfused, compared to intra-operative cell salvage alone. Autotransfusion of post-operative SMB processed with a cell saver, which was also used intra-operatively, has been studied before [7, 8, 10, 13]. In one study a reduction in the number of RBC's transfusions, but not in the number of patients transfused was found [7]. A reduction in the number of RBC's used and in the number of patients transfused was reported in another study, but in this study the intra-operative blood loss during CPB or residual CPB blood was not processed with the cell saver [8]. However, in both studies the control group did not have intra-operative cell salvage at all. Therefore these studies provide no information on the additional effect of post-operative cell salvage. In another study where cell salvage was used only for the post-operative period the number of patients that was transfused with RBC's was significantly reduced [9].

One recent study used a similar cell saver deployment as we did [10]. In contrast to our results, a significant reduction in the mean transfusion requirements of RBC's was found. For an explanation of these contradictory results it is necessary to know the blood volumes that are collected and processed by the cell saver in order tot assess the efficacy of the blood salvage procedure. Unfortunately, most of the mentioned studies do not report these volumes. Weltert et al [10] only report the amount of returned processed blood after 6 hours (350 ml) and the total amount of 24-hour blood loss (720 ml). Considering a typical extraction ratio for blood processing in the order of 0.3 (as we found for both devices), this means that to retransfuse a mean processed amount of blood of 350 ml the original input must have been at least 1000ml in 6 hours, i.e. much more than the fore mentioned amount of total 24-hour blood loss. These volumes are rather high and have a significant impact on allogeneic transfusion data, as around 200-250 mL of processed cell saver blood equals one unit of packed cells. This may therefore explain the different results.

Since the introduction of the transfusion of post-operative unwashed SMB it is known that markers of myocardial damage rise [14]. In our study, the patients who received post-operatively washed SMB had a significant higher level of total CK compared to those that did not receive washed SMB whereas the other markers of myocardial damage such as CK-MB and troponin T were not elevated. The rise in total CK levels was therefore not of cardiac origin. The rise in total CK started after processed blood was retransfused to the patient in the intensive care unit and continued up to 48 hours post-operatively. Conventional anticoagulation with heparin was used in both groups during the intra-operative part of the blood salvage. However in the post-operative setting the CardioPat® does not require anticoagulation of the blood in the reservoir. This likely induces extensive haemolysis in the reservoir and therefore a rise in CK levels that persists despite the washing of the blood.

Compared to earlier studies on auto transfusion of unwashed SMB the rise in creatine kinase was much lower [14-16]. This might be attributed to the washing of the post-operative shed and highly inflammatory mediastinal blood itself, further indicating that the washing process per se improves blood quality [17, 18]. Nonetheless, our data suggest that caution should be exerted even when washed SMB is retransfused.

There are several limitations to our study. First the study was observational and small compared to other studies with post and intra-operative cell saver use. However, clinical practice was strict and the patient demographics demonstrated similar groups. Given the sample size calculation and the confidence limits of the main results it is unlikely that this affected our results. Moreover the quantity of SMB in our study was comparable to the reported quantities of SMB in other studies. A second limitation is that we did not measure the concentration of CK's of the SMB before being processed. In conclusion, continuing cell salvage beyond the operating room does not reduce transfusion requirements compared to intra-operative cell salvage alone but results in elevated total CK levels that suggest haemolysis.

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