Heart and Vessels (2019) 34:1280–1286
https://doi.org/10.1007/s00380-019-01365-6

ORIGINAL ARTICLE

Cell salvage processing of residual cardiopulmonary bypass volume in minimally invasive cardiac surgery

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Received: 8 November 2018 / Accepted: 22 February 2019 / Published online: 27 February 2019

Abstract
Several reports demonstrated positive effects of processing residual cardiopulmonary bypass volume using a cell salvage device in conventional open heart surgery via sternotomy on hemostasis. The present study aimed to investigate whether cell salvage processing has the same effects on postoperative blood loss and transfusion in minimally invasive cardiac surgery. Between July 2015 and April 2018, 80 consecutive patients undergoing minimally invasive aortic valve replacement via right anterolateral minithoracotomy were enrolled in the present study. Perioperative outcomes and coagulation data of 40 patients who were retransfused with processed cardiopulmonary bypass volumes were compared with those of 40 patients receiving unprocessed residual blood (control group). Postoperative blood loss in patients receiving processed residual blood was significantly less than that in the control group at 6 h (115 ± 50 vs. 73 ± 33 ml, $p < 0.001$) and 12 h (167 ± 70 vs. 125 ± 67 ml, $p = 0.009$) after surgery, and the rate of fresh frozen plasma use after surgery was significantly reduced in patients receiving processed residual blood (18 vs. 0%, $p = 0.012$). In conclusion, processing of residual cardiopulmonary bypass volume reduced postoperative blood loss and postoperative use of fresh frozen plasma and could be useful for hemostasis in minimally invasive cardiac surgery.

Keywords Cell salvage device · Minimally invasive cardiac surgery · Residual cardiopulmonary bypass volume · Postoperative blood loss

Introduction

Residual blood of the cardiopulmonary bypass (CPB) circuit had been typically discarded at the end of the procedure, with as much blood products as necessary being used. However, it is well known that blood transfusion results in increased mortality in cardiac surgery [1], and various approaches have been used to reduce the amount of administered blood products. As stated in the blood conservation clinical practice guidelines [2], to demonstrate that the reinfusion of the residual pump blood is a judicious approach to minimize the use amount of blood product used during transfusion, we collected the residual CPB volume in a sterile bag following CPB termination and retransfused it into the patients at the end of the surgery. However, there were concerns regarding the increased risk of bleeding owing to heparin content in the residual CPB volume as well as regarding post-infusion hemostatic disorder due to hemolytic residual CPB blood.

A cell salvage system is a device that washes the collected blood and produces a product of mostly packed red cells, and is now commonly used during cardiovascular surgery [3]. The blood conservation clinical practice guidelines mention that centrifugation, instead of direct infusion, of residual pump blood is reasonable for minimizing post-CPB allogeneic red blood cell transfusion [2]. Accordingly, we began processing the residual CPB volume using a cell salvage device for all patients who underwent cardiac surgery from December 2016. Several studies demonstrated that processing residual CPB volume with a cell salvage device had positive effects on hemostasis during cardiovascular surgery [4, 5]. Elimination of unfractionated heparin and activated

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platelets in the remaining CPB volume are thought to be the mechanism by which secondary hemorrhage is prevented. However, the study subjects were patients undergoing conventional surgery via full sternotomy and it remains unclear whether the same results can be seen in minimally invasive cardiac surgery (MICS), in which coagulation factors are likely to be maintained because of less intraoperative blood loss. The aim of the present study is to evaluate the effect of cell salvage processing on postoperative blood loss and need for blood transfusion in MICS.

Patients and methods

Study population

The present study was approved by the Ethics Committee of The Sakakibara Heart Institute of Okayama and written informed consent was obtained from all patients. Between July 2015 and April 2018, 80 consecutive patients who underwent isolated aortic valve replacement via right anterolateral minithoracotomy were enrolled in the present study. Overall, 40 patients who underwent minimally invasive aortic valve replacement (MIAVR) from July 2015 to November 2016 were transfused with unprocessed residual CPB volumes (control group), and 40 patients who underwent MIAVR between December 2016 and April 2018 were transfused with processed residual CPB blood (CS group). Intraoperative data during CPB and postoperative outcome of the CS group were retrospectively compared with those of the control group. All MIAVR procedures were performed by a single surgeon. In all patients, cell salvage system was used during the surgery and CPB was established by femoro-femoral bypass using peripheral cannulas (PCKC-A/V; Toyobo, Osaka, Japan), without or with additional right axillary arterial cannulation. There were no cases of emergent surgery or hemodialysis in this cohort.

Cardiopulmonary bypass system

The CPB circuit consisted of an oxygenator (Capiox; RX-15/25, TERUMO, Tokyo, Japan), an arterial filter (Filter15, JMS, Tokyo, Japan), a hard-shell reservoir (HVR-FHP4P, JMS, Tokyo, Japan), and a JMS tubing system coated with heparin (COAFREE; JMS Tokyo, Japan). Roller pumps (Heart Assist System II; MERA, Tokyo, Japan) were used in the CPB. The CPB circuit was primed with a mixture of acetic acid Ringer's solution, 300 ml of mannitol, and 4000 units of heparin. Total priming volume was determined by the size of the CPB circuit and ranged from 900 to 1100 ml; blood was not used for CPB priming. A 3/8-in. arterial and a 1/2-inch venous tube were mainly selected and were primed with 1000 ml of solution. In patients weighing < 40 kg, the CPB circuit was primed with 900 ml of solution. In patients weighing > 70 kg, 1/2-in. arterial and 1/2-in. venous roller pump tubing was primed with 1100 ml of solution.

Heparin was administered at an initial dose of 300 U/kg body weight and was added to maintain an active clotting time > 480 s during CPB management. The target pump flow was set at 2.2–2.4 l/m^2, mean blood pressure was maintained at 50 to 80 mmHg, minimum body temperature was kept at 34 °C, and Alpha-stat pH management was used during CPB. Myocardial protection was achieved with antegrade and/or selective administration of cold modified St. Thomas' solution [6]. The hemoglobin level was maintained at > 7 g/dl during surgery.

Intraoperative blood management and blood loss measuring

Cardiotomy suction was essentially used until CPB termination to preserve autologous blood. The suction line connected to a cell salvage system was employed, particularly for a fine suction, such as that for blood backflow from the coronary ostia and suture line bleeding. Intraoperative blood loss was determined as the total volume of blood absorbed by the gauze and the blood volume remaining in the CPB circuit after the collection of the residual CPB volume.

Processing of residual blood and blood sampling

After protamine neutralization, the remaining CPB volume in the control group was collected in a sterile bag using ultrafiltration technique and was retransfused into the patient. In the CS group, the residual volume was collected in a cell salvage device, and retransfusion was performed after processing by centrifugation. A 225-ml Xtra® bowl (LivaNova, London, UK) was used as an autologous blood recovery system. The remaining CPB volume was washed with 200 ml saline at a fixed flow rate of 300 ml/min.

Arterial blood samples were measured using RAPIDLAB Blood Gas System (Siemens, Munich, Germany) after induction of anesthesia (T0), 5 min after protamine neutralization (T1), and on admission to the intensive care unit (T2). The level of fibrinogen and D-dimer were following after CPB termination and retransfusion of the residual CPB volumes. Postoperative blood loss was defined as the total volume from the chest drainage tube and was measured 6 and 12 h after surgery.

Statistical analysis

All values are presented as mean ± standard deviation or number (percentage). Continuous data were analyzed using a two-tailed *t* test or the Mann–Whitney test, and the Chi

square test was used for categorical variables. All statistical analyzes were performed using JMP for Mac 10.11.6. A p value < 0.05 was considered statistically significant.

Results

Patients' demographic characteristics

Patients' demographic characteristics are shown in Table 1. Patient backgrounds were almost the same and no significant differences were found in all variables between the two groups. In comparing the control group with the CS group (Fig. 1), there were no significant differences in the hemoglobin level (12.6 ± 1.8 vs. 12.9 ± 1.4 g/dl; $p = 0.44$), platelet count (17,743 ± vs. 18,440 ± $\times 10^3$/μl; $p = 0.31$), and total protein (7.0 ± 0.5 vs. 7.1 ± 0.4 g/dl; $p = 0.53$) at induction of anesthesia.

Intraoperative data during CPB

As shown in Table 2, no significant differences were found in the operative, CPB, and aortic cross-clamping times between the two groups. Furthermore, there were no significant differences in the residual blood volume, the amount of blood components, and the rate of blood transfusion. However, the time for hemostasis after protamine neutralization in the CS group was significantly shorter than in the control group (control group, 73 ± 14 min vs. CS group, 66 ± 13 min; $p = 0.019$), and the volume of intraoperative blood loss in the CS group was significantly less than in the control group (control group, 26,463 ± ml vs. CS group, 23,854 ± ml; $p = 0.031$). Furthermore, the D-dimer level in the CS group was significantly lower than that in the control group after CPB termination (control group, 1.8 ± 2.7 vs. CS group, 0.8 ± 0.8 μg/ml. $p < 0.001$), although no significant difference was found in the fibrinogen level.

Postoperative outcomes

Postoperative outcomes are shown in Table 3. There were no cases of in-hospital death or major complications including cerebral infarction. The length of intensive care unit stay (ICU) was almost the same between the two groups. No significant differences were found between the control and CS groups (Fig. 1) in the hemoglobin level

Table 1 Patients' demographic characteristics

	Control group ($n = 40$)	CS group ($n = 40$)	p value
Age (years)	73 ± 13	72 ± 10	0.31
Male/female	19/21	25/15	0.18
Body surface area (m^2)	1.53 ± 0.19	1.62 ± 0.27	0.15
Diabetes mellitus	7 (18%)	8 (20%)	0.77
Hypertension	27 (68%)	23 (58%)	0.35
Dyslipidemia	15 (35%)	11 (28%)	0.61
Chronic obstructive pulmonary disease	3 (8%)	1 (3%)	0.30
NYHA functional class (I/II/III)	15/22/3	15/20/5	0.74
Ejection fraction (%)	67 ± 10	66 ± 9	0.52
Aortic insufficiency/aortic stenosis	8/32	12/28	0.30
STS score (risk of mortality) (%)	2.6 ± 1.7	2.1 ± 1.6	0.10
Euro SCORE II (%)	1.6 ± 1.0	1.6 ± 1.0	0.68

NYHA New York Heart Association, *STS* The Society of Thoracic Surgeons

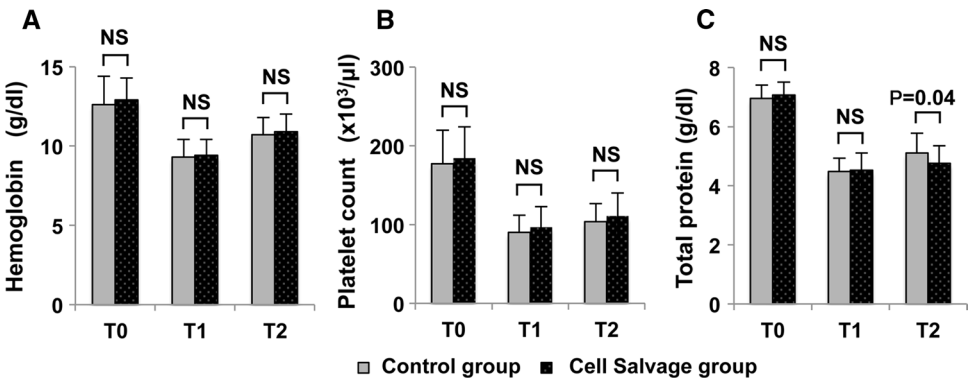

Fig. 1 Hemoglobin (**a**), platelet count (**b**), and total protein (**c**) at 3 time points. *T0* on induction of anesthesia, *T1* 5 min after protamine neutralization, *T2* on admission to intensive care unit

Table 2 Intraoperative data

	Control group ($n=40$)	CS group ($n=40$)	p value
Clinical data			
Operation time (min)	253 ± 33	244 ± 37	0.20
CPB time (min)	15 ± 122	15 ± 025	0.62
Aortic cross-clamping time (min)	99 ± 15	97 ± 18	0.46
Mechanical valve/tissue valve	34/6	37/3	0.48
Time for hemostasis after protamine neutralization (min)	73 ± 14	66 ± 13	0.019
Intraoperative blood loss (ml)	264 ± 63	238 ± 54	0.031
Residual volume in CPB circuit (ml)	575 ± 33	583 ± 38	0.30
Fibrinogen level after CPB termination (mg/dl)	186 ± 49	193 ± 37	0.25
D-dimer level after CPB termination (μg/ml)	1.8 ± 2.7	0.8 ± 0.8	< 0.001
Blood products used in the surgery			
Use of RBC	8 (20%)	7 (18%)	0.77
Use of FFP	6 (15%)	3 (8%)	0.29
Use of PC	0 (0%)	0 (0%)	1.00
The amount of RBC (units)	0.7 ± 1.6	0.6 ± 1.3	0.81
The amount of FFP (units)	0.4 ± 1.0	0.2 ± 0.8	0.29

CPB cardiopulmonary bypass, *FFP* fresh frozen plasma, *PC* platelet concentrates, *RBC* red blood cells

Table 3 Postoperative clinical outcome

	Control group ($n=40$)	CS group ($n=40$)	p value
In-hospital mortality	0 (0%)	0 (0%)	1.00
Stroke	0 (0%)	0 (0%)	1.00
Reexploration for bleeding	0 (0%)	0 (0%)	1.00
Renal failure requiring renal replacement therapy	0 (0%)	0 (0%)	1.00
Atrial fibrillation	9 (23%)	9 (23%)	1.00
PaO_2/FiO_2 ratio at the admission of ICU	374 ± 124	366 ± 118	0.60
Mechanical ventilation time (h)	8.3 ± 5.5	6.9 ± 4.9	0.24
ICU stay (days)	1.9 ± 0.8	2.0 ± 0.6	0.47

ICU intensive care unit

(control group, 10.7 ± 1.1 vs. CS group, 10.9 ± 1.1 g/dl; $p=0.30$) and platelet count (control group, 104 ± 23 vs. CS group, 111 ± 29 × 10^3/μl; $p=0.43$), whereas there was a significant difference in the total protein level (control group, 5.1 ± 0.7 vs. CS group, 4.8 ± 0.6 g/dl; $p=0.04$) on admission to the ICU.

As shown in Table 4, postoperative blood loss in the CS group was significantly less than in the control group at 6 h (control group, 115 ± 50 vs. CS group, 73 ± 33 ml, $p<0.001$) and 12 h (control group, 167 ± 70 vs. CS group, 125 ± 67 ml, $p=0.009$) after surgery, and the rate of postoperative use of fresh frozen plasma (FFP) was significantly reduced in the CS group (control group, 18% vs. CS group, 0%; $p=0.012$). No significant differences were found between the 2 groups in the prothrombin time-international normalized ratio (PT-INR), activated partial thromboplastin time (APTT), and activated clotting time.

Discussion

The aim of the present study was to evaluate the effect of processing residual CPB volume with a cell salvage device on postoperative blood loss and blood transfusion in MICS. We included 80 consecutive patients who underwent MIAVR via a right minithoracotomy in the present study. We started our MICS program from March 2005 and have performed MICS for more than 800 patients to date. In minimally invasive mitral valve repair, the durations of the CPB and cross-clamping depend on the complexity of the mitral valve lesion, and a second pump run is sometimes needed for revision [7]. By contrast, MIAVR comprises the routine procedure using a prosthetic valve. As shown in the present study, the durations of the CPB and aortic cross-clamping were almost the same between

Table 4 Postoperative blood loss and use of blood products

	Control group ($n=40$)	CS group ($n=40$)	p value
Amount of postoperative blood loss (ml)			
6 h after admission to ICU	115 ± 50	733 ± 3	< 0.001
12 h after admission to ICU	167 ± 70	125 ± 67	0.009
Blood products during ICU stay			
Use of RBC	2 (5%)	3 (8%)	0.64
Use of FFP	7 (18%)	0 (0%)	0.012
Use of PC	0 (0%)	0 (0%)	1.00
Amount of RBC (units)	0.1 ± 0.4	0.2 ± 0.5	0.64
Amount of FFP (units)	0.5 ± 1.1	0	0.006
Blood data at admission to ICU			
Activated clotting time (s)	138 ± 15	137 ± 14	0.37
APTT (s)	37 ± 8	46 ± 59	0.92
PT-INR	1.30 ± 0.11	1.33 ± 0.14	0.19
Lactate dehydrogenase level (IU/l)	298 ± 71	253 ± 53	0.002

APTT Activated partial thromboplastin time, *FFP* fresh frozen plasma, *ICU* intensive care unit, *PC* platelet concentrate, *PT-INR* prothrombin time-international normalized ratio, *RBC* red blood cells

the two groups. Therefore, we considered these subjects suitable for investigating the effect of cell salvage processing in MICS in spite of the low study power.

Our results showed that postoperative blood loss and postoperative use of FFP were significantly reduced in the CS group. We focused on the level of D-dimer after CPB termination as a contributing factor in reduced postoperative bleeding. In the present study, the level of D-dimer in the CS group was significantly lower than in the control group. It is well known that the use of an extracorporeal circuit activates intrinsic tissue factor, leading to increased tissue plasmin activator, enhancement of the fibrinolytic system, and risk of hemorrhage [8–10]. Therefore, our result might suggest that processing of residual CPB volumes could inhibit excessive fibrinolytic activation and reduce secondary bleeding. Furthermore, we speculate that reduction of free hemoglobin is another factor reducing postoperative blood loss [11]. Cell salvage devices are known to eliminate free hemoglobin [3]. Free hemoglobin induces platelet activation mediated by von Willebrand factor and causes coagulopathy [12]. Although we could not measure the level of free hemoglobin, the level of lactate dehydrogenase in the CS group was significantly lower than in the control group. Kato et al. reported a strong correlation between lactate dehydrogenase and free hemoglobin in hemolytic blood [13]. Inhibition of excessive fibrinolytic activation and elimination of free hemoglobin may reduce postoperative blood loss, resulting in reduction of postoperative use of FFP.

On the other hand, there exists a concern regarding coagulopathy due to loss of plasma coagulation proteins or the activation of thrombin generation during the centrifugal washing process with a cell salvage system. A randomized study reported by Rubens et al. has demonstrated that processing of CPB blood results in greater blood product use with greater postoperative bleeding in patients undergoing cardiac surgery [14]. Scrascia et al. have reported significantly high level of prothrombin fragment 1.2 after processed blood infusion [15]. Other study also reported that processing with a cell salvage system reduced the levels of coagulation factors and platelets [16]. However, in our results, there were no significant differences between the two groups in platelet counts, fibrinogen levels, PT-INR, and APTT. This result could be attributed to smaller processing volumes compared to those in previous studies. The processed CPB volume in previous studies was approximately 1000 ml, while the processed volume in our study was 583 ± 38 ml. Although the size of CPB circuit has not been noted in their reports, the CPB circuit that we used may be smaller than that they used. The processing of a smaller residual CPB volume without affecting platelets and coagulation factors would minimize the activation of thrombin and would be effective in reducing postoperative bleeding. This finding suggests that the mechanism was inhibition of fibrinolytic activation.

In the present study, processing of residual CPB volume reduced postoperative blood loss and postoperative use of FFP. Cardiac surgeons are more concerned about hemostasis in MIAVR than in minimally invasive mitral valve surgery, because aortic valve surgery involves high arterial pressure at the aortotomy. Hence, devising a method to decrease postoperative blood loss may improve the outcomes of MIAVR. However, the postoperative blood loss observed differed only by 40 ml, with no significant differences in the clinical outcomes noted between the two groups. MIAVR has several advantages, including less bleeding than that observed in the conventional sternotomy approach [17]. The clinical

outcome was satisfactory even in the control group; therefore, cell salvage processing could not improve the clinical outcome. Only a small reduction in the postoperative blood loss may be meaningless in several young patients. However, based on our previous report regarding MIAVR for octogenarians [18], the rate of blood transfusion in octogenarians was significantly higher than that in younger patients. Thus, cell salvage processing might be useful for reducing the amount of blood products required for elderly patients. Furthermore, it could also be useful for patients with comorbidities or in cases of combined surgery with longer CPB durations.

Therefore, the present study suggests that the processing of residual CPB volumes reduced the postoperative blood loss via the inhibition of excessive fibrinolytic activation and reduction of secondary bleeding. However, the present study has some limitations. First, this was a retrospective analysis with a small sample size in a single institute. There may be selection bias. Second, the two groups were derived from different study periods. However, all MIAVR procedures were performed by a single experienced surgeon. There were no significant differences in patient characteristics, surgery-related times, and postoperative coagulation values between the two groups. Thus, these factors probably had little influence on the results. To evaluate the efficacy of the processing of residual CPB volume, a randomized controlled study is necessary and more detailed parameters related to coagulation, such as von Willebrand factor, should be investigated.

Conclusions

Processing of residual volume in the CPB circuit reduced postoperative blood loss and use of FFP. Processing of residual CPB blood may be useful for hemostasis in MICS.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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