A new practical technique to reduce allogeneic blood exposure and hospital costs while preserving clotting factors after cardiopulmonary bypass: the Hemobag®

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Recent data independently linking allogeneic blood use to increased morbidity and mortality after cardiopulmonary bypass (CPB) warrants the study of new methods to employ unique and familiar technology to reduce allogeneic blood exposure. The Hemobag® allows the open-heart team to concentrate residual CPB circuit contents and return a high volume of autologous clotting factors and blood cells to the patient.

Fifty patients from all candidates were arbitrarily selected to receive the Hemobag® (HB) therapy. A retrospective control group of 50 non-Hemobag® (NHB) patients were matched to the HB group patient-by-patient for comparison according to surgeon, type of procedure, age, body surface area (BSA), body weight and CPB time. Many efforts to conserve blood (Cell Saver® and ANH) were employed in both groups. Post-CPB cell washing of circuit contents was additionally employed in the control group.

There were no significant differences between the HB and NHB groups in regard to patient morphology, pre-op cell concentrations, distribution of surgeon or procedures (41% valve, 16% valve/coronary artery bypass graft (CABG), balance CABG), pump and ischemic times and Bayes National Risk scores. The average volume returned to the patient from the HB was 817±198 mL (1 SD). Average processing time was 11 min. The Hemobag® contained an average platelet count of 230±80 K/mm^3, fibrinogen concentration of 413±171 mg/dl, total protein of 8.0±2.8 gm/dl, albumin of 4.4±1.2 gm/dl and hematocrit of 43±7%. Factor VII, IX and X levels in three HB contents averaged 259% greater than baseline. Substantial reductions were achieved in both allogeneic blood product avoidance and cost to the hospital with use of the HB.

Infusion of the Hemobag® concentrate appears to recover safely substantial proteins, clotting factor and cell concentration for all types of cardiac procedures, maintaining the security of a primed circuit. *Perfusion* (2005) **20,** 343–349.

Introduction

Cardiovascular surgery remains responsible for approximately 10–20% of all transfusions in the US despite recent data demonstrating that transfusions are independently linked to increased short- and long-term morbidity and mortality.[1] In the climate of national blood product shortages and concern for disease transmission and immunosuppression, every effort should be made to optimize autologous blood recovery and reduce allogeneic blood usage. The recent voluntary adoption by US health care facilities of Standards for Perioperative Autologous Blood Collection and Transfusion illustrates the shift in focus to minimize allogeneic blood usage.[2]

Cardiopulmonary bypass (CPB) circuit prime has historically contributed, in part, to hemodilution. Condensed circuits with prime volumes of 1000–1500 mL are now the norm and may be retrograde autologous primed (RAP) to reduce hemodilution even further.[3] After minimizing priming volume before bypass, post bypass the circuit blood volume should be carefully considered for optimal blood component salvage. The best-known practices to process the pump contents should be pursued. Residual blood volume remaining in the circuit

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at aortic decannulation traditionally has been salvaged by either red blood cell washing,[4] some form of ultrafiltration,[5,6] or displacing the pump volume into the patient with or without hemoconcentration.[7]

The three main methods of residual extracorporeal circuit (ECC) autologous blood have been studied extensively.[8–11] Cell processing conserves red blood cells, but discards all plasma and its viable proteins.[12,13] Displacing the pump contents into transfer bags for infusion directly into the patient stresses the kidneys to process extra fluid in some patients who are already volume-overloaded, which may contribute to organ dysfunction compared to maintaining normovolemic homeostasis. Karkouti *et al*. demonstrated the independent relationship between a low hematocrit nadir and perioperative renal failure, suggesting that intraoperative hemodilution should be avoided.[14]

In conjunction with the trend to decrease activation of blood components by the increased use of treated ECC surfaces,[15,16] the authors believe that there is sufficient evidence-based support to warrant concentrating the ECC residual blood before patient infusion.[4–6,8,9,11–13,17] The purpose of this communication is to describe the results of a novel method and device to process residual ECC autologous blood. The early results of a case series with a retrospective control group are presented.

Equipment

A new blood conservation method and technology for blood salvaging, the Hemobag® (HB) which deals directly with ECC volume at aortic decannulation, is presented (Global Blood Resources LLC, Somers 06701, CT, USA, www.mybloodfirst.com). The Hemobag® system and technique facilitates conventional ECC ultrafiltration during CPB and the recovery through multi-pass ultrafiltration of autologous whole blood from the ECC after use. The technique maintains the integrity and security of a primed CPB circuit at all times.

Technique

Roeder *et al*. describe the Hemobag® method and results in a controlled laboratory environment.[6] Figure 1 illustrates the hemoconcentrator circuit employed in this case series.

The TS3 tubing set (Figure 2) allows hemoconcentration, both during the case and at the end, and will keep the security of a primed circuit in the immediate post-CPB period. The same Hemobag® is used to collect, concentrate and infuse the patient's own whole blood in a timely manner. The Hemobag® method and instructions for use have been cleared by the US Food and Drug Administration.

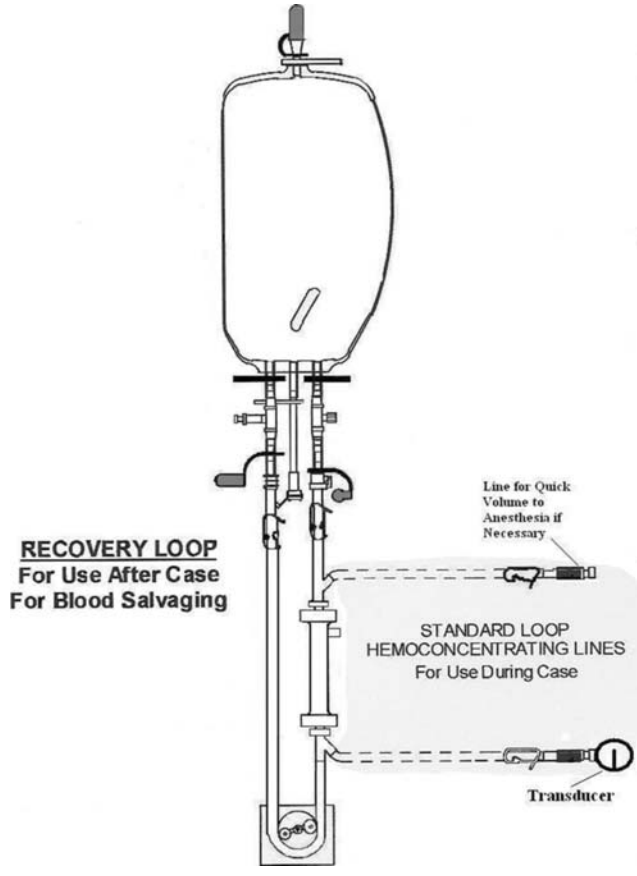

Figure 1 The hemoconcentrator is configured in a standard ECC loop for use during CPB. The Hemobag® contents are recirculated and concentrated in a multipass fashion after blood is displaced from the ECC into the Hemobag® and its recovery loop. ECC: extracorporeal circulation.

CPB management

Both the HB group and the control group CPB circuit employed the SX-1.8 m^2 membrane oxygenator and circuit tubing with X-Coating (Terumo Cardiovascular, Ann Arbor, MI, USA), open venous reservoir, centrifugal arterial pump (Sarns Delphin, Terumo Cardiovascular) and arterial line filtration (Terumo Cardiovascular X-Coated® 37 micron). The ECC prime consisted of balanced pH and electrolyte solution, mannitol and 10 000 IU of porcine heparin. At the initiation of CPB, the effective prime volume after retrograde autologous priming was about 700 mL. The Cell Saver® 5 (Haemonetics® Corporation,

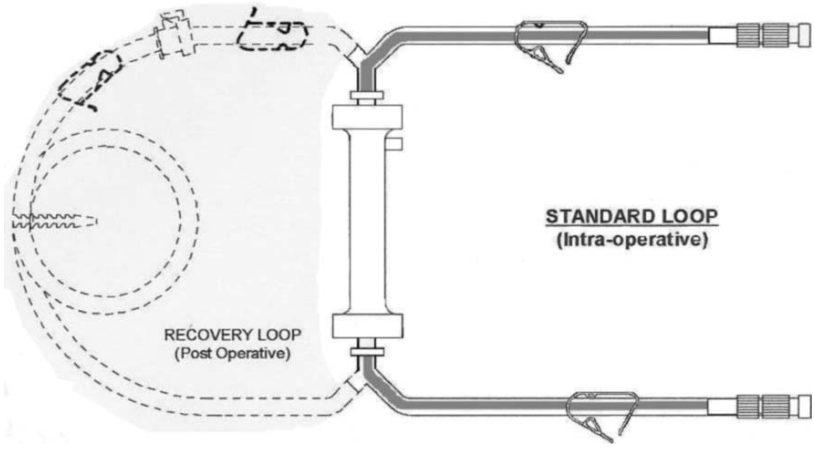

Figure 2 The prepackaged TS3 (standard and recovery loop) tubing set. The standard loop is used for conventional ultrafiltration during the ECC procedure. The recovery loop is used with the Hemobag® for multipass ultrafiltration post ECC use. ECC: extracorporeal circulation.

www.haemonetics.com) was employed in the perioperative period for both groups. The end-bypass residual pump volume was processed by the Cell Saver® 5 in the control group. In both groups, most pericardial suction blood was returned to the Cell Saver®. Hemoconcentrators (Fresenius Hemocare HF5000, Boston, MA, USA; 65 000 Dalton cutoff; prime volume 65 mL) were employed during CPB as indicated by fluid retention or overload, or renal insufficiency. The RBC transfusion trigger for patients <75 years old while on CPB was Hct $<21\%$. For patients >75 years old, the RBC transfusion trigger was Hct $<24\%$.

Methods

After institutional review board approval in a community hospital setting, between October 2003 and October 2004, 50 patients were arbitrarily selected by the surgical team from all presenting patients to receive the Hemobag® (HB) therapy. A retrospective control group (operated prior to October 2003) of 50 non-Hemobag® (NHB) patients were matched to the HB group patient-by-patient for comparison according to the four different surgeons, procedure, age, body surface area (BSA), body weight and CPB time. Many efforts to conserve blood, including the Cell Saver® 5 and pre-CPB whole blood sequestration (ANH), were employed in both groups. Post-CPB cell washing of residual circuit contents was additionally employed in the control group.

Outcome and intraoperative indicators were measured and compared between the study group and the control group. Descriptive statistics were employed to describe the demographics and morphology of the two groups. Data are presented as means and standard deviations. Nominal data are compared by Student's *t*-test and non-categorical data are compared by analysis of variance. All statistical operations were performed using Minitab™ (Minitab, Inc. Release 13, www.minitab.com). In all patients, hematocrit, total protein, and albumin, and in a subset of patients some clotting factor concentrations, were measured in the Hemobag® contents.

Results

Three patients from each group were removed after being identified as outliers (values greater than three standard deviations from the mean) in total donor exposures, intensive care unit (ICU) stay or length of stay (LOS) in the hospital. There were no significant differences between the HB and NHB groups with regard to patient morphology, pre-op cell concentrations, distribution of procedures; pump and ischemic times or Bayes National Risk scores (Table 1). As it turned out, HB patients were cooled to a significantly lower temperature during CPB.

The average volume returned to the patient from the HB was 817 mL (Table 2). Average processing time was 11 min. After processing, the Hemobag contained an average platelet count of 230 K/mm^3, fibrinogen concentration of 413 mg/dl, total protein of 8.0 gm/dl, albumin of 4.4 gm/dl and hematocrit (Hct) of 43%. Factor VII, IX and X levels in the HB contents for three patients averaged a 259% increase compared to patient levels.

Table 1 Group mean ± one standard deviation. Nominal data evaluated by χ^2 analysis; other data analysed by ANOVA. NS, not significant at $p < 0.05$.

Parameter	*Control group*	*Hemobag® group*	p *value*
Patient group size	47	47	
Male (%)	70	70	NS
Age (years)	65 ± 10	65 ± 14	NS
BSA (m^2)	1.99 ± 0.24	2.03 ± 0.24	NS
Pre-op weight (kg)	85 ± 19	90 ± 20	NS
CABG surgery patients (%)	64	62	NS
Valve surgery patients (%)	21	21	NS
Valve + CABG surgery patients (%)	13	15	NS
Redo surgical procedures (%)	2	4	NS
National Bayes risk score	2.5 ± 2.7	3.3 ± 3.9	NS
CPB time (min)	126 ± 43	126 ± 43	NS
Ischemic (min)	84 ± 35	91 ± 32	NS
Low CPB (°C)	33.0 ± 1.4	30.3 ± 7.7	0.020

BSA: body surface area; CABG: coronary artery bypass graft; CPB: cardiopulmonary bypass.

There were no significant differences in ICU stay, time on the ventilator, chest tube drainage and total hospital stay between the two patient groups (Table 3). However, the use and cost of blood products was substantially different (Tables 3 and 4).

There was no difference in postoperative hematocrit and chest tube drainage, but the percentage drop from baseline to the Hct nadir was significantly higher in the HB group. Although not statistically significant, the HB patients received less donor exposures and the cost of allogeneic blood was substantially lower in the HB group (Table 4). Figure 3 presents the frequency distribution for the number of donor exposures for patients in each group. The median number of donor exposures in the HB group was zero and the NHB group median was one exposure.

Table 5 lists the clotting factors measured in the contents of the Hemobag in a subset of patients.

Discussion

The Hemobag® method offers a new way safely and efficiently to salvage autologous CPB circuit whole blood for patients. Use of the Hemobag® offers advantages over other technologies of salvaging blood from ECCs, while increasing the potential to improve patient outcomes. Specifically, in this case series, the percentage reduction from baseline to the hematocrit nadir was more favorable for the HB group. In a large patient series, Defoe *et al*. found a relationship between low Hct and mortality.[18] Karkouti *et al*. discovered a relationship between low Hct and perioperative renal failure.[14] Toraman's group discovered that age >70 years and intraoperative volume overload increased blood transfusions and length of stay in a large series of CABG patient.[19] The results of this causal-comparative study suggest that the use of the Hemobag® helps to avoid a low Hct during CPB and is associated with a strong tendency to reduce allogeneic donor exposures.

Hemobag® patients received fewer donor exposures in this series, which resulted in a lower cost for blood products despite the fact that the HB patients were cooled to a lower CPB temperature. Although platelet function was not measured in this case series, the HB patient blood exposure to lower temperatures may have increased the chance of

Table 2 Group mean ± one standard deviation. Nominal data evaluated by χ^2 analysis; other data analysed by ANOVA. [ ] and NS are not significant at $p < 0.05$, NA is not applicable.

Parameter	*Control group*	*Hemobag® group*	p *value*
Patient group size	47	47	
Pre-op Hct (%)	40.3 ± 4.9	39.2 ± 4.4	NS
Pre-op platelet (K/mm^3)	221 ± 71	229 ± 93	NS
Hemobag® content platelet (K/mm^3)	NA	230 ± 80	NA
Post-CPB platelet (K/mm^3)	NM	133 ± 57	NM
Post-op platelet (K/mm^3)	104 ± 37	109 ± 47	NS
Baseline post-op platelet count (%)	−49 ± 26	−50 ± 18	NS
Hemobag® content volume (mL)	NA	817 ± 198	NA
Hemobag® content fibrinogen (mg/dl)	NA	413 ± 117	NA
Post-CPB fibrinogen (gm/dl)	NM	253 ± 82	NM
Pre-CPB autologous blood draw (cc/kg)	5.2 ± 3.2	5.5 ± 2.9	NS
Total heparin dose (K IU/kg)	846 ± 427	821 ± 240	NS
Hemobag® content Hct (%)	NA	42.9 ± 7.0	NA
Low operative Hct (%)	23.6 ± 3.3	24.3 ± 2.8	NS
Baseline drop to low Hct (%)	−41 ± 9	−38 ± 9	[0.052]

Hct: hematocrit; K: 10^3; IU: international units.

Table 3 Group mean ± one standard deviation. Nominal data evaluated by χ^2 analysis; other data analysed by ANOVA. NS, not significant at $p < 0.05$.

Parameter	*Control group*	*Hemobag® group*	p *value*
Patient group size	47	47	
Ventilator hours	18 ± 44	23 ± 52	NS
ICU hours	53 ± 77	61 ± 73	NS
Total hospital days	8.2 ± 7.1	8.1 ± 4.2	NS
Patients free from pulmonary complications (%)	76	67	NS
Patients free from neurologic complications (%)	80	77	NS
Patients free from renal complications (%)	79	79	NS
Patients free from coagulopathy (%)	98	95	NS

Table 4 Group mean ± one standard deviation. Nominal data evaluated by χ^2 analysis; other data analysed by ANOVA. [ ] and NS are not significant at $p < 0.05$.

Parameter	*Control group*	*Hemobag® group*	p *value*
Patient group size	47	47	
FFP units per patient	0.9 ± 3.0	0.8 ± 1.6	NS
Platelet pheresis packs per patient	0.6 ± 1.2	0.4 ± 0.7	NS
RBC transfusions per patient	1.6 ± 3.0	1.0 ± 1.6	NS
Post-op bleeding (cc/kg)	8.5 ± 6.6	8.1 ± 7.9	NS
Donor exposures per patient	3.2 ± 6.8	1.8 ± 2.8	NS
Median ± SEM donor exposures	1.0 ± 0.6	0.0 ± 0.4	NS*
Patients with no transfusions (%)	40	55	[0.148]
Cost blood products per patient ($US)	1104 ± 2049	734 ± 1047	NS
Cost of blood products for group ($US)	52 064	34 476	NA

*Kruskal–Wallis test for medians. NA, not applicable.

platelet dysfunction, and patients whose platelets are sensitive to hypothermia may have a greater chance of neuro-cognitive decline compared to the NHB group.[20,21] A clinical trial employing the Thrombelastograph® (Haemoscope Corporation, Niles, IL, USA) to measure the effect of the HB therapy on platelet function has begun.

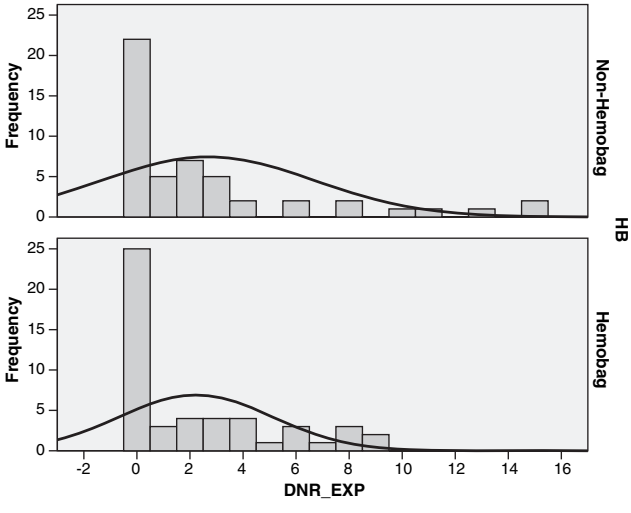

Figure 3 Frequency plot of total donor exposures per patient for 50 patients in each group. HB patients received fewer total donor exposures. HB: Hemobag; DNR_EXP: donor exposures.

The total cost of donor blood for the 47 patients in the HB group was $US17 588 (34%) less than the control group. The cost of blood products remained the same for the comparison and HB groups during the study. The 34% cost savings reflects direct savings from the avoidance of blood product usage only. These savings do not include the costs associated with the use and complications inherent with allogeneic blood usage. There are numerous reports of the 'off-license' use of recombinant FVIIA to treat uncontrolled bleeding.[22] The higher clotting factor

Table 5 Group mean ± one standard deviation. (*n*) = sample size. Data analysed by ANOVA. [ ] and NS are not significant at $p < 0.05$.

Parameter	*ECC blood* (n)	*Hemobag® contents* (n)	p *value*
Volume (mL)	NA	817 ± 198 (50)	NA
Hct (%)	24.3 ± 2.8 (47)	42.9 ± 7.0 (50)	< 0.001
Total protein (gm/dl)	3.1 ± 0.8 (27)	8.0 ± 2.5 (27)	< 0.001
Albumin (gm/dl)	1.7 ± 0.4 (27)	4.4 ± 1.0 (27)	< 0.001
Platelet count (K/mm^3)	132 ± 57 (50)	230 ± 78 (50)	< 0.001
Fibrinogen (mg/dl)	200 ± 80 (50)	413 ± 163 (50)	< 0.001
Factor VII (%)	66 ± 11 (2)	191 ± 46 (2)	[0.064]
Factor IX (%)	113 (1)	275 (1)	NA
Factor X (%)	53 (1)	130 (1)	NA
Plasma free Hb (mg/dl)	NM	17 ± 5 (3)	NA

NM, not measured and NA, not applicable. ECC: extracorporeal circulation; Hct: hematocrit; K: 10^3; Hb: hemoglobin.

concentrations in the HB contents (Table 5) suggest that CPB autologous clotting factors can be preserved and may reduce the need for expensive allogeneic factor transfusion.

There may be theoretical concern that activated cells and proteins infused to the patient with the HB technique may cause patient reactions.[8,11–13] In this study, the Hemobag® blood was filtered (SQ40, Pall Medical, East Hills, NY, USA) as it was transfused. Clinical signs of the inflammatory reaction to the infusion of HB contents deserve further study.[23] However, the absence of adverse reactions and no difference in morbidity (Table 3) in the HB group reinforces the safety of the HB technique.

Comparing HB patients to a well-matched retrospective control group is not as strong an experimental plan as a prospective design. Clinical studies are needed where patients are randomized to the HB treatment group to assess the patient outcomes and to measure reduction of allogeneic blood product use.

The Hemobag® technique quickly and safely recovers substantial proteins, clotting factors and cell concentrates for all types of cardiac procedures. Use of this new technique offers advantages over other technologies for salvaging blood components and factors from ECCs.

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