Neonates and infants undergoing cardiac surgery significantly reduce RBC and coagulant product transfusions and donor exposures: Results of a Prospective, Randomized, Clinical Trial

Jill M. Cholette, MD; Karen S. Powers, MD; George M. Alfieris, MD; Ronald Angona, CCP; Kelly F. Henrichs, MT(ASCP); Debra Masel, MT(ASCP)SBB; Michael F. Swartz, PhD; L. Eugene Daugherty, MD; Kevin Belmont, CCP; Neil Blumberg, MD

Objective: To evaluate whether transfusion of cell saver salvaged, stored at the bedside for up to 24 hrs, would decrease the number of postoperative allogeneic RBC transfusions and donor exposures, and possibly improve clinical outcomes.

Design: Prospective, randomized, controlled, clinical trial.

Setting: Pediatric intensive care unit.

Patients: Infants weighing less than 20 kg (n = 106) presenting for cardiac surgery with cardiopulmonary bypass.

Interventions: Subjects were randomized to a cell saver transfusion group where cell saver blood was available for transfusion up to 24 hrs after collection, or to a control group. Cell saver subjects received cell saver blood for volume replacement and/or RBC transfusions. Control subjects received crystalloid or albumin for volume replacement and RBCs for anemia. Blood product transfusions, donor exposures, and clinical outcomes were compared between groups.

Measurements and Main Results: Children randomized to the cell saver group had significantly fewer RBC transfusions (cell saver: 0.19±0.44 vs. control: 0.75±1.2; p = 0.003) and coagulant product transfusions in the first 48 hrs post-op (cell saver: 0.09±0.45 vs. control: 0.62±1.4; p = 0.013), and significantly fewer donor exposures (cell saver: 0.60±1.4 vs. control: 2.3±4.8; p = 0.019). This difference persisted over the first week post-op, but did not reach statistical significance (cell saver: 0.64±1.24 vs. control: 1.1±1.4; p = 0.07). There were no significant clinical outcome differences.

Conclusion: Cell saver blood can be safely stored at the bedside for immediate transfusion for 24 hrs after collection. Administration of cell saver blood significantly reduces the number of RBC and coagulant product transfusions and donor exposures in the immediate postoperative period. Reduction of blood product transfusions has the potential to reduce transfusion-associated complications and decrease postoperative morbidity. Larger studies are needed to determine whether this transfusion strategy will improve clinical outcomes. (Pediatr Crit Care Med 2013; 14:137–147)

Key Words: cardiopulmonary bypass; congenital heart disease; pediatric cardiac surgery; red blood cells; transfusion
savers feasible for the small volume requirements of neonates and infants (10).

Observational studies suggest that cell saver systems safely decrease the volume of RBC transfusions in children (11) and small infants (12) undergoing surgical procedures, and those undergoing cardiac surgery with CPB (13). Despite this, there is only a single prospective nonrandomized cohort study describing experience with postoperative transfusion of intraoperative cell salvage using a dedicated pediatric system (14), and that work was limited by availability of cell saver salvaged blood for only 6 hrs after its collection.

We hypothesized that transfusion of cell saver salvaged blood, for up to 24 hrs after collection, can be performed safely, and will reduce the number of postoperative allogeneic RBC transfusions and donor exposures. Reduction of the number of RBC transfusions will limit the known risks of RBC transfusions, will reduce transfusion-associated complications, and may improve clinical outcomes.

The objective of this study is to determine the impact of intraoperative cell saver blood collection, as a blood conservation technique, on postoperative allogeneic blood product administration. The primary aim of the study is to compare the number of allogeneic blood product transfusions in the first 48 hrs post-op between patients randomized to receive cell saver blood vs. current standard-of-care for RBC transfusions and volume replacement. Secondary aims are to compare donor exposures, clinical outcome measures and complication rates between patients randomized to receive cell saver blood vs. current standard-of-care.

**MATERIALS AND METHODS**

**Subjects**

Children weighing less than or equal to 20kg presenting to the University of Rochester Medical Center (URMC) for cardiac surgical repair/palliation with CPB were eligible. Exclusion criteria were weight more than 21kg, if their parent/guardian did not speak English, or if consent could not be obtained. The protocol was approved by the URMC Research Subjects Review Board and was registered with ClinicalTrials.gov (NCT01211366).

Subjects were enrolled at their preanesthesia visit, with properly witnessed and documented informed consent. Once enrolled, subjects were divided into groups according to their weight (≤10kg or ≥11kg) and risk-adjusted congenital heart surgery (RACHS-1) score (1–3 “less severe” or 4–6 “more severe”) (15). Block randomization was used to randomize subjects to the cell saver or control transfusion strategy.

**Transfusion and Volume Replacement Strategy**

The transfusion and volume replacement strategy was initiated after completion of CPB in the operating room (OR) and maintained for 24 hrs after either collection of cell saver salvaged blood or discontinuation of CPB.

**Cell Saver Group**

**Volume Replacement.** Subjects received crystalloid, colloid, or allogeneic RBC transfusions for hemodynamic compromise (tachycardia, hypotension, poor pulses/perfusion, rising lactate, low central venous pressure (CVP), and poor urine output) with/without anemia as per our current standard-of-care.

**Blood Component Transfusions.** Subjects received cell saver blood for volume replacement if there was evidence of hemodynamic compromise (as described above) without anemia and their hemoglobin level was less than or equal to 13g/dL (to avoid causing polycythemia). If they had evidence of hemodynamic compromise and their hemoglobin level was > 13g/dL they were given crystalloid or albumin instead of cell saver blood.

**Control Group**

**Volume Replacement.** Subjects received crystalloid, colloid, or allogeneic RBC transfusions for hemodynamic compromise (tachycardia, hypotension, poor pulses/perfusion, rising lactate, low central venous pressure (CVP), and poor urine output) with/without anemia as per our current standard-of-care.

**Blood Component Transfusions.** For patients with evidence of hemodynamic instability and/or poor oxygenation and anemia, allogeneic RBCs (10–15 cc/kg) are transfused. Our pediatric cardiac ICU (PICICU) standard-of-care is to carefully consider each individual patient’s clinical condition in the decision to transfuse RBCs. We do not have a specific transfusion protocol, but take into account the presence or absence of cyanosis, cardiac function, single or biventricular physiology, and the particular cardiac procedure, to ensure that all transfusions are clinically based. Generally, our cyanotic children with single ventricle physiology are transfused for hemoglobin levels less than 9.0–10 g/dL and children after biventricular repairs for hemoglobin levels less than 7.0–8 g/dL, unless there are signs of clinical compromise (poor hemodynamics or significant oxygen requirement) or ongoing bleeding. This allows the PICICU attending to use their best clinical judgment, based on each subjects’ condition, as to type of volume replacement—saline, albumin, or RBCs. Coagulant products are transfused according to factor or platelet deficiency with ongoing bleeding.
With the exception of the initial volume/hemoglobin replacement strategy, all participating subjects received the current standard-of-care for their medical and surgical management.

**Surgical Management**
Operative and perioperative management including the initiation of anesthesia, CPB technique, and surgical repair/palliation procedures were performed per current standard-of-care at URMC with the sole exception being the collection of cell saver blood at the end of CPB for subjects assigned to that group. The cardiac surgeon was blinded to study assignment to prevent any potential bias of the surgical and/or CPB management. Obvious differences in packaging and labeling of blood products prevented blinding of the perfusionists, anesthesiologists, and PCICU personnel.

Vasoactive medications (epinephrine, dopamine, or milrinone drips) were used to maintain hemodynamics during transition after CPB at the discretion of the cardiac surgical team. All patients remained intubated and sedated for transfer to the PCICU. Surgical, CPB and transfusion details were collected, as well as any intraoperative complications (i.e., arrhythmias, acidosis, bleeding, or poor ventricular function).

**CPB Procedures for All Subjects**
Two bypass circuits were used in this study. All cases used the Terumo System 1 Heart Lung Machine (Terumo, Tokyo, Japan).

1) For subjects weighing less than 11 kg: an Fx05 oxygenator with hardshell reservoir and integrated arterial line filter (Terumo) was used. The circuit A/V loop consisted of 3/16” × 1/4” tubing (Medtronic, Minneapolis, MN), and a roller pump with 1/4” raceway used in the arterial position. Only the oxygenator is coated with Terumo’s X-coating. Conventional ultrafiltration was used on all cases and modified ultrafiltration on none.

The bypass prime consisted of 200 mg/kg mannitol, 1000 units heparin, 25 mg/kg cephazolin (up to 1 g), methylprednisolone 30 mg/kg (only in subjects <6 months of age or in cases requiring deep hypothermic circulatory arrest), aminocaproic acid 250 mg, 10–15 mEq 8.4% sodium bicarbonate, 25% albumin, and RBCs as needed to achieve an “acceptable” hematocrit on CPB (as determined by cardiocoracic surgeon and perfusionists per current standard-of-care). Circuits primed with RBCs used 25 mL of 25% Albumin, and asanguinous primed used 50 mL of 25% albumin.

2) For subjects weighing from 11 to 20 kg: the Terumo RX-15 oxygenator (Terumo) with hard-shell reservoir was utilized with a stand-alone arterial line filter, the Pediatric Affinity (Medtronic). The circuit A–V loop consisted of 1/4” × 3/8” tubing, and a roller pump with 3/8” raceway in the arterial position. Only the oxygenator is coated with Terumo’s X-coating. Again, conventional ultrafiltration was used on all subjects, and modified ultrafiltration on none. The bypass circuit for these subjects contained the same kilogram dosages of mannitol, cephazolin, methylprednisolone, aminocaproic acid, and sodium bicarbonate as described above including 2000 units of heparin, 50 mL 25% albumin, and RBCs. Again, RBCs were added if needed to obtain an “acceptable” on-CPB hematocrit.

After the termination of CPB and sequestration of the volume in the venous line, the residual pump volume was hemo-concentrated to the lowest possible level. For infants, some of this remaining pump volume was transferred into syringes for re-infusion by the Anesthesia team during the remainder of the intraoperative period. For older subjects, some of this volume was transferred into a 600-mL collection bag for re-infusion by the Anesthesia team as needed.

**Cell Saver Blood Collection**
Any blood not re-infused by the anesthesiologist was returned to the perfusionist at the end of the case. This “pump salvage” was then infused into the Fresnius Continuous AutoTransfusion System (CATS; Terumo). The residual volume in the bypass circuit was also chased into the CATS, and the total volume processed, washed, and transferred into a collection bag labeled with a unique label for patient identification stating “autologous use only”. The cell saver salvaged red cells were transported to the PCICU in a designated “cell saver” blood temperature-controlled and monitored cooler. Aliquots for transfusion were drawn off this bag aseptically using a needleless adapter by PCICU nursing staff.

Cell saver coolers were managed at the subject’s bedside maintained between 1 and 6°C, in keeping with New York State blood bank regulation 58-2.25, allowing blood to be stored up to 24 hrs from collection (16). Blood bank staff performed quality assurance checks every 4 hrs to ensure proper temperature regulation. Cell saver blood not utilized during the intervention period was discarded (after 24 hrs from collection).

**Postoperative Management**
Subjects were managed postoperatively per the current standard-of-care aside from their transfusion strategy. At the URMC, a PCICU attending is “in house” 24 hr/day and therefore weaning from mechanical ventilation and/or inotropes occurs around the clock. Subjects were weaned from mechanical ventilation and extubated as their cardiopulmonary status allowed. Crystalloid or 5% albumin were infused in 5–20 cc/kg boluses for clinical findings of hypovolemia and poor cardiac output (i.e., tachycardia, poor pulses and perfusion, low urine output, or hypotension) as needed to maintain hemodynamic stability. Vasoactive medications were adjusted to maintain hemodynamics and end-organ perfusion. Subjects received anticoagulation (i.e., aspirin, enoxaparin, warfarin) per the current PCICU Anticoagulant strategy as appropriate for their type of cardiac defect, surgical palliation/repair, and postoperative medical management.

**URMC Blood Bank Procedures**
Transfusion of RBC, platelet, thawed whole-plasma, and cryoprecipitate products were based on a standard PCICU protocol, which was adhered to throughout the trial. The RBC transfusion protocol takes into account the cardiac defect and
RESULTS
From November 2010 to December 2011, 119 children were eligible for study participation, see CONSORT diagram (Fig. 1). Families of two subjects refused participation, in four cases families were unavailable before consent could be obtained, and a significant language barrier existed in three cases preventing acquisition of informed consent. In total, 110 children were randomized but in three cases surgery was able to be performed without CPB and in one case surgery was postponed. Of the total, 106 (89% of original eligibility; 95% of eligible subjects undergoing CPB) subjects underwent study procedures; 53 per group. No subjects were lost to follow-up. No protocol violations occurred. All subjects were analyzed according to intent-to-treat.

Subject Characteristics
There were no statistically significant differences in baseline characteristics between each treatment group. There were trends toward smaller, younger, and more surgically complex subjects (higher RACHS score and single ventricle physiology) in the cell saver group. A larger number of subjects in the control group received coagulant products in the OR and had delayed sternal closure than subjects in the cell saver group. The CPB duration and surgical management were similar. The hemoglobin and arterial lactate levels were similar at PCICU admission (Table 1). The cardiac morphology and surgical procedures of subjects in each group is presented in Table 2.

Number of RBC Transfusions
The mean number of RBC transfusions in the first 24 hrs after discontinuation of CPB was significantly less in subjects randomized to the cell saver group than the control group (cell saver: 0.04 ± 0.19 vs. control: 0.51 ± 0.91; \( p = 0.001 \); Fig. 2). This reduction in RBC transfusions was maintained for the first 48 hrs post-op (cell saver: 0.19 ± 0.44 vs. control: 0.75 ± 1.2; \( p = 0.003 \)).

When the first 7 days post-op were examined to see whether the study intervention transfusion strategy had a longer-term impact, the total number of RBC transfusions remained numerically less in the cell saver group, but did not reach statistical significance (cell saver: 0.64 ± 1.24 vs. control: 1.1 ± 1.4; \( p = 0.07 \); Fig. 3).

Number of Coagulant Product Transfusions
The mean number of component transfusions (platelets, FFP, and cryoprecipitate) administered in the first 2 PODs was significantly less in subjects randomized to the cell saver group as compared with controls (platelets: cell saver: 0 ± 0 vs. control: 0.11 ± 0.38; \( p = 0.03 \); FFP: cell saver: 0 ± 0 vs. control: 0.15 ± 0.46; \( p = 0.02 \); cryoprecipitate: cell saver: 0 ± 0 vs. control: 0.08 ± 0.27; \( p = 0.04 \); Fig. 2). This effect persisted over the POD 0–7 (cell saver: 0.09 ± 0.45 vs. control: 0.62 ± 1.43; \( p = 0.012 \); Fig. 3). Only two subjects, both in the control group received any coagulant products after the first 48 hrs post-op. One of these subjects received one platelet and one FFP transfusion on POD#3, and the other received one cryoprecipitate transfusion on POD #3.
Donor Exposures
The mean number of RBC donor exposures during the first seven post-op days was numerically but not statistically less in the cell saver group when compared with controls (cell saver: 0.43 ± 0.8 vs. control: 0.75 ± 1.0; \( p = 0.07 \)). However, the mean number of total donor exposures (RBC and coagulant products) during this period was significantly less in the cell saver group when compared with controls (cell saver: 0.60 ± 1.35 vs. control: 2.3 ± 4.8; \( p = 0.019 \); Fig. 2).

When subgroup analysis was performed with subjects divided according to low or high RACHS scores, and blood transfusions and donor exposures were compared between study intervention groups, the results remained consistent with those for the entire subject population for both time periods. Therefore, even the lower risk subjects randomized to the cell saver group received significantly fewer autologous RBC transfusions in the first 48 hrs post-op and had significantly fewer donor exposures.

Cell Saver Utilization
Cell saver blood salvage was collected in 50 of 53 (94%) subjects assigned to that group. In three cell saver subjects, there...
was insufficient volume at the end of the case for collection. The mean volume of cell saver collected in those 50 subjects was 38.6 ± 20.5 mL/kg (range: 4–107 mL/kg). Cell saver was transfused in the OR in 45 of 50 (90%) of subjects where it was available. In the five cases where it was not given in the OR, four subjects received cell saver salvaged RBCs postoperatively in the PCICU. Therefore, cell saver blood was utilized in 49 of 50 (98%) subjects in which it was collected, or 49 of 53 (92.4%) of subjects randomized to the cell saver group.

**Clinical Outcomes**

Overall survival was 102 subjects (96%); the four children who died had single ventricle physiology. Of the three deaths in the cell saver group, the first occurred in a neonate with renal, hepatic, and severe right ventricular dysfunction before Norwood with Sano modification. She died several hours after surgery before any cell saver blood was transfused. The second death was a neonate with hypoplastic left heart syndrome who was 16 days s/p Norwood with Sano modification after multiple cardiac arrests. The third death was a 6 yr old with hypoplastic left heart syndrome s/p BGD with diminished RV function and severe tricuspid valve regurgitation, who underwent a fenestrated Fontan and tricuspid valve repair. He died POD 22 from *Klebsiella pneumoniae* with pulmonary hypertension. The control group fatality was a neonate with critical aortic stenosis and mitral valve stenosis who died POD 112 from respiratory failure secondary to pulmonary hypertension and bacterial and viral pneumonia.

No subjects required extracorporeal membrane oxygenation either pre- or postoperatively. Only one subject (<1%) in the control group required surgical re-exploration for bleeding post-op. There were no significant differences in postoperative clinical outcome variables between subjects in each treatment group (Table 3). Seventeen (16%) of all subjects were diagnosed with a nosocomial infection confirmed with microbiology culture during hospital admission (bacteremia in nine cases, pneumonia in seven, necrotizing enterocolitis in one, and pneumonia and bacteremia in two cases). No infections occurred before POD 4. There was no difference in the number of infections between treatment groups (cell saver: 9 vs. control group: 8; $z = -0.263; p = 0.792$). There was no significant difference in POD 1 and 2 wrCRP between treatment groups.

### TABLE 1. Subject Characteristics and Surgical Details

<table>
<thead>
<tr>
<th></th>
<th>Control Group ($n = 53$)</th>
<th>Cell Saver Group ($n = 53$)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>5 (0.3–72)</td>
<td>3 (0.1–84)</td>
<td>$z = -0.983; p = 0.326$</td>
</tr>
<tr>
<td>Neonate (≤30 days)</td>
<td>16 (30.2%)</td>
<td>44 (83%)</td>
<td>$z = -0.816; p = 0.414$</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>5.3 (1.8–18)</td>
<td>4.5 (2.3–17.2)</td>
<td>$z = -1.087; p = 0.277$</td>
</tr>
<tr>
<td>Male sex</td>
<td>23 (43.4%)</td>
<td>25 (35.7%)</td>
<td>$z = -0.388; p = 0.698$</td>
</tr>
<tr>
<td>RACHS score 4–6</td>
<td>14 (26.4%)</td>
<td>22 (31.4%)</td>
<td>$z = -1.633; p = 0.102$</td>
</tr>
<tr>
<td>Cyanotic</td>
<td>27 (50.9%)</td>
<td>30 (42.9%)</td>
<td>$z = -0.582; p = 0.561$</td>
</tr>
<tr>
<td>Single ventricle</td>
<td>10 (18.9%)</td>
<td>16 (22.9%)</td>
<td>$z = -1.348; p = 0.178$</td>
</tr>
<tr>
<td>Admission Hb (g/dL)</td>
<td>12.7 ± 1.8</td>
<td>12.8 ± 1.65</td>
<td>$p = 0.764$</td>
</tr>
<tr>
<td>Admit lactate (mmol/L)</td>
<td>3.55 ± 2.52</td>
<td>3.13 ± 1.51</td>
<td>$p = 0.295$</td>
</tr>
<tr>
<td>CPB time (mins)</td>
<td>125 ± 59</td>
<td>130 ± 60</td>
<td>$p = 0.676$</td>
</tr>
<tr>
<td>Aortic cross clamp</td>
<td>46 (87%)</td>
<td>46 (87%)</td>
<td>$p = 1.0$</td>
</tr>
<tr>
<td>Time (mins)</td>
<td>79 ± 54</td>
<td>77 ± 50</td>
<td>$p = 0.861$</td>
</tr>
<tr>
<td>DHCA</td>
<td>5 (9%)</td>
<td>12 (23%)</td>
<td>$z = -1.43; p = 0.153$</td>
</tr>
<tr>
<td>Time (mins)</td>
<td>27 ± 10</td>
<td>33 ± 14</td>
<td>$p = 0.449$</td>
</tr>
<tr>
<td>Dressing time (mins)</td>
<td>69 ± 39</td>
<td>61 ± 21</td>
<td>$p = 0.147$</td>
</tr>
<tr>
<td>RBC in prime</td>
<td>35 (66%)</td>
<td>39 (74%)</td>
<td>$z = -0.842; p = 0.400$</td>
</tr>
<tr>
<td>Coagulant products</td>
<td>6 (11.3%)</td>
<td>2 (3.7%)</td>
<td>$z = -1.464; p = 0.143$</td>
</tr>
<tr>
<td>OR duration (mins)</td>
<td>267 ± 98</td>
<td>270 ± 82</td>
<td>$p = 0.860$</td>
</tr>
<tr>
<td>Delayed sternal closure</td>
<td>8 (15%)</td>
<td>4 (8%)</td>
<td>$z = -1.585; p = 0.113$</td>
</tr>
</tbody>
</table>

RACHS = risk adjusted congenital heart surgery score; Hb = hemoglobin; CPB = cardiopulmonary bypass; DHCA = deep hypothermic cardiac arrest; OR = operating room.

Data is presented as median (range); mean ± SD or number (%). Student t tests were used for normally distributed data and Wilcoxon Signed Ranks test for data that was not normally distributed. Z test for two proportions was utilized to compare number (%).
TABLE 2. Surgical Palliations and Procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Control Group (n = 53)</th>
<th>Cell Saver Group (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norwood (Sano) or Damus-Kaye-Stanse</td>
<td>1 (1.9%)</td>
<td>7 (13.2%)</td>
</tr>
<tr>
<td>Blalock-Taussig or central shunt</td>
<td>3 (5.7%)</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>Arterial switch</td>
<td>5 (9.4%)</td>
<td>5 (9.4%)</td>
</tr>
<tr>
<td>Systemic to pulmonary shunt + PA unfocalization</td>
<td>1 (1.9%)</td>
<td>3 (5.7%)</td>
</tr>
<tr>
<td>Interrupted aortic arch or hypoplastic aortic arch ± coarct repair</td>
<td>4 (7.5%)</td>
<td>3 (5.7%)</td>
</tr>
<tr>
<td>PA band and aortic arch repair</td>
<td>0</td>
<td>2 (3.8%)</td>
</tr>
<tr>
<td>Truncus arteriosus repair</td>
<td>2 (3.8%)</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>Atroventricular septal defect repair</td>
<td>4 (7.5%)</td>
<td>7 (13.2%)</td>
</tr>
<tr>
<td>Bidirectional glenn</td>
<td>3 (5.7%)</td>
<td>6 (11.3%)</td>
</tr>
<tr>
<td>Fontan (extra-cardiac conduit)</td>
<td>5 (9.4%)</td>
<td>3 (5.7%)</td>
</tr>
<tr>
<td>Tetralogy of fallot ± coarct repair</td>
<td>5 (9.4%)</td>
<td>5 (9.4%)</td>
</tr>
<tr>
<td>Rastelli</td>
<td>1 (1.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Ross</td>
<td>2 (3.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Aortic root reconstruction</td>
<td>1 (1.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary valve repair</td>
<td>2 (3.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Anomalous coronary artery repair</td>
<td>0</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>Total anomalous pulmonary venous return repair</td>
<td>4 (7.5%)</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>Right ventricle o pulmonary artery conduit</td>
<td>1 (1.9%)</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>ASD ± ventricular septal defect repair or AP window</td>
<td>7 (13.2%)</td>
<td>5 (9.4%)</td>
</tr>
<tr>
<td>Aortic membrane resection</td>
<td>0</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>Partial anomalous pulmonary venous return and ASD repair</td>
<td>2 (3.8%)</td>
<td>1 (1.9%)</td>
</tr>
</tbody>
</table>

PA = pulmonary artery; coarct = aortic coarctation; IAA = interrupted aortic arch; ASD = atrial septal defect; VSD = ventricular septal defect; AP = aortopulmonary.

Figure 2. Number of red blood cell and component transfusions in the first 48 hrs postoperatively between each group.

Figure 3. Number of transfusions and donor exposures postoperative days 0–7 between each group.
DISCUSSION

Adults undergoing cardiac surgical procedures who receive large numbers of blood product transfusions have worse clinical outcomes (3–5,18). Transfusion of salvaged cell saver blood during adult cardiac surgery is commonly performed to limit the number of allogeneic blood products administered (19-22). A 2009 meta-analysis examined 31 randomized trials of 2,282 patients and found that use of intraoperative cell saver blood reduced the rate of exposure to RBCs and/or coagulant blood products, and decreased the mean volume of blood products transfused per patient (23). Children having cardiac surgical procedures also receive large numbers of blood product transfusions with the associated risks of those transfusions (6–8), but processing systems of salvaged blood for autotransfusion have been unavailable until recently. Technical advancements now allow for volume-independent collection of salvaged blood (24) that can be utilized for even the smallest infants, but prospective clinical studies exploring the effect of cell saver salvaged blood in pediatric cardiac surgery are lacking.

We present the first prospective randomized clinical trial examining the impact of transfusion of cell saver salvaged blood in pediatric cardiac surgery on clinical outcomes. We found that transfusion of washed intraoperative cell saver blood salvage significantly decreased the need for allogeneic RBCs in the first 48 hrs post-op. A numeric but not quite statistically significant decrease in RBC transfusions throughout POD 0–7 was also seen. These results would indicate that transfusion of cell saver blood salvage is a useful blood conservation strategy in this heavily transfused population. Certainly as the number of ICU days increases, the immediate reduction in allogeneic transfusions will have less of an impact on the overall number of transfusions that follow. However, transfusion of autologous cell saver salvage blood instead of additional allogeneic RBCs may reduce the immunogenic, inflammatory, and infectious impact on the recipient, and may reduce ensuing postoperative complications.

The reduced number of platelet, FFP, and cryoprecipitate transfusions required for patients in the cell saver treatment arm was unexpected but significant. There were a greater number of delayed chest closures in control group subjects, which raises the question whether this group had more postoperative bleeding that required coagulant product transfusions. The reason for delayed chest closure was not included in our data collection. At our institution, delayed chest closure is routinely performed for hemodynamic instability, inadequate oxygenation or ventilation, and/or pulmonary hypertension, in addition to concern for inadequate hemostasis. We did not include the volume of MT drainage in our data collection, which is a limitation of this study. Data regarding MT volume and thickness would have provided more information regarding the indication for coagulant and RBC product transfusions in respect to bleeding. Future studies with more attention to postoperative bleeding are needed to confirm these results. It is possible that the use of autologous RBC transfusion in the form of cell saver may have improved hemostatic function than stored allogeneic RBCs. Conversely, because the study is not blinded, the availability of cell saver red cells may have caused attending staff to be less aggressive in their use of procoagulant products. In general, our patients rarely receive platelets, FFP, or cryoprecipitate, so the differences seen may not be generalizable to environments where these products are more freely administered.

The only prospective study describing use of cell savers in pediatric open heart surgery was performed by Hanna Golab

<table>
<thead>
<tr>
<th>TABLE 3. Secondary Outcome Variables Between Treatment Groups.</th>
<th>Control Group (n = 53)</th>
<th>Cell Saver Group (n = 53)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical vent (days)</td>
<td>3 (0.04–112)</td>
<td>2 (0.13–37)</td>
<td>z = –1.377; p = 0.168</td>
</tr>
<tr>
<td>Inotropic/pressor (days)</td>
<td>4 (0–30)</td>
<td>3 (0.08–38)</td>
<td>z = –0.917; p = 0.359</td>
</tr>
<tr>
<td>Crystallloid post-op (cc/kg)</td>
<td>3.57 (0–100)</td>
<td>0 (0–111.5)</td>
<td>z = –1.157; p = 0.247</td>
</tr>
<tr>
<td>Albumin post-op (cc/kg)</td>
<td>0 (0–178)</td>
<td>0 (0–195)</td>
<td>z = –1.220; p = 0.222</td>
</tr>
<tr>
<td>Infection (culture proven)</td>
<td>8 (15%)</td>
<td>9 (18.8)</td>
<td>z = –0.263; p = 0.792</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>5 (9.4%)</td>
<td>2 (2.9%)</td>
<td>z = –1.142; p = 0.253</td>
</tr>
<tr>
<td>Cerebral vascular accident</td>
<td>1 (1.9%)</td>
<td>0</td>
<td>z = –0.917; p = 0.322</td>
</tr>
<tr>
<td>Mediastinal tube drainage (days)</td>
<td>10 (5–34)</td>
<td>8 (4–27)</td>
<td>z = –1.276; p = 0.202</td>
</tr>
<tr>
<td>PCICU LOS (days)</td>
<td>5 (2–112)</td>
<td>5 (2–45)</td>
<td>z = –0.780; p = 0.435</td>
</tr>
<tr>
<td>Hospital LOS (days)</td>
<td>12 (5–112)</td>
<td>10 (5–67)</td>
<td>z = –1.357; p = 0.175</td>
</tr>
<tr>
<td>Survival</td>
<td>52 (98.1%)</td>
<td>50 (94%)</td>
<td>z = –1.015; p = 0.310</td>
</tr>
<tr>
<td>wrCRP POD 1 (mg/L)</td>
<td>29.4 (0.6–114)</td>
<td>53 (4.5–116)</td>
<td>z = –1.731; p = 0.083</td>
</tr>
<tr>
<td>wrCRP POD 2 (mg/L)</td>
<td>44.9 (0.2–203)</td>
<td>573 (5.9–220)</td>
<td>z = –1.202; p = 0.229</td>
</tr>
</tbody>
</table>

PCICU = pediatric cardiac ICU; LOS = length of stay; wrCRP = wide range C-reactive protein; POD = postoperative day.
et al (14). Despite protocol violations, they found a reduction in allogeneic blood transfusions and no adverse effects in infants who received intraoperative collected cell salvage. The Golab study is important as it provides evidence for the safety of intraoperative cell salvage in pediatric patients. However, the study is limited as it used cell salvage only for up to 6 hrs postoperatively. It is well recognized that a predictable and significant decrease in cardiac output occurs 7–10 hrs post-CPB, which is the time during which volume and RBC resuscitation is most likely to be required (17). Therefore, the Golab study did not encompass the most critical period during which cell salvage would be of greatest benefit. Furthermore, the Golab study focused on 6-hr and 24-hr blood transfusions as their outcome. However, Golab cites that in many cases allogeneic blood was transfused in the ICU even though there was sufficient amount of cell saver product available. They state this as a major study limitation, and indeed lack of compliance with their study protocol hampers confidence in their results. Additionally, they did not follow subjects for other clinical outcome measures such as duration of mechanical ventilation or ICU length of stay.

This study was designed to examine the impact of transfusion strategy on RBC transfusions in the immediate postoperative period (first 48 hrs), but also explored its impact on the first 7 days post-op. In this, study cell saver blood was transfused not only for clinically significant anemia, but also for volume expansion. Transfusion of cell saver blood (in the place of albumin or crystalloid) likely also contributed to our findings, maintaining intravascular volume and optimizing hemodynamics in lieu of additional RBC transfusions.

Although not powered to assess differences in clinical outcomes, data regarding the known complications of transfusions were examined for the entire hospitalization. There was a trend toward fewer thrombotic events, fewer inotropic, ventilator, and MT days, and hospital length of stay. The heterogeneous nature of the study subjects resulted in large ranges of our clinical outcome variables and may have prevented finding a greater between-group difference. It is possible that a more homogenous population would demonstrate a greater effect of the cell saver on administration of crystalloid/colloid in the first 48 hrs, which possibly would lead to less peripheral and pulmonary edema and shorter duration of mechanical ventilation and MT drainage. It is also possible that this study is underpowered to demonstrate an effect on late complications and larger studies powered for clinical outcomes and focused on both short- and long-term complications are warranted.

Last, the Golab study included FFP in their pump prime and a postoperative transfusion trigger of a hematocrit of 30%. At the URMC, we neither use FFP in our prime, nor use a transfusion trigger and allow the hematocrit to fall lower than 30% in stable patients before transfusing pRBCs. This difference in transfusion practices likely influenced their results and may have exaggerated the benefit of use of cell salvage in their study. Indeed, at URMC hemoglobin levels are commonly accepted as low as 7.0 g/dL even in these children status after cardiac surgical repairs or palliations. If our transfusion protocol goals involved a higher threshold hemoglobin level, a greater between-group difference likely would have been found.

Whether future advances in blood banking will allow for cell saver blood to be maintained for more than 24 hrs after collection remains unknown. Certainly, if cell saver blood could be transfused over a longer time period after its collection, the number of allogeneic RBC transfusions would only decrease further.

This was a pilot study to assess feasibility of this blood conservation strategy. Therefore, it was not powered to assess for clinical outcomes. A larger study with a more homogenous population focusing on clinical outcomes would be of great interest. Certainly, the clinical indication for blood cell transfusion (i.e., hemodynamic instability, poor cardiac function, postoperative bleeding), in addition to the transfusion itself, directly impacts clinical outcomes. Future trials designed to independently examine the effect of blood cell transfusions, controlling for severity of illness are needed.

Although not powered to assess clinical outcome variables, the association between greater number of RBC transfusions and worse clinical outcomes is well established. Any transfusion strategy that decreases the number of allogeneic RBC transfusions will decrease transfusion-associated infectious risks, thrombotic complications, transfusion-related immunomodulation, and potentially overall mortality.

In this specific patient population that commonly requires multiple cardiac surgeries and RBC transfusions and/or cardiac transplantation, increased donor exposures makes future transfusions and matching for transplant more difficult. Any strategy that limits donor exposure in this patient population is highly desirable.

A single RBC unit costs the URMC $205 to obtain from a regional blood center. That price is increased with required testing, reagents, and processing, raising the price to $220.00 in variable costs. Consumables for the cell saver system cost $203.00/subject. Reduction of transfusion-related complications and/or decreased duration of mechanical ventilation and PCICU length of stay would make cell saver systems extremely cost-effective. As blood is a limited resource, continued blood conservation efforts are highly desirable.

This is a small, single institution study that was not powered to assess for clinical outcome differences. Increased subject numbers would allow for comparison of postoperative complications between the two groups (i.e., thrombosis, infection, duration of mechanical ventilation, vasoactive agents, and length of stay) which would be of great interest. Restriction of eligible patients to those weighing less than or equal to 10 kg, and/or those with the highest RACHS scores, which are our most heavily transfused subjects, would potentially illustrate a greater impact of the study intervention as well and be most cost-effective.

A limitation of this study is the variability of the subject population. Larger studies with a more homogeneous population focusing on neonates and smaller infants powered to test for clinical outcomes would be of great interest. Another limi-
tation is the potential bias inherent to nonblinded studies. Ob-
vIOUS differences in packaging and labeling of blood products
prevented blinding of the attending physician. The decision
to transfuse RBCs (in the form of salvaged cell saver blood or
allogeneic RBCs) or crystalloid/albumin for volume replace-
ment relied upon the judgment of the attending physician.
Because the attending physician was not blinded to the subjects’
treatment group assignment, he/she was likely influenced by
having, or not having, salvaged cell saver blood immediately
available at the bedside.

The attending physician may have been more judicious in
their volume replacement or more tolerant of a lower hemoglo-
in level, knowing that a RBC product was immediately
available for transfusion if the subject’s clinical condition were
to change rapidly. In such a setting, the attending physician
may have been more restrictive in their transfusion and/or volume
replacement with the security of having the salvaged blood im-
mediately available. Alternatively, the attending physician may
have been more liberal with their transfusion and/or volume
replacement in subjects in the cell saver group simply owing to
the fact that salvaged cell saver blood was immediately avail-
able, did not require the typical steps to prepare and obtain
allogeneic RBCs from the blood bank, and because it did not
constitute an additional donor exposure. Strict targeting of ho-
moglobin levels might have made transfusion management of
our intervention groups more uniform, but does not allow for
clinical judgment of the physician, which by definition is not in
the best interest of the study subjects.

To our knowledge, this is the only prospective random-
ized trial of clinical outcomes after readministration of cell
saver blood stored for up to 24 hrs at the bedside. This study is
strengthened by its high enrollment, with excellent capture of
eligible subjects. There was an extremely high rate of collection
of subjects randomized to the cell saver group, and subject data
were analyzed according to intent-to-treat. Also, as there were
no protocol violations and no subjects were lost to follow-up,
we believe our results are a true reflection of the impact of the
study intervention.

CONCLUSIONS
Cell saver blood can be safely stored at the bedside, with multiple
aliquots drawn off for transfusion up to 24 hrs after col-
lection. This strategy is highly desirable as it allows RBCs to be
immediately available, without increased donor exposure, to
correct for anemia and for volume replacement in a critically
ill population. Rate of infections and inflammation were not
increased in subjects receiving cell saver blood.

Cell saver use significantly reduced the number of RBC
transfusions in the immediate postoperative period. Further-
more, subjects receiving cell saver blood required significantly
fewer coagulant product transfusions and donor exposures.
There was a trend toward decreased volume of crystalloid
infused post-op, decreased thrombosis, and shorter duration of
mechanical ventilation and inotropes. Larger studies are
needed to confirm these results and to determine whether

the decreased number of blood product transfusions and ex-
posures are associated with improved clinical outcomes. Cell
savers are cost-effective. Use of cell savers to limit RBC transfu-
sions and donor exposures should be considered in pediatric
cardiac surgery with CPB.

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REFERENCES
1. Willems A, Harrington K, Lacroix J, et al; TRIPICU investigators; Ca-
nadian Critical Care Trials Group; Pediatric Acute Lung Injury and
Sepsis Investigators (PALISI) Network: Comparison of two red-cell
transfusion strategies after pediatric cardiac surgery: a subgroup
transfusion in pediatric patients undergoing open heart operations.
3. Murphy GJ, Reeves BC, Rogers CA, et al: Increased mortality, post-
operative morbidity, and cost after red blood cell transfusion in pa-
4. Koch CG, Li L, Duncan AI, et al: Morbidity and mortality risk associ-
ated with red blood cell and blood-component transfusion in isolated
1616
sion on long-term survival after cardiac operation. Ann Thorac Surg
2002; 74:1180–1186
critically ill children is independently associated with increased mor-
7. Kipps AK, Wypij D, Thigaarajan RR, et al: Blood transfusion is as-
associated with prolonged duration of mechanical ventilation in infants
undergoing reparative cardiac surgery. Pediatr Crit Care Med 2011;
12:52–56
pediatric cardiac surgery is associated with prolonged hospital stay.
Ann Thorac Surg 2011; 91:204–210
tive cell saver during cardiac surgery: a meta-analysis of randomized
sion in small children: an in vitro investigation to study its feasibility.
Anesth Analg 1999; 88:763–765
vage during surgical correction of craniosynostosis in infants. Br J
Anesth 2000; 85:550–555
erative blood salvage and postoperative reinfusion of drained blood
during surgical correction of craniosynostosis in infants. Paediatr An-
aesth 2003; 13:797–804
cells on neonates undergoing corrective cardiac surgery. ASAIO J
2007; 53:680–683
infants undergoing elective cardiac surgery: a prospective trial. Eur J
Cardiothorac Surg 2008; 34:354–359


