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Efficacy of cell salvage in neonates and children undergoing cardiac surgery

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EFFICACY OF CELL SALVAGE IN NEONATES AND CHILDREN UNDERGOING CARDIAC SURGERY

by

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EFFICACY OF CELL SALVAGE IN NEONATES AND CHILDREN UNDERGOING CARDIAC SURGERY

WILLIAM N. STEVENS

ABSTRACT

Background

Cell salvage (CS) techniques are used to reduce exposure to allogeneic packed red blood cell (pRBC) transfusion in patients undergoing cardiac surgery. However, some studies suggest that inappropriate use of these techniques is associated with increased incidences of thrombocytopenia, excessive bleeding, and transfusion of non-red blood cell blood products, including fresh frozen plasma (FFP), cryoprecipitate, and platelets. Pediatric patients undergoing cardiac surgery are at higher risk for increased perioperative bleeding and blood product transfusion requirement. To date, limited evidence supports the use of CS to reduce pRBC transfusion in neonates and children undergoing cardiac surgery.

Objectives

This study analyzed the efficacy of systematic use of CS in neonates and children undergoing cardiac surgery with cardiopulmonary bypass (CPB) compared to a historic cohort of children in whom CS was not used. Our primary endpoints included the incidences of pRBC, cryoprecipitate, and platelets transfusion occurring within 48 hours after CPB.
Methods

We performed a retrospective medical chart review to study all neonates and children who underwent cardiac surgery with CPB between January 2013 and December 2014 at Boston Children’s Hospital (BCH). Considering that CS has been systematically applied at BCH since January 2014, children were separated into a control group (before January 2014) and a CS group (after January 2014). Children treated with CS before January 2014 were excluded. We used uni- and multivariable logistic regression analysis to assess the effect of CS on the odds of blood products transfusion.

Results

Among 1228 patients included in the analysis, 730 were included in the CS group and 498 in the control group. The results of our multivariate logistic regression analysis showed that age < 12 months (odds ratio (OR): 2.95, 95% confidence interval (CI): 2.26-3.84), American Society of Anesthesiologists Physical Status Classification (ASA) > 3 (OR: 2.95, 95% CI: 2.26-3.84), Risk Adjustment for Congenital Heart Surgery score (RACHS) > 3 (OR: 1.78, 95% CI: 1.28-2.49), and the use of CS (OR: 0.57, 95% CI: 0.44-0.73) were good predictors for perioperative transfusion. Using univariable analysis, the use of CS was associated with a significant reduction in pRBC transfusion (OR: 0.76, 95% CI: 0.61-0.96, p = 0.021), but a significant increase in cryoprecipitate (OR: 1.37, 95% CI: 1.08-1.76, p = 0.009) and platelets transfusions (OR: 1.37 95% CI: 1.08-1.76, p = 0.004). However, after adjustment for age < 12 months, ASA > 3, and
RACHS > 3, the use of CS significantly reduced pRBC transfusion (OR: 0.57, 95% CI: 0.44-0.73, p < 0.001), with no effect on cryoprecipitate (OR: 1.08, 95% CI: 0.83-1.41, p = 0.543) and platelets transfusions (OR: 1.05, 95% CI: 0.81-1.36, p = 0.694).

**Conclusion**

The use of CS in neonates and children undergoing cardiac surgery with CPB significantly reduced the incidence of pRBC transfusion. Although the systematic use of CS in adults has been associated with an increased incidence of non-pRBC transfusions, the use of CS in a high risk pediatric population (age < 12 months, ASA > 3, RACHS > 3) was associated with a 43% reduction of pRBC transfusion without any increases in cryoprecipitate and platelets transfusions.
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LIST OF ABBREVIATIONS

ASA............ American Society of Anesthesiologists Physical Status Classification
B .............................................................. regression coefficient
BCH ................................................................ Boston Children’s Hospital
CHD ................................................................ congenital heart defect
CI ................................................................. confidence interval
CICU .......................................................... cardiac intensive care unit
CPB ................................................................ cardiopulmonary bypass
DHCA......................................................... deep hypothermic circulatory arrest
FFP .................................................................. fresh frozen plasma
ICU ..................................................................... intensive care unit
MUF ................................................................ modified ultrafiltration
OR ................................................................... odds ratio
pRBC ............................................................ packed red blood cells
RACHS ....................................................... Risk Adjustment for Congenital Heart Surgery score
RBC ................................................................ red blood cells
SCP ................................................................ selective cerebral perfusion
SE ................................................................... standard error
INTRODUCTION

Neonates and children who undergo cardiac surgery with cardiopulmonary bypass (CPB) are at increased risk of perioperative bleeding, and blood product transfusion requirements (Guzetta et al., 2015). In pediatric patients undergoing open heart surgeries, bleeding risk and blood products transfusion rates are related to age, with neonates being at higher risk (Williams et al., 1998). The perioperative coagulopathy observed in patients undergoing cardiac surgery with CPB is multifactorial and complex. Despotis et al. characterized CPB-induced coagulopathy by the following interactions: (i) hemodilution coagulopathy secondary to cardioplegia, the volume of CPB prime, and administration of fluids in the perioperative period, (ii) contact activation (activation of factor X and thrombin generation) due to tissue injury, tissue factor production, and activation of fibrinolytic pathways, and (iii) consumption coagulopathy due to thrombin, plasmin, and inflammation mediated processes (Despotis et al., 1999). All of these factors can generate a vicious cycle leading to increased coagulopathy and a systemic inflammatory response. In addition to coagulopathy, techniques used to promote anticoagulation using unfractionated heparin, reversal of heparin anticoagulation using protamine, and other physiological disturbances such as hypothermia, acidemia, and hypocalcemia, will increase the risk of bleeding (Paparella et al., 2004).
Although all of these mechanisms are observed in both adult and pediatric patients, there are increased risks of coagulopathy, perioperative bleeding, and transfusion requirements in children when compared with adults (Osthaus et al., 2008). Risk factors for coagulopathy specific to children with congenital heart defects (CHD) include surgery in the newborn period, cyanotic CHD, and complex or repeat cardiac surgery. Cardiac operations in pediatric populations are inherently dangerous; surgeries are often long, performed at low temperatures, and require suture lines that can cover an extensive surface area of a patient with miniscule body size (Guzzetta et al., 2015). In addition, hemostatic abnormalities due to cardiac surgery are noted because of the necessary use of anticoagulants and the activation of clotting factors during surgery, creating a very complex hemostatic environment (Hartmann et al., 2006). Indeed, some necessary clotting factors are either not effectively produced or activated by neonates and infants, minimizing the abilities of natural clotting and, therefore, increasing perioperative bleeding (Guzzetta and Miller, 2011). For example, coagulation factors do not cross the placenta throughout gestation, and factors II, VII, XIII and fibrinogen are reduced to about 50% of normal adult values at birth (Pichler and Pichler, 2008). Neonatal platelet levels are similar to normal adult values at birth, but they seem to be hypoactive (Pichler and Pichler, 2008).

As a consequence of the summation of these factors, neonates and children have an increased and eminent need for four major hemostatic
transfusion products: packed red blood cells (pRBC), platelets, fresh frozen plasma (FFP), and cryoprecipitate (Guzzetta et al., 2015). pRBC are transfused to improve oxygen delivery to tissues in critically ill children when hemoglobin falls to a range of 7-9 grams per deciliter (Lacroix et al., 2007). Platelets recognize damaged blood vessels and form hemostatic thrombi to accelerate the process of coagulation (Rand et al., 2003), and are indicated when a patient exhibits thrombocytopenia secondary to hemorrhage (Sharma et al., 2011). FFP is the liquid portion of blood (Mayr, 2007). Plasma contains all coagulation factors and is used for reversal of anticoagulation changes that are often a surgical necessity (Sharma et al., 2011). Cryoprecipitate is a concentrated solution containing fibrinogen, fibronectin, von Willebrand factor, platelet microparticles, and clotting factors VIII and XIII (Callum et al., 2009). Because FFP contains all coagulation factors in, at best, physiologic concentrations, large volumes of plasma are required to significantly increase the plasmatic concentration in a bleeding patient (Chowdhury et al., 2004). For this reason, cryoprecipitate is prepared by centrifuging FFP and collecting the precipitate, and is transfused in patients with massive hemorrhaging because it contains significantly higher concentrations of fibrinogen and some other factors (Levy et al., 2012). Altogether, these blood products are transfused to return the hemostatic system in a distressed patient to homeostasis.

In a study of 802 postoperative admissions to the cardiac intensive care unit (CICU) at Boston Children’s Hospital (BCH), 46 percent of patients who
required pRBC transfusion within the first 48 postoperative hours were younger, required a more complex cardiac surgery, and using risk scores, were diagnosed as more acutely ill than the 52 percent of patients who were not transfused (Salvin et al., 2011). Risk scores are important tools in preoperative assessment to describe patient-specific variables and create a uniform system for analysis (Geissler et al., 2000). American Society of Anesthesiologists Physical Status Classification (ASA) (Saklad, 1941; Haynes and Lawler, 1995) and Risk Adjustment for Congenital Heart Surgery score (RACHS) (Jenkins et al., 2002) are two examples of risk scores that assess patients for anesthetic and CHD procedures, respectively. This study also found that transfusion is associated with prolonged hospitalization, with the strongest association between the most transfused groups (Salvin et al., 2011). It is known that transfusion occurs in nearly half of all pediatric intensive care unit (ICU) patients (Bateman et al., 2008), and it has been proposed that transfusion may have significant influences on overall morbidity and mortality after cardiac surgery (Guzzetta et al., 2015). Because a restrictive transfusion strategy has been found to be more efficacious than a liberal strategy (Lacroix et al., 2007), it is vital to identify risk factors for bleeding to apply a more contemplative and reasonable approach to the administration of blood products to patients.
Allogeneic transfusions

The allogeneic transfusion, the transfer of blood products from the circulation of a donor to the circulation of a recipient (Learoyd, 2012), is one of the most common procedures performed in hospitals in the United States and is administered at a cost of billions of dollars each year (Anthes, 2015). Transfusions have experienced a dramatic growth in use and popularity among clinicians during the last century due to their reputation as an easy to use and readily available hemostatic therapy (Shander et al., 2013). Blood product transfusions are undoubtedly lifesaving measures in cases of severe hemorrhage or dangerously low hemoglobin levels (Murphy et al., 2007; DiNardo, 2013), yet allogeneic transfusions are identified by The Joint Commission as one of the most overused procedures in healthcare (jointcommission.org) and are pervasively associated with adverse outcomes in many surgical settings (Koch et al., 2006; Chelemer et al., 2002). In some patients, a transfusion may correct a physiologic imbalance and yet be associated with worse clinical outcomes (Bernard et al., 2009; Glance et al., 2011; Ferraris et al., 2012). A concise summary of allogeneic transfusion risks by Goodnough is infection (via agents that are routinely tested for, such as human immunodeficiency virus, and agents that are not tested for, such as malaria), hemolytic reactions, alloimmunisation, medical errors, transfusion-associated acute lung injury, transfusion-associated circulatory overload, iron overload, immunomodulation, and storage lesions due to the age of transfused products (Goodnough, 2013). Modern medical
knowledge and clinical practices place a few of these risks at an all-time low, however, new and emerging dangers are a constant threat (Vamvakas and Blajchman, 2009; Shander et al., 2016).

Allogeneic transfusions are associated with adverse outcomes. Populous studies of noncardiac surgery patients have found increased mortality and morbidity to be associated with both intraoperative (Glance et al., 2011) and postoperative transfusions (Abdelsattar et al., 2015). A study of 8,724 cardiac surgery patients found perioperative pRBC transfusion to be associated with increased infection, morbidity, mortality, and prolonged length of hospital stay (Murphy et al., 2007). Death within the first 30 postoperative days was almost 6 times higher in transfused populations when compared to non-transfused populations (Murphy et al., 2007). Shander et al. performed a literature review of 19 substantial studies evaluating the clinical outcomes of allogeneic pRBC transfusions in various patient populations and found that transfusions do little to improve the patient condition, undermining their clinical effectiveness (Shander et al., 2011a).

These reported negative risks and outcomes become alarming when the large variation in transfusion practices is considered (Shander et al., 2012). Studies have shown significant inter-institutional variability in transfusion rates of all hemostatic products (Rogers et al., 2009; Bennett-Guerrero et al., 2010; Frank et al., 2012). In addition, a large observational study of 102,270 patients showed enormous variability in coronary artery bypass graft surgery across a large
number of hospitals in the United States (Bennett-Guerrero et al., 2010). In 2011, The United States Department of Health and Human Services Advisory Committee for Blood Safety and Availability stated that this wide variation is a clear indicator of excessive and inappropriate use of transfusions (US Department of Health).

There is poor integration on a national level of scientific evidence with recognized guidelines to determine when hemostatic products should be transfused (Murphy et al., 2007). Murphy et al. states that pRBC transfusion is harmful in almost all cardiac surgery patients as is used today because it is difficult to identify those who truly do need transfusion using standard indicators (Murphy et al., 2007). For instance, hematocrit level is a common indication in critically ill patients, but this trigger is not supported by many studies (Murphy and Angelini, 2006; Murphy et al., 2007) because isolated hematocrit levels are poor indicators of tissue hypoxia (Torres Filho et al., 2005). Perioperative monitoring of hematocrit is also unsupported because it is often invasive (Murphy and Angelini, 2006) and equations used to determine blood component levels do not always assess oxygen consumption appropriately (Kemming et al., 2002). Lack of application of evidence-based indications or noncompliance with existing guidelines may also be leading to this excessive and unnecessary administration of blood components (Snyder-Ramos et al., 2008). These issues become amplified in populations that are at a significant risk for receiving blood transfusions, making it imperative to minimize blood loss and set clear
transfusion thresholds to assure that pediatric patients specifically receive the most effective care (Bateman et al., 2008).

**Blood management programs**

Perioperative management of blood products has significantly changed over the past decade with the development of blood management programs to counteract the negative characteristics of allogeneic transfusions (Shander et al., 2012). These programs apply an evidence-based, multidisciplinary approach to medical and surgical situations to optimize hemoglobin levels and hemostasis in order to rationalize and to decrease blood product transfusion, as well as to improve patient outcomes (Goodnough and Shander, 2012; sabm.org). Programs aim to minimize blood product transfusion by correcting preoperative anemia, enhancing perioperative assessment of coagulopathy, reducing perioperative bleeding, and including a more rational administration of blood products via the development of restrictive transfusion algorithms (Shander et al., 2012; Spahn et al., 2008). The desire to develop these programs is evidenced by studies to determine the appropriateness and effectiveness of blood product transfusion strategies (Shander et al., 2011b; de Gast-Bakker et al., 2013) and the establishment of The Society for the Advancement of Blood Management in 2001 to research and educate (sabm.org).

One analysis summarizes blood management programs in four principles (Hohmuth et al., 2014). First, low preoperative red blood cell (RBC) volume due
to anemia or the small body size of pediatric patients is a risk factor for blood transfusion (Goobie et al., 2016) and has been identified as a predictor of morbidity, mortality, and increased length of hospital stay (Spahn et al., 2008). Blood management programs should detect, evaluate, and correct low RBC values in advance of elective surgery as this will reduce the need for allogeneic blood (Boucher and Hannon, 2007). Second, point-of-care testing can quickly identify hemostatic abnormalities in regard to coagulation. Testing has shown positive outcomes in surgical settings (Meybohm et al., 2013) as it lowers perioperative blood loss and therefore decreases the need for transfusion products (Hohmuth et al., 2014). Patient-specific protocols must be utilized to discontinue drugs that may hinder coagulation (Boucher and Hannon, 2007). Third, intraoperative blood loss is unsurprisingly associated with increased death risk (Wong and Intragumtornchai, 2006). Blood loss and transfusion rates can be minimized with the coordination of interdisciplinary approaches to blood conservation; intraoperative blood recovery (Waters, 2004), energy-based technologies (Sileshi et al., 2010), and sealant agents (Sileshi et al., 2010) are all used to aid in hemostasis and reduce allogeneic transfusion. Lastly, approaching blood management as an individualized process helps ensure that each patient receives appropriate and excellent care (Hohmuth et al., 2014). Improved outcomes are observed in fluid medical atmospheres when physicians provide complete, understandable treatment information and patients are free to communicate their therapeutic preferences (Friedman et al., 2012).
In addition to product safety issues, adverse transfusion outcomes, and questionable efficacy of transfusions as previously explained, one analysis identifies demand and cost as two other variables shifting the medical community towards blood management programs (Hofmann et al., 2011). The demand for pRBC transfusion, which is already at an all-time high in most developed nations (Hofmann et al., 2011), will only increase when current transfusion practice is considered along with potential population aging and growth (Hofmann et al., 2009). Supply of blood products from an age-restricted donor base will decrease, which will accelerate the gap between supply and demand (Hofmann et al., 2011). The United States is not the only nation with this issue; European studies based in both Finland (Ali et al., 2010) and Germany (Greinacher et al., 2011) have focused on identifying the causes of and dealing with this demand. A full cost assessment of transfusion includes logistics for acquiring blood, lab tests, pretransfusion examinations, administration of blood products, postoperative monitoring, and treating adverse reactions (Hofmann et al., 2011). A study analyzed transfusion in two hospitals and identified transfusion cost per surgical patient to be $2,696 and $3,589 (Hofmann et al., 2011), and the annual hospital acquisition cost for pRBC alone is greater than $3 billion (US Department of Health). Allogeneic transfusion is clearly expensive.

Hemostatic complications are increasingly and preferably corrected by patient-centered blood management programs as opposed to product-centered allogeneic transfusion therapies (Shander et al., 2013). The allogeneic
transfusion is performed often although it may not always be fully supported, and patient blood management is a new frontier in the way hemostatic products are used in transfusion medicine (Shander et al., 2013).

**Cell Salvage (CS)**

Blood management programs aim to avoid allogeneic transfusion of pRBC, and, therefore, allogeneic transfusion related risks. Some interventions designed to achieve this goal avoid transfusion altogether; these techniques include providing a patient with drugs such as aprotinin and tranexamic acid to minimize blood loss (Faraoni et al., 2012; Koster et al., 2015), or agents such as erythropoietin and iron to maximize RBC production (Waters, 2004; Carless et al., 2010). Other interventions to avoid allogeneic transfusion concentrate on transfusing a patient’s own blood that is collected via preoperative donation, acute normovolemic hemodilution, or the utilization of CS systems (Waters, 2004; Carless et al., 2010). This reinfused blood is an autologous transfusion, or autotransfusion. The use of preoperative autologous donation is no longer recommended (Boulton and James, 2007) because the technique has been associated with higher incidence of pRBC transfusion due to iatrogenic anemia (Singbartl et al., 2013).

CS summarizes numerous techniques in which a patient’s blood is collected from intraoperative surgical sites or postoperative wounds, processed, and autotransfused either intra- or postoperatively (Carless et al., 2010).
Indication for CS use has previously been if blood loss was expected to be 20% or more of total blood volume (American Association, 1997), but more recent analysis suggests that CS should be used when smaller blood loss is expected because autologous transfusions are efficacious and cheaper than the allogeneic alternative (Esper and Waters, 2011). A multitude of CS devices exist that process blood differently (Carless et al., 2010). In addition, salvaged blood can be washed in a saline solution or unwashed prior to autotransfusion (Ashworth and Klein, 2010). Washing removes unwanted byproducts including cytokines, fat particles, free hemoglobin, inflammatory mediators, and other tissue and chemical debris (Muñoz et al., 2011) but also removes viable coagulation proteins and substances that are essential to hemostasis (Wang et al., 2009). There is not widespread agreement on which technique is more efficient, but unwashed blood is viewed less favorably than washed blood (Carless et al., 2010) even though numerous studies support the notion that unwashed transfusions are safe (Muñoz et al., 2011). Studies of cardiac surgeries show that there is no significant difference in allogeneic transfusion rates when comparing washed and unwashed blood (Carless et al., 2010). Hemoglobin and hematocrit values are lower in shed blood but strong data suggests that collected blood contains RBC that are fully viable (Muñoz et al., 2011).

The systematic use of CS has been shown to significantly reduce the incidence of pRBC transfusion in different surgical settings. Carless et al. performed a meta-analysis of 75 randomized CS trials that were carried out
between 1979-2008. This analysis found that CS reduced overall perioperative allogeneic pRBC transfusion by 38% and that the risk of exposure to pRBC transfusion was slightly lower in washed cells (Carless et al., 2010). On a large scale, CS is favored over allogeneic transfusion because widespread evidence suggests that CS does not appear to cause major adverse clinical outcomes (Carless et al., 2010).
SPECIFIC AIMS

The research and implementation of systematic blood management programs are a necessity in today’s blood transfusion climate. CS is one option that has shown extreme benefit in certain situations. As more is learned about the technique, its benefits, and its limitations, studies based on populations undergoing specific surgeries are necessary. Although CS is being used nationwide, limited evidence supports the use of the technique to reduce allogeneic pRBC transfusions in neonates and children undergoing cardiac surgery.

At BCH in Boston, MA, CS has been systematically used in neonates and children undergoing cardiac surgery with CPB since January 2014. This retrospective before-and-after study aims to determine changes in the transfusion of pRBCs and other hemostatic products, assess the incidence of postoperative thrombocytopenia and coagulopathy, and determine changes in resource utilization following the implementation of a systematic intraoperative CS strategy. CS techniques are beneficial as they reduce the need for allogeneic pRBC, but a potential increase in need for other hemostatic products and questions regarding pediatric populations suggests that the technique may not be efficacious when used all the time. This study aims to determine when CS is most appropriately used in pediatric cardiac surgeries.
METHODS

Study population

We performed a retrospective medical chart review to study all neonates and children who underwent cardiac surgery with CPB between January 2013 and December 2014 at BCH. Considering that CS has been systematically applied since January 2014, children were separate into a CS group (after January 2014) and a control group (before January 2014). Children treated with CS before January 2014 were excluded.

Data recorded

Demographic data and surgical characteristics were recorded and collected from the subject’s medical and anesthesia records, perfusion, and CICU records; all data were entered into a computer database (RedCap). Patient specific information included: gender, date of birth, diagnosis, date of surgery, procedure, surgeon, procedure note, and patient medical history. RACHS was used to classify surgical operating procedures based on the surgical complexity. Duration of the surgery was defined as the time between skin incision and the last surgical stitch. The type of oxygenator, use of modified ultrafiltration (MUF) and amount of MUF (in milliliters per kilogram) was recorded. Blood product transfusion was defined as any intraoperative exposure to pRBC, FFP,
reconstituted whole blood, cryoprecipitate, or platelet concentrates that occurred during or after CPB, as well as exposure during the first 48 hours of CICU stay.

We recorded CPB characteristics including prime volume, CPB duration, aortic clamp duration, and duration of deep hypothermic circulatory arrest (DHCA) selective cerebral perfusion (SCP). Pre-, intra-, and postoperative blood analyses routinely performed (such as standard laboratory tests and blood gases) were recorded. In addition, we recorded outcome parameters including duration of mechanical ventilation, incidence of postoperative cardiac failure, respiratory failure, acute kidney injury, need for renal replacement therapy, neurological complication, postoperative extracorporeal membrane oxygenation, length of ICU stay, length of hospital stay, mortality in ICU, and in-hospital mortality.

During the study period, anesthesia technique and CPB management were standardized. The anesthetic technique included midazolam, high-dose fentanyl, neuromuscular blockade, and inhaled agent, as tolerated. The CPB circuit included a Terumo FX05 oxygenator (Terumo Cardiovascular Systems Europe, Bagshot, Surrey, United Kingdom) and a reservoir. CPB flow rates were adjusted for hypothermia. Continuous ultrafiltration was performed to effectuate hemoconcentration, and zero balance ultrafiltration was not performed. Therefore, no additional fluid was added to the CPB circuit in conjunction with ultrafiltration. After January 2014, the Continuous Auto Transfusion System (Fresenius, Oberursel, Germany) was used in all patients to process the blood obtained from the cardiotomy suction during the all CPB duration, and returned to
the patient as needed. During the study period, the transfusion algorithm was left at the discretion of the surgeon and anesthesiologist in charge.

Statistical analysis

Demographic and baseline characteristics were compared between the CS group and the historical control group using statistical analysis. Categorical variables are expressed as number and percentage, and continuous variables are expressed as median and interquartile range. Variables were compared between the groups ‘CS’ and ‘control’ using chi-square or Mann-Whitney U test. To control for possible confounding among variables, we used multivariable logistic regression using backward selection to determine the independent predictors for in-hospital mortality using a univariable cut off of $P < 0.10$ for inclusion and $P > 0.05$ for removal. The results are expressed as regression coefficient ($B$) and standard error ($SE$), the odds ratio ($OR$) as a measure of risk, the 95% confidence interval ($CI$), and $P$-values obtained from the Wald test. Statistical analysis was performed using Stata software (version 14.1 for Mac OS, Stata Corporation, College Station, Texas).
RESULTS

Among 1228 patients included in the study, 730 were included in the CS group and 498 in the control group. When comparing age, weight, risk scores (ASA and RACHS), and information regarding CPB, aortic clamping, DHCA, and SCP (Table 1), it was found that age was lower in the CS group (7 months (2-52) vs. 13 months (3-63), p = 0.049) but no other differences in demographic and surgical characteristics were observed between groups.

Laboratory values of hemoglobin, platelets, and fibrinogen between the control and CS group were compared (Table 2). 48 control patients received transfused pRBC and 42 CS patients received transfused pRBC (Figure 1 and 2). 31 control patients and 39 CS patients received perioperative cryoprecipitate transfusion (Figure 3). 31 control patients and 39 CS patients received perioperative platelets transfusion (Figure 4). The results of our multivariate logistic regression analysis showed that age < 12 months (OR: 2.95, 95% CI: 2.26-3.84), ASA > 3 (OR: 2.95, 95% CI: 2.26-3.84), RACHS > 3 (OR: 1.78, 95% CI: 1.28-2.49), and the use of CS (OR: 0.57, 95% CI: 0.44-0.73) were good predictors for total perioperative RBC transfusion (Table 3).

Table 4 and Figure 5 describe the OR (95% CI) for the effect of CS on pRBC, cryoprecipitate, and platelets transfusion. Using univariable analysis, the use of CS was associated with a significant reduction in pRBC transfusion (OR: 0.76, 95% CI: 0.61-0.96, p = 0.021), but a significant increase in cryoprecipitate
(OR: 1.37, 95% CI: 1.08-1.76, p = 0.009) and platelets transfusions (OR: 1.37
95% CI: 1.08-1.76, p = 0.004). However, after adjustment for age < 12 months,
ASA > 3, and RACHS > 3, the use of CS significantly reduced RBC transfusion
(OR: 0.57, 95% CI: 0.44-0.73, p < 0.001), with no effect on cryoprecipitate (OR:
1.08, 95% CI: 0.83-1.41, p = 0.543) and platelets transfusions (OR: 1.05, 95% CI:
0.81-1.36, p = 0.694).
Table 1. Comparison of demographic and surgical characteristics between controls and children exposed to CS.

<table>
<thead>
<tr>
<th>Characteristic measured</th>
<th>Controls (n=498)</th>
<th>CS (n=730)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (months)</td>
<td>13 (3-63)</td>
<td>7 (2-52)</td>
<td>0.049</td>
</tr>
<tr>
<td>body weight (kilograms)</td>
<td>8.9 (4.6-19.2)</td>
<td>6.7 (3.9-15.7)</td>
<td>0.009</td>
</tr>
<tr>
<td>ASA</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>12 (2)</td>
<td>16 (2)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>250 (51)</td>
<td>223 (31)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>224 (46)</td>
<td>472 (66)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3 (1)</td>
<td>6 (1)</td>
<td></td>
</tr>
<tr>
<td>RACHS</td>
<td></td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>1</td>
<td>40 (8)</td>
<td>39 (5)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>229 (46)</td>
<td>358 (49)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>156 (32)</td>
<td>221 (30)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>51 (10)</td>
<td>56 (8)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>14 (3)</td>
<td>19 (3)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>7 (1)</td>
<td>35 (5)</td>
<td></td>
</tr>
<tr>
<td>CPB time (minutes)</td>
<td>119 (75-160)</td>
<td>120 (84-163)</td>
<td>0.433</td>
</tr>
<tr>
<td>aortic clamp (yes/no)</td>
<td>440 (88)</td>
<td>631 (86)</td>
<td>0.324</td>
</tr>
<tr>
<td>aortic clamp time (minutes)</td>
<td>78 (51-114)</td>
<td>73 (51-105)</td>
<td>0.426</td>
</tr>
<tr>
<td>DHCA (yes/no)</td>
<td>125 (17)</td>
<td>66 (13)</td>
<td>0.066</td>
</tr>
<tr>
<td>DHCA time (minutes)</td>
<td>25 (9-46)</td>
<td>15 (7-27)</td>
<td>0.001</td>
</tr>
<tr>
<td>SCP (yes/no)</td>
<td>24 (5)</td>
<td>73 (10)</td>
<td>0.001</td>
</tr>
<tr>
<td>SCP time (minutes)</td>
<td>71 (28-92)</td>
<td>49 (40-80)</td>
<td>0.290</td>
</tr>
<tr>
<td>CPB prime (milliliter per kilogram)</td>
<td>38 (29-55)</td>
<td>41 (28-63)</td>
<td>0.133</td>
</tr>
</tbody>
</table>
Table 2. Comparison of laboratory values between controls and children exposed to CS.

<table>
<thead>
<tr>
<th>Blood product (when recorded)</th>
<th>Controls (n=498)</th>
<th>Cell-Saver (n=730)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>hemoglobin (baseline)</td>
<td>13.0 (11.9-14.2)</td>
<td>13.2 (12.0-14.8)</td>
<td>0.024</td>
</tr>
<tr>
<td>hemoglobin (ICU admittance)</td>
<td>12.4 (11.1-14.0)</td>
<td>13.0 (11.7-14.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hemoglobin (day 1)</td>
<td>12.4 (11.1-13.9)</td>
<td>13.0 (11.8-14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>platelet count (baseline)</td>
<td>297 (234-368)</td>
<td>298 (130-381)</td>
<td>0.993</td>
</tr>
<tr>
<td>platelet count (ICU admittance)</td>
<td>166 (118-226)</td>
<td>179 (127-248)</td>
<td>0.154</td>
</tr>
<tr>
<td>platelet count (day 1)</td>
<td>169 (122-230)</td>
<td>177 (123-344)</td>
<td>0.409</td>
</tr>
<tr>
<td>fibrinogen (baseline)</td>
<td>275 (240-380)</td>
<td>306 (130-386)</td>
<td>0.879</td>
</tr>
<tr>
<td>fibrinogen (ICU admittance)</td>
<td>276 (231-366)</td>
<td>281 (227-348)</td>
<td>0.969</td>
</tr>
<tr>
<td>fibrinogen (day 1)</td>
<td>261 (209-311)</td>
<td>263 (199-330)</td>
<td>0.930</td>
</tr>
</tbody>
</table>
Table 3. Multivariate logistic regression analysis to predictors associated with total pRBC transfusion.

<table>
<thead>
<tr>
<th></th>
<th>B (SE)</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA &gt; 3</td>
<td>1.08 (0.14)</td>
<td>2.95</td>
<td>2.26-3.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>age &lt; 12 months</td>
<td>0.44 (0.13)</td>
<td>1.56</td>
<td>1.22-2.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RACHS &gt; 3</td>
<td>0.58 (0.17)</td>
<td>1.78</td>
<td>1.28-2.49</td>
<td>0.001</td>
</tr>
<tr>
<td>CS (yes/no)</td>
<td>-0.56 (0.13)</td>
<td>0.57</td>
<td>0.44-0.73</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Table 4. OR for blood product transfusion in children treated with intraoperative CS before and after adjustment for risk factors.

* Adjusted for ASA>3, Age < 12 months, RACHS>3

<table>
<thead>
<tr>
<th>Blood Product</th>
<th>OR (95% CI)</th>
<th>P value</th>
<th>*OR (95% CI)</th>
<th>*P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>intraoperative pRBC (yes/no)</td>
<td>0.88 (0.68-1.15)</td>
<td>0.356</td>
<td>0.70 (0.53-0.93)</td>
<td>0.014</td>
</tr>
<tr>
<td>postoperative pRBC (yes/no)</td>
<td>0.80 (0.63-1.02)</td>
<td>0.075</td>
<td>0.64 (0.49-0.83)</td>
<td>0.001</td>
</tr>
<tr>
<td>total pRBC (yes/no)</td>
<td>0.76 (0.61-0.96)</td>
<td>0.021</td>
<td>0.57 (0.44-0.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>intraoperative cryoprecipitate (yes/no)</td>
<td>1.57 (1.22-2.01)</td>
<td>&lt;0.001</td>
<td>1.24 (0.95-1.63)</td>
<td>0.108</td>
</tr>
<tr>
<td>postoperative cryoprecipitate (yes/no)</td>
<td>0.70 (0.44-1.13)</td>
<td>0.143</td>
<td>0.60 (0.37-0.98)</td>
<td>0.040</td>
</tr>
<tr>
<td>total cryoprecipitate (yes/no)</td>
<td>1.37 (1.08-1.76)</td>
<td>0.009</td>
<td>1.08 (0.83-1.41)</td>
<td>0.543</td>
</tr>
<tr>
<td>Intraoperative platelet (yes/no)</td>
<td>1.58 (1.26-2.00)</td>
<td>&lt;0.001</td>
<td>1.26 (0.98-1.63)</td>
<td>0.074</td>
</tr>
<tr>
<td>Postoperative platelet (yes/no)</td>
<td>0.65 (0.45-0.93)</td>
<td>0.019</td>
<td>0.54 (0.37-0.78)</td>
<td>0.001</td>
</tr>
<tr>
<td>total platelet (yes/no)</td>
<td>1.37 (1.08-1.76)</td>
<td>0.004</td>
<td>1.05 (0.81-1.36)</td>
<td>0.694</td>
</tr>
</tbody>
</table>
Figure 1: Volume of pRBC transfused in controls and children treated with CS.
Figure 2: Incidence of pRBC transfusion in controls and children treated with CS.

![Graph showing incidence of pRBC transfusion](image)
Figure 3: Incidence of cryoprecipitate transfusion in controls and children treated with CS.
Figure 4: Incidence of platelet transfusion in controls and children treated with CS.
Figure 5: OR for the effect of CS on perioperative blood product transfusion.

*Multivariate logistic regression adjustment for age < 12 months, ASA > 3, and RACHS>3
DISCUSSION

Principle findings

Our retrospective study analyzed 1,228 pediatric patients who underwent cardiac surgery with CPB over a two-year period (January 2013-December 2014) at BCH. This study focused on the effect CS usage on perioperative blood product transfusion. Analysis of the whole study population demonstrates that the use of CS was associated with a significant reduction in pRBC transfusion but a significant increase in cryoprecipitate and platelets transfusions. However, when adjusted for predictors of perioperative hemostatic product transfusion (a high risk population of age < 12 months, ASA > 3, RACHS > 3), we found that the utilization of CS significantly reduced pRBC transfusion with no effect on cryoprecipitate and platelets transfusions.

Transfusion in cardiac surgery

Cardiac procedures in general consume more than 80% of hemostatic products transfused during all surgeries (Ferraris et al., 2007; McQuilten et al., 2014). Allogeneic transfusions have inherent risks, are associated with adverse outcomes, and lack extensive guidelines for widespread, systematic practice. These factors make transfusions dangerous to patients. There is widespread understanding throughout the medical community that further studies are needed to determine the true necessity for allogeneic blood transfusions (Murphy et al.,
Prevalent negativity surrounding allogeneic transfusions is steadily leading the medical community to research and potentially implement a more restrictive strategy for transfusion (Frank et al., 2015). In 2011, the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists jointly released updated guidelines on blood conservation management in an attempt to better transfusion therapy (Ferraris et al., 2011). Numerous organizations included the Joint Commission, the American Medical Association, the American Society of Anesthesiology, and the World Health Organization are also vocal in regards to this goal (Practice guidelines, 2015).

The enhanced blood loss during cardiac surgeries demonstrates the need for blood management programs specifically for these patients. CS is one program that may aid these patients as it significantly reduces exposure to allogeneic blood products in cardiac procedures, specifically pRBC transfusion (Wang et al., 2009). One meta-analysis of 13 cardiac surgery trials shows that CS reduced allogeneic transfusion by 23% with an average saving of one unit of allogeneic blood per patient (Carless et al., 2010). Many randomized controlled trials support the use of CS to reduce blood transfusions in cardiac surgery (Dietrich et al., 1989; Daane et al., 2003; Damgaard and Steinbrüchel, 2006; Goel et al., 2007); as a result, CS techniques are increasingly included in the perioperative management of patients undergoing cardiac surgery (Wang et al., 2009). On the other hand, some studies do demonstrate that routine CS does not reduce allogeneic blood transfusion (Klein et al., 2008). A meta-analysis reported
that the efficacy of cell saver to reduce blood product transfusion requirements varies depending on the timing and the way the cell saver is used intra- and postoperatively (Wang et al., 2009).

Some controversies exist regarding a potential increased bleeding risk, an increased incidence of thrombocytopenia, and coagulopathy in patients exposed to CS pRBC (Djaiani et al. 2007; Rubens et al., 2007). Washing the CS product prior to autotransfusion removes platelets and other essential hemostatic factors (Wang et al., 2009) that may need to be transfused allogeneically. Djaiani et al. found that patients who received FFP transfusion had a significant increase in the amount of autologous pRBC transfused from processed cardiotomy blood (Djaiani et al. 2007). This suggests that CS may lead to increased bleeding secondary to a critical loss of coagulation factors (Despotis et al., 1996; Djaiani et al. 2007). Rubens et al. suggests that there may be little justification to systematic CS usage as trials found that CS processing of cardiotomy blood leads to increased postoperative bleeding and, therefore, need for allogeneic blood products (Rubens et al., 2007). The results observed in those two prospective studies were discussed in a systematic review with meta-analysis published by Wang et al. in 2009 (Wang et al., 2009). Based on current evidence, the authors suggest that the use of a cell saver reduces exposure to pRBC transfusion for patients undergoing cardiac surgery. However, subanalyses also suggest that the use of CS may be beneficial only when it is used for shed blood and/or residual blood or during the entire operative period.
Processing cardiotomy suction blood with a CS only during CPB has no significant effect on blood conservation and increases FFP transfusion.

CS in pediatric populations

Neonates and children undergoing cardiac surgery with CPB are at an increased risk of bleeding (Willems et al., 2010); when undergoing cardiac surgery this group is at a unique risk for allogeneic blood product, and therefore benefit from blood management programs. Little data regarding CS usage in pediatric cardiac surgical cases exists, mostly because technical limitations have prevented CS usage for pediatric patients (Booke et al., 1999; Golab et al., 2008). Recent advancements have made CS usage possible for the small volume requirements of this population (Cholette et al., 2013). Observational studies suggest that CS can be safely used to decrease allogeneic transfusion in non-cardiac surgeries of children (Dahmani et al., 2000) and neonates and small infants (Orliaguet et al., 2003). A study that used an alternative autotransfusion system to administer pRBC to neonates undergoing heart surgery found autotransfusion to be beneficial in this population (Liu et al., 2007). One prospective nonrandomized cohort study describing postoperative transfusion of CS in a dedicated pediatric system exists. Although CS blood was only available for autotransfusion for 6 hours after its collection, this study found that CS was a safe and effective method to reduce postoperative allogeneic pRBC transfusion (Golab et al., 2008). In a recent study, Cholette et al. reported that the
administration of cell salvage salvaged blood, stored at the bedside during 24 hours, significantly reduced the number of red blood cells (RBCs) and coagulant products transfused in neonates and infants undergoing open-heart surgery (Cholette et al., 2013).

**Comparison of data and literature**

Our study follows trends that Golab *et al.* and Cholette *et al.* have described in similar patients. This study adds important information to a necessary but currently inadequate database on the efficacy of CS in pediatric patients undergoing cardiac surgery. This population is at an inherent risk for hemostatic products, yet the most effective methods for blood product restitution are unknown. Our study provides data that will help further knowledge regarding CS utilization. In addition, our study supports the finding reported in the adult population, confirming that if the systematic use of CS to proceed cardiotomy suction during CPB may increase the risk of non-pRBC transfusions, its uses in high risk neonates and children could help decrease the requirement of pRBC without increasing the need for cryoprecipitate and platelets transfusions.

**Limitations**

We performed a retrospective analysis of data collected from a single-centre departmental database and the results can only be applied to our study
population. While strong associations were found between CS utilization and pRBC transfusion rates, the present results should be considered as preliminary and need to be validated in a much larger cohort. In addition, the retrospective nature of this study could not guarantee the absence of bias. In order to decrease this bias as much as possible, we performed univariable and multivariable regression analyses, which are recommended in the case of retrospective design. This study presents data that should be regarded as a segment of a much larger conversation.
CONCLUSION

The use of CS in neonates and children undergoing cardiac surgery with CPB significantly reduced the incidence of allogeneic RBC transfusion. Although the systematic use of CS in adults has been associated with an increased incidence of non-RBC transfusions, the use of CS in a high risk pediatric population (i.e. age < 12 mo, ASA > 3, RACHS > 3) was associated with a 43% reduction of RBC transfusion without an increase in cryoprecipitate and platelet transfusions.

Implications for future research

Future studies will identify other biomarkers that are associated with transfusion. These markers may include neutrophil to lymphocyte ratio or lactate levels, and will be analyzed by reevaluating medical charts. In addition, intraoperative equipment such as mechanical pumps may cause hemolysis with increased flow and may need to be analyzed. Comprehensively evaluating transfusion predictors will better blood management programs for all patients, with a specific emphasis on our study population.

Other studies are required to identify transfusion cost-saving maneuvers. We may obtain resource utilization data from individual hospital bills or the Pediatric Health Information System, an administrative database coordinated through the Children’s Hospital Association that collects information from the
hospital bills from more than 40 children’s hospitals in the United States, to analyze cost differences between allogeneic and autologous transfusions. This financial information will evaluate if CS is financially advantageous.
REFERENCES


DiNardo, JA. (2013). Blood transfusions might be bad for you; that is unless you are bleeding. *Anesthesia & Analgesia*, 116(6), 1201-1203.


Waters, JH. (2004). Indications and contraindications of cell salvage. Transfusion, 44(S2), 40S-44S.


CURRICULUM VITAE

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EDUCATION

Boston University School of Medicine Boston, MA
September 2014-May 2016
Master of Science in Medical Science

Ohio University Athens, OH
January 2011-May 2014
Bachelor of Science in Biological Science
Minor in Spanish

Ohio Northern University Ada, OH
September-December 2010

RESEARCH AND FIELD EXPERIENCE

Boston Children’s Hospital Pediatric Anesthesiology Research Internship
May 2015-Present Mentor: Dr. David Faraoni Boston, MA
- Participate in hematology research as a primary author in the department of pediatric anesthesiology
- Perform as an anesthesia technician with concrete experience in the operating room
- Present at a weekly Grand Rounds

Ohio University Department of Biomedical Sciences
August 2011- May 2014 Mentor: Dr. Nancy Stevens Athens, OH
- Perform group and individual research as a primary author regarding the first record of alestid fishes from the late Oligocene Nsungwe Formation in the Rukwa Rift Basin of Tanzania, Africa
- Utilize specimen-based microscopy, morphometric techniques, and µCT analysis using state-of-the-art equipment
American Museum of Natural History  
*June-August 2013  Mentor: Dr. John Maisey  New York, NY*  
- One of 12 students accepted into the Research Experience for Undergraduate Internship Program in Systematics and Evolutionary Biology, funded by the National Science Foundation  
- Aid in the exploration of relationships between numerous genera in the subclass Elasmobranchii

**WIDECAST: Wider Caribbean Sea Turtle Network**  
*June-July 2012  Limón, Costa Rica*  
- Conduct sea turtle research and conservation efforts in the field as a round-the-clock research assistant  
- Perform nightly surveillance, tissue sampling, and data collection  
- Use Spanish in a natural environment

Ohio University Department of Biological Sciences  
*Dec. 2011- June 2012  Mentor: Dr. Matthew White  Athens, OH*  
- Execute group research regarding gene variation of the lamprey from the Midwestern United States and nautilus from Pacific Ocean sites  
- Master DNA sequencing and amplification using PCR and DNA gel electrophoresis

**ORGANIZATIONS AND INVOLVEMENT**

**Boston Children’s Hospital**  
*Boston, MA*  
- Perform over 100 hours as an anesthesia technician to support members of the anesthesia care team  
- Familiar with the latest anesthesia technology, equipment, and procedures

**O’Bleness Memorial Hospital**  
*Athens, Ohio*  
- Volunteer over 75 hours in the emergency department  
- Tasks include aiding doctors and nurses in daily occurrences, both patient- and resource-centered

**Student Alumni Board**  
*Ohio University, Athens, Ohio*  
- Dedicate over 110 hours as a three-year member of the Alumni Engagement committee  
- Tasks include organizing events, planning workshops, and working with both alumni and students
**Alpha Lambda Delta National Honor Society**  Ohio University, Athens, Ohio

- Co-lead the Ohio University chapter of Alpha Lambda Delta National Honor Society for first year students as the 2011-2012 vice president
- Participate in weekly meetings to supervise and direct the 10-member executive board
- Attend the Alpha Lambda Delta National Leadership Workshop in Charlotte, North Carolina on October 21-23, 2011 as one of two Ohio University students present

**Undergraduate Research Immersion Program**  Ohio University, Athens, OH

- Involved member in both the 2012 and 2013 class

**Nelsonville-York Elementary School**  Nelsonville, OH

- Instruct kindergarten students in Spanish language and culture through comprehension and involvement as a student teacher from March-June, 2012

**PRESENTATIONS AND GRANTS**

- Two-time poster presenter at the Society of Vertebrate Paleontology International Meeting in 2012 and 2013
- Published as a primary author in the Journal of Vertebrate Paleontology regarding alestid fishes from Tanzania
- Presenter of master’s research at the 2016 Congenital Cardiac Anesthesia Society international meeting, the 2016 Society for Pediatric Anesthesiology international meeting, and the 2016 Principles of Pediatric Anesthesia and Critical Care conference
- Presenter of an extended research talk at the 2013 REU Symposium at the American Museum of Natural History
- Two-time presenter at the Ohio University Student Research Expo on April 11, 2013 and April 10, 2014
- Recipient of multi-year grants totaling $1780 to travel and present research from the Ohio University Travel Fund and the Ohio Center for Ecology and Evolutionary Studies Undergraduate Research Award
SKILLS

- Possess a leadership certificate through Ohio University’s 21st Century Leadership Series; mastering topics including ethics and values, emotional intelligence, team development, leadership branding, professionalism, and more

- Conversationally fluent in the Spanish language with a strong background in culture, customs, and history of both Spain and Latin America; have practiced the language long-term in a Spanish speaking country

- Proficient in Avizo, Mimics, and Helicon Focus software, microscopy, CT scanning, PCR, gel electrophoresis, and more