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A structured blood conservation program in pediatric cardiac surgery

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Abstract. – OBJECTIVE: The limitation of alternative transfusion practices in infants increases the benefits of blood conservation. We analyzed the efficacy of a structured program to reduce transfusions and transfusion-associated complications in cardiac surgery

PATIENTS AND METHODS: Our pediatric surgery database was reviewed retrospectively, comparing outcomes from two different time periods, after the implementation of an effective blood conservation program beginning in March 2014. A total of 214 infants (8.1±3.4 months) who underwent biventricular repair utilizing CPB (Group 1 – Blood conservation) were studied in a 12-month period (March 2014-February 2015) after the implementation of the new program, and compared with 250 infants (7.91±3.2 months) (Group 2 – Control-No blood conservation) of the previous 12 – month period (March 2013-February 2014).

RESULTS: The proportion of patients transfused with red blood cells was 75.2% (N=188) in control group and reduced by 16.4% in the study group (58.8% – 126 patients, $p < 0.01$). The mean number of transfusions was 1.25 ± 0.5 units per patient in control group and decreased to 0.7 ± 0.5 units per patient after the start of the program ($p = 0.035$). Cerebral oximetry demonstrated better follow-up during the operative period confirming less hemodilution in Group 1. Respiratory support, inotropic need and ICU stay were significantly better in the study group.

CONCLUSIONS: These findings, in addition to attendant risks and side effects of blood transfusion and the rising cost of safer blood products, justify blood conservation in pediatric cardiac operations. Circuit miniaturization, ultrafiltration, and reduced postoperative bleeding, presumably secondary to higher fibrinogen and other coagulation factor levels, contributed to this outcome.

Key Words:

Are Blood management, Conservation, Consequences, Pediatric, Cardiopulmonary bypass, CPB (set-ups, equipment, Surface coatings, etc.).

Introduction

Surgery for congenital heart defects in pediatric patients undergoing cardiopulmonary bypass (CPB) has induced up to a 300% hemodilutional effect due to circuit prime volumes¹. Condensing surface area and prime volume are especially important in neonatal patients where the volume from the CPB circuit can be the major determinant in the patient's metabolic response to surgery². This is due not only to the profound difference in the patient's size with respect to the CPB prime volume but also from the deleterious effects of CPB on their immature organ function³. Additionally, hemodilution effect due to prime volume can result in multiple blood product exposures, all of which have been shown to further increase the morbidity of CPB^{4,5}. Thus, attempts to condense the circuit prime volume can result in a reduction of exposure to blood products⁶. Despite the recent introduction of a number of technical and pharmacologic blood conservation measures, bleeding and allogeneic transfusion remain persistent problems in open-heart surgical procedures. The use of blood products carries several risks, such as immunologic sensitization, anaphylactic reaction, and disease transmission. The underlying pathophysiology has not been described entirely; however, there is evidence on the activation of inflammatory genes and cytokines in circulating leukocytes with transfusion of red blood cells⁷. Efforts should be made to decrease or completely avoid transfusions to avoid these negative reactions.

In an effort to reduce the negative impact of the CPB on the adult population outcome, the minimized systems were developed to significantly reduce the hemodilution of the patient and reduce the foreign surface area that comes in continuous contact with the patient circulating blood volume. Redu-

cing the size of the perfusion apparatus has two obvious and immediate effects: firstly, a reduction in the contact surface area for potential blood-bio-material contact; secondly, a reduction in priming volume requirement-less hemodilution with a consequential reduction in perioperative hematocrit⁸.

This concept later targeted pediatric population. Smaller, lower prime-volume circuits are now available with low line pressures and excellent reliability and it is now possible to review the basic need for hemodilution and hypothermia⁹. There is wide variation in the prevalence of perioperative transfusions in cardiac surgery. The large differences between institutions cannot be explained just by differences in patient characteristics. Most likely, institutional and individual differences in transfusion practice, guidelines and attitudes influence the frequency and number of transfusions. The decision to transfuse is based on multiple patient factors and it is impossible to designate a single transfusion trigger. The high prevalence initiated a multifactorial blood conservation program with the intention of reducing transfusions without compromising patient safety¹⁰.

The aim of this retrospective study was to evaluate the efficacy of a structured program to reduce transfusions and transfusion-associated complications in pediatric cardiac surgery.

Patients and Methods

After institutional Review Board approval (14/227) in tertiary pediatric cardiac centers, the database was reviewed retrospectively, comparing outcomes from two different one-year periods with and without blood conservation strategy.

A total of 214 infants (8.1±3.4 months) who underwent biventricular repair utilizing cardiopulmonary bypass (CPB) (Group 1 – Blood conservation) were studied in a 12-month period (March 2014-February 2015) after the implementation of the new program, and compared with 250 infants (7.91±3.2 months) (Group 2 – Control-No blood conservation) of the previous 12-month period (March 2013-February 2014). The outcome (dependent variable) was stated as blood transfusion. Independent variables were identified. None of the patients were premature.

Exclusion criteria consisted of known coagulopathy and endocarditis. The remainder of the patients who did not have the exclusion criteria was included in the study.

Pathologies in group 1 were: VSD repair in 88, cavo-pulmonary anastomosis in 46, aortic valvotomy in 17, arterial switch+VSD repair in 9, arterial switch in 44, TAPVR repair in 10 patients. Pathologies in group 2 were: VSD repair in 104, AVSD repair in 5, atrial septectomy+shunt in 16, cavo-pulmonary anastomosis in 95, arterial switch+VSD repair in 8, TAPVR repair in 7, AP window in 9, truncus repair in 3 and Senning operation in 3 patients.

The blood conservation program was designed as follows:

- Education: All the staff involved in the care of the patients, including surgeons, anesthetists, residents, OR-, ICU- and ward nurses, nurse helpers, physiotherapists and perfusionists were educated about the risks and benefits of blood transfusions and the new transfusion guidelines in a 45-min lesson. The lesson was repeated for all new employees.
- Guidelines: we revised our guidelines for transfusions based on the Society of Thoracic Surgeons Guidelines¹¹. In the institutional guidelines, the decision to transfuse red cells perioperatively should be based on clinical judgment of the patient's clinical and hemodynamic status. Patients received red blood cell when a hematocrit level of < 20%, mixed venous oxygen saturation < 60% and regional cerebral oxygenation (rSO₂) < 50%. The final decision to transfuse or not was always at the discretion of the physician responsible.
- Transfusion log: a specific transfusion log was added to the patient records. In this log, all transfusion episodes were registered together with time of transfusion, indication for transfusion, type of blood product, amount (units), patient status including blood pressure, pulse, mixed venous oxygenation, hematocrit levels and the prescribing physician.
- Reduction in IV fluid volume: we initiated a series of measures aimed at reducing hemodilution volume. All sources and volumes of IV fluid were obtained from the medical record.
- CPB Circuit Design: significantly less prime volume via oxygenator with integrated arterial filter, condensed circuit, pole mounted vents, microplegia, ultrafiltration, use of cerebral oxymetry-rSO₂, retrograde autologous priming, vacuum assisted venous drainage and cell salvage of the residual blood from the circuit without treatment

Operative Technique

As a part of the blood conservation program, the bypass circuit was aseptically assembled using

a low-prime integrated oxygenator and reservoir (Terumo Medical Corporation, Ann Arbor, MI, USA) in Group 1 and a Terumo System 1 pump console. All of the roller heads of the pump were remotely mounted to minimize tubing length and circuit surface area. Isothermic blood cardioplegia was administered directly into the aorta at the surgical field using premixed syringes of a 1:4 hyperkalemic solution (1 part blood: 4 parts crystalloid) (Pharmedium, Portland, OR, USA). The static prime volume for the circuit was approximately 220 ml. The pump prime consisted of the following additives:

(Total 95-110 cc): 1 mg/kg (100 unit/kg) heparin, 20 mg/kg cefamezin, 2.5 cc/kg, 20% mannitol, 10 mEq sodium bicarbonate, plasmalyte, red blood cell and fresh frozen plasma estimated at target hematocrit 25-30%.

As part of our previous routine, control group consisted of a conventional oxygenator and reservoir (Sorin, Arvada, CO, USA) that has a static priming volume of 350 cc.

The pump prime for control circuits consisted of the following additives:

(Total 200-215 cc): 1 mg/kg (100 unit/kg) heparin, 20 mg/kg Cefamezin, 2.5 cc/kg, 20% mannitol, 10 mEq sodium bicarbonate, plasmalyte, red blood cell and fresh frozen plasma estimated at target hematocrit 25-30%.

Anticoagulation status was monitored using the Medtronic HMS+ (Medtronic, Minneapolis, MN, USA) system. Samples of blood for measuring activated clotting times (ACT) and heparin concentrations were drawn every 30 minutes on CPB. Adequate anticoagulation was defined as ACT greater than 500 seconds and heparin concentration assays greater than or equal to 3.0 mg/kg, as measured by the HMS+ device. Midazolam, sevoflurane, fentanyl and norcuronium were used as anesthetic agents. After median sternotomy, the patient was systemically anticoagulated using 339 units/kg of intravenous heparin. The pulse pressure was verified, retrograde autologous priming (RAP) was initiated, and approximately 75-85 ml of crystalloid prime was removed. During the RAP sequence, venous cannulas (Edwards Lifesciences, Irvine, CA, USA) were placed in the superior vena cava and inferior vena cava, respectively.

Vacuum-assisted venous drainage was utilized to allow for the use of the smaller venous cannula and venous circuit. Upon initiation of bypass, crystalloid in the venous line was diverted into a collection bag and discarded. Full flow to the

patient was achieved with no hemodynamic instability within five minutes of aortic cannulation.

CPB flow was maintained at 125-150 mL/kg/minute. Moderate hypothermia (28-34°C) and alpha stat blood gas management were used.

After the repair, heart was aggressively de-aired. The aortic cross-clamp was removed and the patient was systemically rewarmed to normothermia. A second blood gas was drawn to ensure proper electrolyte balance prior to termination of CPB support. The resultant hematocrit was around 20%. Continuous ultrafiltration was performed while the patient was on CPB and approximately a total of 80-90 ml of plasma water was removed.

Circuit integrity was maintained until the patient was transported to the pediatric intensive care unit.

Perioperative Follow-up

For each patient, the following factors were evaluated before discharge and documented:

Hemodynamic parameters, perfusion and cross clamp duration, intubation period, postoperative hemorrhage, use of blood (as units) during the hospital stay, use of inotropic support, complications and infection, the duration of ICU stay and hospital stay, perioperative mortality. Comparison between groups was performed retrospectively.

Blood Samples and Assays

Complete blood count [hemoglobin, hematocrit, erythrocyte, white blood cell (WBC) and platelet counts] was recorded. Results of standard blood and urine chemistry were documented. Blood samples were collected in potassium-EDTA (ethylene di-amine-tetra acetic acid) tubes using a radial or femoral artery catheter at the following intervals:

- Baseline: After induction of anesthesia (T1)
- OFF- CPB: 15 min. after reversal with protamine (T2)
- ICU: 24 h postoperatively (T3)

Statistical Analysis

Data was expressed as the mean \pm the standard error of the mean. Analysis of variance for comparison of parameters with a normal distribution and Mann Whitney U test for comparison of parameters without normal distribution were used. Univariate analysis was performed on a large number of preoperative and intraoperative variables in our database to identify those variables that might be associated with allogeneic blood of the variables with a higher *p*-value were retained

for subsequent analysis. They were entered into a stepwise multiple logistic regression analysis to select the ones that were significant independent predictors of the need for transfusion. Data were analyzed using SPSS program (Inc. Chicago, IL, USA). $p < 0.05$ was considered statistically significant.

Results

The time interval between birth and operative repair was not significantly different in both groups. There was not any significant difference with respect to age, gender, height, weight and body surface area between groups.

Preoperative physical and laboratory evaluation revealed no difference among patient groups. List of variables that were screened for possible association with transfusion (dependent variable: transfused allogeneic blood) and significant predictors of allogeneic transfusions was listed in Table I.

There was a significant decrease in transfusions when the program was started. The proportion of patients transfused with red blood cells was 75.2% ($N=188$) in control group and reduced by 16.4% in the study group (58.8% – 126 patients, $p = 0.0089$). The mean number of transfusions was 1.25 ± 0.5 units per patient in control group and decreased to 0.7 ± 0.5 units per patient after the start of the program ($p = 0.035$).

Cerebral oximetry demonstrated significantly better follow-up during the operative period confirming less hemodilution in Group 1. Respiratory support duration, inotropic need and IUCU stay were significantly better in blood conservation group. Perioperative data is summarized in Table II.

No mortality occurred in Group 1; however, two patients needed prolonged respiratory support for pneumonia and one required the implantation of a permanent pacemaker. Mortality was two patients in Group 2 due to pulmonary hypertension. Moreover, two patients in this

group needed prolonged respiratory support for pneumonia and one had a permanent pacemaker implanted.

Discussion

Blood administration is never without the risk for patients. As such, it is desirable to attempt to reduce or eliminate allogeneic blood product transfusions. More families and patients are becoming aware of the long and short-term risks associated with the administration of blood and are asking for bloodless techniques even if it is not a religious preference.

Blood conservation has become popular following STS Guidelines but focused on adult cardiac surgery. Ferraris et al¹² on 2011 update noted the statement “for almost all topics reviewed only evidence relating to adult patients entered into the final recommendations, primarily because of limited availability of high quality evidence relating to pediatric patients having cardiac procedures”. Jonas¹³ later commented by underlining related studies on pediatric population. In 2008 Wypij et al¹⁴ published the combined results of 2 prospective randomized trials of hematocrit levels during CPB in infants. The authors concluded that a hematocrit level of approximately 24% or higher during CPB was associated with higher psychomotor development index scores at 1 year of age and reduced lactate levels intraoperatively. Lower hematocrit levels were also associated with more positive intraoperative fluid balance. These 2 large National Institutes of Health-supported trials also demonstrated that a goal hematocrit level of either 30% or 35% could be achieved during bypass without greater need for transfusion relative to the standard hematocrit level of 20% that was previously applied widely for pediatric CPB before these trials. Circuit miniaturization, ultrafiltration, and reduced postoperative bleeding, presumably secondary to higher fibrinogen and other coagulation factor levels, contributed to this outcome^{14, 15}.

Table I. Significant Predictors of Allogeneic Transfusions.

Risk factors	Odds Ratio	Confidence interval	Multivariate p -value
Lower Body Surface Area	3.160	1.300-10.3	0.006
Lower Preoperative Hematocrit	4.3	1.300-9.500	0.003
Lower Red Blood Cell Mass	1.1	0.950-0.970	0.056
Increased Total Crystalloid Volume	4.1	1.2-12.5	0.035
Conventional Circuit Size	5.8	1.190-20.540	0.021
Increased Postoperative bleeding in 24 h	3.7	1.250-9.150	0.005

Table II. Perioperative evaluation of patients.

	Group 1 (Blood Conservation)	Group 2 (Control)	p
Duration of CPB (min)	120.4±56	122±39	=0.75
Duration of x-clamp (min)	84.4±26	92.2±27	=0.24
rSO ₂ desaturation risk>6000 (yes or no) (%)	15.8±9*	27.8±11	=0.038
t-intub (h)	11.4±7*	19.8±8	=0.041
Postop hemorrhage (mL)	145±50	175±55	=0.16
Blood transfusion (Unit)	0.7±0.5*	1.25±0.5	=0.035
Inotropic support (n)	69(32%)*	149(59.6%)	=0.014
ICU stay (day)	3.2±1.1*	5.9±1.2	=0.045
Hospital stay (day)	10.4±3	15.5±4	=0.055
Mortality (n)	-	2	=0.24

Tx: Transfusion; CPB: Cardiopulmonary bypass; X-clamp: Aortic cross clamp; t-intub: respiratory support time; ICU: Intensive care unit; rSO₂: Regional cerebral O₂ saturation

Ootaki et al¹⁶, in a prospective, non-continuous study of 75 pediatric patients undergoing cardiac surgery using a criteria-driven transfusion protocol, achieved 70% transfusion free procedures. Mean weight of the transfusion free group was 24.6 ± 13.4 kg.

We tried to implement a simple blood conservation program including education, introduction of guidelines, follow-up of transfusions and restrictions on fluid balance. We made every possible effort intraoperatively by using CPB-related techniques to avoid hemodilution.

CPB exerts intended and unintended effects on the enzymatic and formed elements of the coagulation system. Compared with adults, children are at special risk for known, and unknown, differences in their hemostatic systems. Although children have relatively larger circulating blood volumes when compared with adults, their low absolute blood volume accentuates their dilutional coagulopathy. Further, their small blood volume creates practical limitations on the use of certain blood conservation strategies such as autologous donation and cell saver¹⁷.

Changes in oxygenator and CPB pump system design in the last 5 years and their introduction to the clinical arena have enabled significant reductions in priming volume in pediatric bypass circuits. The pediatric population, excluding neonates, provides the challenge of deciding whether a bloodless prime can be used for a specific patient.

One of the greatest benefits of the low prime condensed circuits is in the reduction of CPB prime by eliminating an external arterial line filter and the associated filter bypass loop and extra tubing needed to encompass the use of an arterial

line filter. The elimination of an external arterial filter has not only reduced the overall CPB surface area but has also allowed us to decrease our overall prime volumes. This has been accomplished through a reduction in static prime volume and also by allowing placement of the oxygenator closer to the patient⁶.

Our paper is a retrospective study and this is one of the main limitations of the data. We accept this data as preliminary to build a strategy and started a newer protocol and assessment based on current outcomes obtained from retrospective evaluation.

In our series of blood conservation patients, we were able to achieve 41.2% of them (88/214) transfusion free procedures compared to 24.8 (62/250) in control.

We studied through variables related to preoperative and intraoperative period and demonstrated that the most significant risk factors for transfusion were body surface area (OR: 3.16), preoperative hematocrit (OR: 4.3), red blood cell mass (OR: 1.1), total crystalloid volume (OR: 4.1), conventional circuit (OR: 5.8), postoperative bleeding in 24 h (OR: 3.7). The results of the present study demonstrate that a structured blood conservation program reduces transfusion prevalence and this can be achieved without compromising patient safety.

The large variability in children, cardiac pathology and surgical techniques has made large, randomized, clinical trials hard to conduct and difficult to analyze. Consequently, much practice has evolved from the application of animal data and shared experience. Currently, there is a lack of quality randomized, prospective clinical trials to support evidence-based practice. In order to

continue to improve surgical outcomes, we must continue to ask the correct questions and attempt to answer them with the appropriate researches. Our patient population is small. That may be a reason not to get clear significant differences in most of the clinical parameters.

Conclusions

We may say that there is incomplete evidence regarding to the transfusion decisions during pediatric CPB. Our findings confirm that transfusion of red blood cells during CPB may cause an undesirable clinical outcome. It is clear that blood management with multiple strategies is valid for pediatric population. Hemodilution becomes more important in lower body surface area. We believe novel CPB technologies may be contributory in blood management strategies regarding pediatric patients undergoing open-heart surgery.

Conflict of Interest

The authors declare no conflicts of interest.

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