Children with single-ventricle physiology do not benefit from higher hemoglobin levels post cavopulmonary connection: Results of a prospective, randomized, controlled trial of a restrictive versus liberal red-cell transfusion strategy*

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Objective: **To examine the impact of a restrictive vs. liberal transfusion strategy on arterial lactate and oxygen content differences in children with single-ventricle physiology post cavopulmonary connection. Children with single-ventricle physiology are routinely transfused postoperatively to increase systemic oxygen delivery, and transfusion thresholds in this population have not been studied.**

Design: **Prospective, randomized, controlled, clinical trial.**

Setting: **Pediatric cardiac intensive care unit in a teaching hospital.**

Patients: **Infants and children (n = 60) with variations of single-ventricle physiology presenting for cavopulmonary connection.**

Interventions: **Subjects were randomized to a restrictive (hemoglobin of <9.0 g/dL), or liberal (hemoglobin of ≥13.0 g/dL) transfusion strategy for 48 hrs post operation. Primary outcome measures were mean and peak arterial lactate. Secondary end points were arteriovenous ($C(a\text{-}v)O_2$) and arteriocerebral oxygen content ($C(a\text{-}c)O_2$) differences and clinical outcomes.**

Measurements and Main Results: **A total of 30 children were in each group. There were no significant preoperative differences. Mean hemoglobin in the restrictive and liberal groups were 11 ± 1.3 g/dL and 13.9 ± 0.5 g/dL, respectively ($p < .01$). No differences in mean (1.4 ± 0.5 mmol/L [Restrictive] vs. 1.4 ± 0.4 mmol/L [Liberal]) or peak (3.1 ± 1.5 mmol/L [Restrictive] vs. 3.2 ± 1.3 mmol/L [Liberal]) lactate between groups were found. Mean number of red blood cell transfusions were 0.43 ± 0.6 and 2.1 ± 1.2 ($p < .01$), and donor exposure was 1.2 ± 0.7 and 2.4 ± 1.1 to ($p < .01$), for each group, respectively. No differences were found in $C(a\text{-}v)O_2$, $C(a\text{-}c)O_2$, or clinical outcome measures.**

Conclusion: **Children with single-ventricle physiology do not benefit from a liberal transfusion strategy after cavopulmonary connection. A restrictive red blood cell transfusion strategy decreases the number of transfusions, donor exposures, and potential risks in these children. Larger studies with clinical outcome measures are needed to determine the transfusion threshold for children post cardiac repair or palliation for congenital heart disease. (Pediatr Crit Care Med 2011; 12: 39–45)**

KEY WORDS: lactate; transfusion; hemoglobin; pediatric cardiac surgery; congenital heart disease; cavopulmonary connection

Data regarding the optimal hemoglobin concentration in children with congenital heart disease and in children post cardiac surgical procedures are lacking. Children with cardiac defects are commonly transfused to higher hemoglobin levels to increase their oxygen-carrying capacity, particularly post cardiac surgery and during periods of cardiorespiratory stress (1–3).

Children with complex congenital heart disease often require palliative interventions that maintain intracardiac mixing lesions and cyanosis. Postoperatively, these children are relatively anemic and may have poor cardiac function. Practitioners typically maintain elevated hemoglobin concentrations in these children immediately post palliative procedures for concern that they cannot increase their cardiac output to compensate for low systemic oxygen delivery (2, 3). The risk/benefit ratio of this practice is unknown, and clinical practice varies greatly (4, 5).

Given the cost and risks of blood product administration in critically ill adults (6, 7) and children (8) and the evidence that a restrictive transfusion strategy in critically ill adults (9) and children (10) is well tolerated, it is important to determine whether children with cardiac disease and those undergoing cardiac surgery (specifically for single-ventricle physiology) can tolerate relative anemia. Subgroup analysis (11) of the transfusion requirements in a pediatric intensive care (TRIPICU) study that focused on children post cardiac surgery found no difference in new or progressive multiorgan dysfunction syndrome (primary outcome variable) in the restrictive vs. liberal group; however, patients with cyanotic heart disease and those having palliative interventions (including Bidirectional Glenn [BDG] and Fontan procedures) were excluded.

We hypothesize that a restrictive strategy of RBC transfusion is as effective as,

*See also p. 107.

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and possibly superior to, a liberal transfusion strategy in children with single-ventricle physiology undergoing cavopulmonary connection. Our primary aim is to compare peak and mean arterial lactate in children post cavopulmonary connection randomized to a restrictive vs. liberal transfusion protocol. Our secondary aims are to compare surrogate measures of oxygen delivery, specifically the arteriovenous and arteriocerebral oxygen content differences, and clinical outcomes between transfusion groups.

MATERIALS AND METHODS

Subjects. Infants and children presenting to the University of Rochester Medical Center for elective partial or total cavopulmonary connection (BDG or Fontan procedures) were eligible. Children were excluded only if consent could not be obtained. The protocol was approved by the University of Rochester Medical Center Research Subjects Review Board and registered with ClinicalTrials.gov (NCT00350220). Interim review was performed every 6 months by an independent medical safety monitor.

Subjects were enrolled at their preanesthesia visit. Properly witnessed and documented informed consent was obtained from a parent/guardian. Once enrolled, subjects were divided into those having BDG or Fontan procedures, and block randomization (block size 8) was used to randomize subjects to either the restrictive or liberal transfusion strategy (stratified randomization). The transfusion strategy was initiated on postoperative admission to the pediatric cardiac intensive care unit (PCICU) and continued until 48 hrs from the time of admission after which RBC transfusions were utilized, according to current best practice at University of Rochester Medical Center.

Baseline Assessment. Baseline measures were collected at the time of surgery. Preoperative hemoglobin concentration, partial pressure of oxygen in arterial blood (Pao_2), arterial oxygen saturation (Sao_2), venous oxygen saturation (Svo_2), and regional cerebral oxygen saturation (rSo_2) were collected. Left forehead cerebral oximeters, using the INVOS system (Somanetics Inc., Troy, MI), were utilized for rSo_2 measurements. These data were also collected in the operating room after cardiopulmonary bypass (CPB). Surgical details and intraoperative use of blood products were recorded.

Surgical Procedures. A single surgeon (G.M.A.) performed all surgeries. Cavopulmonary connection was achieved with a BDG or Fontan procedure. In general, BDG was done as part of a staged correction that ultimately would lead to Fontan. The BDG directed superior vena caval blood flow to the confluent pulmonary arteries. The Fontan was an extracardiac, total cavopulmonary connection utilizing a 16–20 mm polytetrafluoroethylene Impra or Gore-Tex conduit (Bard Peripheral Vascular Inc., Tempe, AZ; or W. L. Gore & Associates Inc., Flagstaff, AZ). The extracardiac total cavopulmonary connection included a 4–5 mm fenestration between the polytetrafluoroethylene graft and the lateral wall of the right atrium. CPB was established, using single arterial, bicaval cannulation. All patients were maintained at normothermia. Aortic cross-clamping with global myocardial ischemia was rarely necessary.

The Terumo RX05 oxygenator (Terumo Cardiovascular Systems, Ann Arbor, MI) was used for subjects weighing $\leq$10 kg, and the Terumo RX15 oxygenator was used for subjects weighing $>$10 kg. Red blood cells (RBCs) were used in the CPB prime for infants wighing $<$10 kg. All patients were managed intraoperatively on CPB with unfractionated heparin adjusted according to activated clotting times and reversed with protamine. All patients on CPB received epsilon aminocaproic acid.

Additional RBC, platelets, fresh-frozen plasma, and/or cryoprecipitate were given at the discretion of the cardiac surgeon and anesthesiologist. Central venous and arterial catheters and mediastinal drainage tubes were placed in the operating room. Vasoactive medications (epinephrine and/or dopamine and/or milrinone) were utilized to maintain hemodynamics during transition off CPB at the discretion of the cardiac surgical team. All patients remained intubated and sedated for transfer to the PCICU.

PCICU Procedures. All subjects received current PCICU standard of care aside from their transfusion strategy. Subjects were weaned from mechanical ventilation and extubated as their cardiopulmonary status allowed. Crystalloid and/or 5% albumin were infused in 10–20 mL/kg boluses for clinical findings of hypovolemia and poor cardiac output (i.e., tachycardia, poor pulses and perfusion, low urine output and/or hypotension) as needed to maintain hemodynamic stability. Vasoactive agents were adjusted to maintain hemodynamics and end-organ perfusion. Subjects were transferred to the general inpatient units once they no longer required intensive care.

Transfusion Strategy. The cardiac surgeon, anesthesiologist, perfusionist, and operating room staff were blinded to study assignment. Transfusion of blood products in the operating room, both on and off CPB, proceeded as per standard practice. The study protocol was initiated at the time of PCICU admission.

Liberal Transfusion Group. The liberal transfusion group required 10 mL/kg of RBCs for any hemoglobin of $<$13.0 g/dL regardless of whether there was a clinical indication for transfusion.

Restrictive Transfusion Group. The restrictive transfusion group required 10 mL/kg of RBCs for any hemoglobin of $<$9.0 g/dL accompanied by clinical findings suggestive of symptomatic anemia (i.e., tachycardia and/or hypotension unresponsive to crystalloid or colloid infusion; poor perfusion and/or worsening oxygenation).

Prestorage leukocyte-reduced, irradiated RBC units were used for all transfusions. When possible, RBC units were split to reduce donor exposure. RBC transfusions were typically given rapidly for $\geq$3 hrs at the discretion of the intensivist. RBC transfusions were begun within 1 hr of reaching the hemoglobin threshold. The transfusion protocol was applied for the first 48 hrs of PCICU admission. The protocol could be suspended at the discretion of the cardiac intensivist for hemodynamic instability, refractory hypoxemia, active bleeding, and/or need for surgical intervention. Clinical staff and patient families were aware of transfusion group assignment; the independent data safety monitor was blinded to the assignment.

Transfusion of fresh-frozen plasma, platelets, and/or cryoprecipitate was performed as clinically indicated for both groups. According to our practice, all subjects received aspirin daily beginning on the first postoperative day. In addition, subjects having Fontan procedures were begun on warfarin once patients were tolerating oral medications (goal international normalized ratio, 2–2.5).

Ongoing Measurements. Hemoglobin concentration, Pao_2, Sao_2 Svo_2, rSo_2, mean arterial blood pressure, central venous pressure proximal to the BDG or Fontan, and blood lactate were measured at PCICU admission and every 4 hrs for 48 hrs. Arterial, venous, and cerebral oxygen content (from rSo_2 values) was derived from established formulas and $C(a\text{-}v)o_2$ and $C(a\text{-}c)o_2$ were calculated.

Outcome Measures. Mean and peak arterial lactate level during the initial 48 hrs were the primary outcome measures. Secondary outcomes were the $C(a\text{-}v)o_2$ and $C(a\text{-}c)o_2$ and clinical outcomes (length of mechanical ventilation, length and dose of vasoactive agent administration, PCICU and hospital length of stay, mediastinal tube drainage, and volume of crystalloid and albumin infused during the study period).

Statistical Analysis. Sample size calculations were performed before initiating the study. We defined the two treatments as equivalent if the mean and peak lactate during the study period did not differ by $>$2 mmol/L. Based on our experience, we expected the SD of arterial lactate to be 1.5 mmol/L. We set type I error rate to 0.05. Based on these assumptions, we determined that 29 subjects would be needed per group to have 80% power to reject the null hypothesis.

Primary analysis compared mean and peak arterial lactate levels between each treatment group. Data from each time point for each variable were collated, and the mean, median, and SD values were determined. Comparisons were made, using analysis of variance and Student's *t* tests for normally distributed data. For

data that were not normally distributed (specifically clinical outcome measures), Mann-Whitney tests were performed. A $p < .05$ was considered statistically significant. The z tests of two proportions were calculated to compare proportions; a z score <-2.0 or >2.0 was considered statistically significant.

All subject data were analyzed at study completion in the manner of "intention-to-treat" to ensure proper statistical interpretation of the study results. The statistical package for the social sciences (SPSS) version 17.0 (SPSS Inc., Chicago, IL) was used for all statistical analyses.

RESULTS

From August 2006 to September 2009, 63 children were eligible for study participation. Sixty-two children and families agreed to participate and gave informed consent. Thirty-one subjects were randomized to each group. One subject in each group was unable to have surgery performed and was excluded. One could not be endotracheally intubated secondary to Klipple Feil syndrome, and the other had bleeding complications before going on CPB. Thirty subjects underwent surgery and completed study procedures. No subjects dropped out of the study, and none was lost to follow-up. Adherence to data collection for each study variable was ≥97% with missed data points due to discontinuation of arterial and/or venous access. There was 100% compliance with study procedures; the protocol was never suspended. All transfusions were initiated <60 mins of meeting transfusion criteria.

Thirty-three (55%) subjects underwent BDG, and 27 (45%) underwent the Fontan procedure. Fifty-nine (98.3%) cases were performed on CPB. The one case performed off CPB was a BDG randomized to the liberal group. Mean CPB time was 75 ± 35 mins. No subjects required reexploration for bleeding. There were no significant differences in baseline characteristics between groups, or admission hemoglobin, lactate, and oxygen saturations (Table 1).

Arterial Lactate Levels. Mean (restrictive: 1.4 ± 0.5 mmol/L; liberal: 1.4 ± 0.4 mmol/L) and peak (restrictive: 3.1 ± 1.5 mmol/L; liberal: 3.2 ± 1.3 mmol/L) arterial lactate levels were similar between the two treatment groups (Table 2; Fig. 1).

Oxygen Utilization. $C(a\text{-}v)O_2$ (restrictive: 3.86 ± 1; liberal: 4.15 ± 0.09; $p = .234$) and $C(a\text{-}c)O_2$ (restrictive: 2.77 ± 1.07; liberal: 2.72 ± 0.91; $p = .84$) did not differ between the study groups. Similarly, when the largest differences for each patient over the 48 hrs were compared between groups, no statistically significant differences were found (restrictive: 5.74 ± 1.64; liberal: 6.36 ± 1.42; $p = .119$) and $C(a\text{-}c)O_2$ (restrictive: 4.13 ± 1.4; liberal: 4.42 ± 1.27; $p = .417$). Both analyses showed a nonsignificant trend to a narrower $C(a\text{-}v)O_2$ in restrictive patients (Fig. 2). Table 3 summarizes the data used in these calculations.

RBC Transfusions/Donor Exposures. Mean hemoglobin for the restrictive group was significantly lower (11.1 ± 1.3 g/dL) than that of the liberal group (13.9 ± 0.5 g/dL) ($p < .01$) (Table 2). Patients in the restrictive group received fewer transfusions (0.43 ± 0.6 vs. 2.1 ± 1.2; $p < .001$). Nineteen (63.3%) of 30 restrictive subjects did not require any RBC transfusions; only one (3%) in the liberal group did not receive any RBC transfusion ($z = 4.656$; $p < .01$). Five restrictive group subjects received an RBC transfusion after the 48-hr study pe-

Table 1. Group characteristics

Variable	Restrictive Group (n = 30)	Liberal Group (n = 30)	p and z
Baseline			
Age, mos, range	27 ± 23	32.5 ± 27	$p = .4$
Weight, kg, range	10.9 ± 4.5	12.2 ± 5.7	$p = .36$
Male sex, %	17 (56.6)	17 (56.6)	$z = .261$
Diagnosis (%)			
HLHS	12 (40)	13 (43.3)	$z = .0$
DILV	4 (13.3)	5 (16.6)	$z = .001$
Tricuspid atresia	2 (6.6)	6 (20)	$z = 1.139$
Pulmonary atresia	2 (6.6)	3 (10)	$z = .0$
DORV	3 (10)	1 (3.3)	$z = .518$
Ebstein's anomaly	1 (3.3)	0	$z = -.001$
Unbalanced AVSD	4 (13.3)	1 (3.3)	$z = .934$
Hypo RV variant	2 (6.6)	1 (3.3)	$z = .001$
Surgery (%)			
Bidirectional Glenn	16 (53.3)	17 (56.6)	$z = .001$
Fontan	14 (46.6)	13 (43.3)	$z = .001$
CPB	30 (100)	29 (96.6)	$z = -.01$
CPB duration (mins)	79 ± 39.5	71 ± 31	$p = .39$
Ao. X-clamp (Fontan)	9 (64)	6 (46)	$z = .56$
RBC prime	16 (53.3)	18 (60)	$z = .261$
Preop			
Hemoglobin, g/dL	14.6 ± 1.8	14.6 ± 1.7	$p = .93$
Sao_2, %	84 ± 9.9	85 ± 8.3	$p = .59$
Svo_2, %	66 ± 9.9	63 ± 13.2	$p = .34$
rSo_2, %	74 ± 11.4	69 ± 13.9	$p = .21$
Pao_2, mm Hg	61.4 ± 14.8	75.5 ± 49	$p = .14$
After CPB:			
Hemoglobin, g/dL	11.8 ± 1.3	12.4 ± 1.7	$p = .14$
Sao_2, %	88 ± 10.7	88 ± 8.0	$p = .89$
Svo_2, %	62 ± 8.3	66 ± 11.3	$p = .34$
rSo_2, %	71 ± 13.2	70 ± 16.1	$p = .2$
Pao_2, mm Hg	101 ± 72.3	97.5 ± 85.4	$p = .14$
Surgery duration, hr	4.4 ± 1.3	4.3 ± 0.8	$p = .78$
On PCICU Admission			
Lactate, mmol/L	2.3 ± 1.3	2.4 ± 1.2	$p = .61$
Hemoglobin, g/dl	12.1 ± 1.3	12 ± 11.4	$p = .99$
Sao_2, %	88 ± 7.9	89 ± 6.6	$p = .67$
Svo_2, %	66 ± 12.5	67 ± 11.3	$p = .89$
rSo_2, %	71 ± 13.4	71 ± 14.4	$p = .89$
Pao_2, mm Hg	76.6 ± 43.6	80.2 ± 45.3	$p = .75$
MAP, mm Hg	63 ± 9.9	63 ± 11.6	$p = .87$
CVP,[a] mm Hg	12 ± 3.1	14 ± 5.6	$p = .11$

HLHS, hypoplastic left heart syndrome; DILV, double inlet left ventricle; DORV, double outlet right ventricle; AVSD, atrioventricular septal defect; Hypo RV, hypoplastic right ventricle; CPB, cardiopulmonary bypass; Ao. X-clamp, aortic cross clamp; RBC, red blood cell; Sao_2, arterial oxygen saturation; Svo_2, venous oxygen saturation; rSo_2, regional cerebral saturation; Pao_2, partial pressure of oxygen in arterial blood; PCICU, pediatric cardiac intensive care unit; MAP, mean arterial pressure; CVP, central venous pressure (Fontan or Glenn pressure).

[a]Fontan or Bidirectional Glenn pressure. The t tests were performed for normally distributed continuous variables. The z tests for two proportions were utilized with 95% confidence interval, two-tailed.

Table 2. Between-group comparisons of laboratory and clinical outcomes

Variable	Restrictive Strategy (n = 30)	Liberal Strategy (n = 30)	*p*
Peak lactate, mmol/L	3.1 ± 1.5	3.2 ± 1.3	.85
Mean lactate, mmol/L	1.4 ± 0.5	1.4 ± 0.4	.99
Mean hemoglobin, g/dL	11.1 ± 1.3	13.9 ± 0.5	<.01
No. RBC transfusions	0.43 ± 0.6	2.1 ± 1.2	<.01
No. FFP transfusions	1	0	.193
No. Plt or cryo transfusions	0	0	1.0
No. exposures, OR + PCICU	1.2 ± 0.7	2.4 ± 1.1	<.01
MAP, mm Hg	68 ± 7.2	74 ± 8.2	<.01
CVP,[a] mm Hg	14 ± 3.8	14 ± 4.1	.986
MT drainage POD 0, mL/kg/hr	1.5 ± 1.3	1.7 ± 1.4	.65
MT drainage POD 1, mL/kg/hr	1.3 ± 1.8	1.5 ± 2.1	.64
MT drainage POD 2, mL/kg/hr	1.2 ± 1.3	1.4 ± 2.2	.60
Normal saline, mL/kg	9.5 (0–186)	0 (0–218)	$z = -1.79$; $p = .07$
Albumin, mL/kg	0 (0–234)	0 (0–503)	$z = -.06$; $p = .94$
Mechanical ventilation, hrs	23 (5–625)	20 (4–216)	$z = -1.05$; $p = .29$
Inotropic/pressor support, days	3.25 (1–27)	3.0 (1.5–9)	$z = -.11$; $p = .91$
PCICU admission, days	6.6 ± 6.4	5.4 ± 3.3	.365
Hospital admission, days	11 (4–78)	9.5 (5–62)	$z = -.84$; $p = .39$
Survived to discharge	30 (100%)	29 (96%)	$z = -.01$

RBC, red blood cell; FFP, fresh frozen plasma; Plt, platelet; Cryo, cryoprecipitate; OR, operating room; PCICU, pediatric cardiac intensive care unit; MAP, mean arterial pressure; CVP, central venous pressure; MT, mediastinal tube; POD, postoperative day.

[a]Fontan or Bidirectional Glenn procedures. Data are represented as mean (SD), median (range), or number(%). The *t* tests were performed for all normally distributed continuous variables. The *z* test of proportions was performed to compare survival. Mann-Whitney tests were performed for data that were not normally distributed.

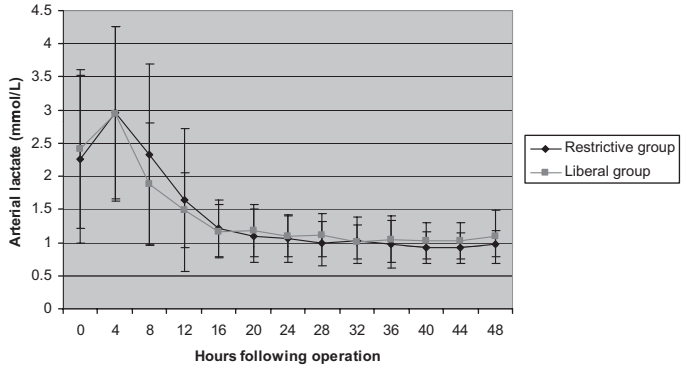

Figure 1. Change in arterial lactate over time.

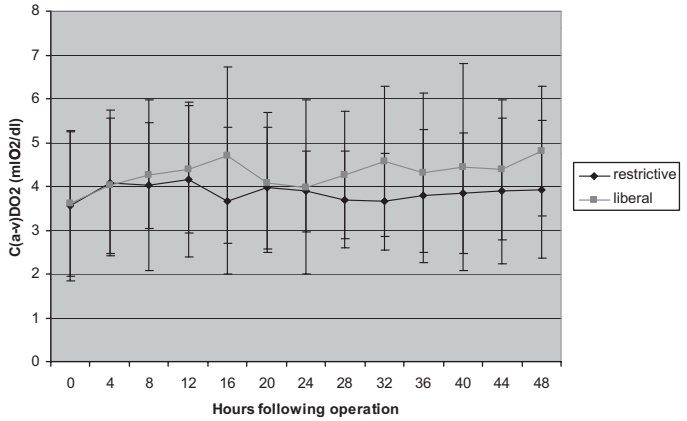

Figure 2. Change in arteriovenous oxygen content difference [$C(a - v)O_2$] over time.

riod and before hospital discharge, compared with three liberal group subjects. There was no substantial difference in the results when these five subjects were removed from analysis.

Twenty-nine (96.6%) restrictive subjects at one time point had a measured hemoglobin of <13.0 g/dL and would have received at least one additional RBC transfusion had they been assigned to the liberal group. The mean number of donor exposures (including RBCs given in the OR) was different between groups (restrictive: 1.2 ± 0.7; liberal: 2.4 ± 1.1, $p < .01$).

Clinical Outcomes. Although not powered to test for statistical differences, mortality, PCICU and hospital length of stay, duration of mechanical ventilation, dose and duration of inotropic support, total colloid infusion, coagulant product infusions, and total mediastinal tube drainage were similar between subject groups. There was a trend toward increased crystalloid infusion in the restrictive group (27.1 mL/kg vs. 14.6 mL/kg; $p = .07$) (Table 2). One subject in the liberal transfusion strategy died on postoperative day 39 from *staphylococcal* sepsis. No restrictive strategy subjects died.

Subgroup Analysis of BDG and Fontan Subjects. Although not powered to test for statistical differences, subgroup analysis of BDG and Fontan subjects revealed similar results (Table 4). Peak and mean arterial lactate and mean $C(a\text{-}c)O_2$ did not differ between study groups for subjects specifically receiving BDG or Fontan procedures. In BDG subjects, mean $C(a\text{-}v)O_2$ was significantly lower in the restrictive group (restrictive: 3.6 ± 0.5; liberal: 4.2 ± 0.9; $p = .04$). These results were not duplicated in Fontan subjects (restrictive: 4.2 ± 1.3; liberal: 4.1 ± 0.9; $p = .89$).

DISCUSSION

Despite their uniquely compromised physiology, children with single-ventricle physiology and lower hemoglobin concentrations were able to maintain adequate tissue oxygen delivery post cavopulmonary connection and did not seem to benefit from a liberal transfusion strategy. Mean and peak arterial lactate levels were similar in children managed with a restrictive and liberal transfusion strategy. The adverse effects of RBC transfusions are well described (12–14), and those subjects maintained at higher hemoglobin concentrations received greater numbers of RBC transfusions, do-

Table 3. Between group comparisons of oxygen utilization

Variable	Restrictive Strategy (n = 30)	Liberal Strategy (n = 30)	p
Sa_{O_2}, %	83 ± 5.8	85 ± 5.2	.23
Sv_{O_2}, %	57 ± 6.4	62 ± 6.6	.003
rS_{O_2}, %	64 ± 8.0	69 ± 8.3	.01
Pa_{O_2}, mm Hg	55 ± 12.6	59 ± 13.2	.268
$C(a\text{-}v)O_2$, mL_{O_2}/dL	3.86 ± 1.00	4.15 ± 0.09	.234
$C(a\text{-}c)O_2$, mL_{O_2}/dL	2.77 ± 1.07	2.72 ± 0.91	.84
O_2 extraction, %	0.31 ± 0.07	0.26 ± 0.06	.013
Largest $C(a\text{-}v)O_2$, mL_{O_2}/dL	5.74 ± 1.64	6.36 ± 1.42	.119
Largest $C(a\text{-}c)O_2$, mL_{O_2}/dL	4.13 ± 1.4	4.42 ± 1.27	.417

Sa_{O_2}, arterial oxygen saturation; Sv_{O_2}, venous oxygen saturation; rS_{O_2}, regional cerebral oxygen saturation; Pa_{O_2}, partial pressure of oxygen in arterial blood; $C(a\text{-}v)O_2$, arteriovenous oxygen content difference; $C(a\text{-}c)O_2$, arteriocerebral oxygen content difference.

Data are represented as mean (SD) or number (%). The *t* tests were performed for all normally distributed continuous variables. The *z* test of proportion was performed to compare percentages between groups.

Table 4. Subgroup analysis of Bidirectional Glenn and Fontan subjects

	BDG			Fontan		
	Restrictive (n = 16)	Liberal (n = 17)	p	Restrictive (n = 14)	Liberal (n = 13)	p
Initial Hb, g/dL	11.5 ± 1.0	11.4 ± 0.9	.68	12.8 ± 1.3	13.0 ± 1.3	.58
Mean Hb, g/dL	10.6 ± 1.0	13.7 ± 0.5	<.01	11.7 ± 1.3	14.0 ± 0.5	<.01
Mean lactate, mmol/L	1.1 ± 0.2	1.1 ± 0.2	.28	1.8 ± 0.4	1.8 ± 0.3	.73
Peak lactate, mmol/L	2.1 ± 0.6	2.3 ± 0.9	.34	4.3 ± 1.4	4.3 ± 0.7	.97
Mean Sa_{O_2}, %	80 ± 2.8	82 ± 3.3	.11	86 ± 6.8	88 ± 5.3	.38
Mean Sv_{O_2}, %	55 ± 5.9	58 ± 5.6	.04	59 ± 6.0	66 ± 5.6	.007
Mean rS_{O_2}, %	61 ± 8.0	66 ± 7.5	.09	67 ± 6.9	74 ± 6.7	.01
RBC transfusions	0.50 ± 0.5	2.4 ± 0.8	<.01	0.36 ± 0.7	1.62 ± 1.4	.008
Donor exposures[a]	1.4 ± 0.5	2.8 ± 0.9	<.01	0.9 ± 0.9	1.8 ± 1.0	.024
$C(a\text{-}v)O_2$, mL_{O_2}/dL	3.6 ± 0.5	4.2 ± 0.9	.04	4.2 ± 1.3	4.1 ± 0.9	.89
Largest $C(a\text{-}v)O_2$, mL_{O_2}/dL	5.2 ± 0.9	6.4 ± 1.4	.12	6.3 ± 2.0	6.4 ± 1.5	.93
$C(a\text{-}c)O_2$, mL_{O_2}/dL	2.6 ± 0.9	2.9 ± 1.0	.46	2.9 ± 1.2	2.5 ± 0.7	.27
Largest $C(a\text{-}c)O_2$, mL_{O_2}/dL	3.9 ± 1.4	4.7 ± 1.4	.12	4.3 ± 2.5	4.0 ± 1.0	.54
O_2 extraction, %	0.32 ± 0.06	0.28 ± 0.06	.09	0.29 ± 0.08	0.24 ± 0.05	.056

BDG, Bidirectional Glenn procedure; Hb, hemoglobin; Sa_{O_2}, arterial oxygen saturation; Sv_{O_2}, venous oxygen saturation; rS_{O_2}, regional cerebral oxygen saturation; RBC, red blood cell; $C(a\text{-}v)O_2$, arteriovenous oxygen content difference; $C(a\text{-}c)O_2$, arteriocerebral oxygen content difference.

[a]Includes transfusions in the operating room and pediatric cardiac intensive care unit. Data are presented as mean ± SD. Independent samples *t* tests were used to compare groups.

nor exposures, and risk of RBC transfusions without apparent clinical benefit.

Peak and mean arterial lactate were selected as primary outcome measures as use of a primary clinical outcome measure (such as illness severity scores) would be less sensitive to subtle changes and require subject numbers that would necessitate multicentered participation. Lactate was chosen as it is an easily available, objective, and reliable marker of illness severity, indicating circulatory compromise and inadequate oxygen delivery and/or utilization (15–18). Serial lactate levels have been found to correlate with morbidity and mortality post pediatric cardiac surgery (19–24). The mean arterial lactate level over 48 hrs represented a rough summation of hemodynamics during the period, whereas the peak level represented the worst hemodynamics of the period. Venous and regional oxygen saturations were collected to serve as surrogate measures of oxygen delivery and to generate $C(a\text{-}v)O_2$ and $C(a\text{-}c)O_2$ differences as indices of cardiac output and cerebral blood flow.

Measures of Sv_{O_2} and rS_{O_2} were lower in the restrictive group, and although statistically significant, it is unclear whether these differences are clinically important. Additional studies with larger subject numbers and long-term follow-up data that explore for an association between hemoglobin, venous and cerebral oxygen saturations, and neurodevelopmental outcomes are warranted. In the restrictive group, Ca_{O_2}, Cv_{O_2}, and Cc_{O_2} were lower as a consequence of lower hemoglobin concentrations, but significant increases in $C(a\text{-}v)O_2$ and $C(a\text{-}c)O_2$ were not found. When combined with stable blood lactate levels, this suggests that children in the restrictive group were not disadvantaged by their lower Ca_{O_2}, and were able to maintain adequate tissue oxygen delivery and utilization.

This study did not specifically examine the effect of hemoglobin on systemic and pulmonary vascular resistance. Data regarding heart rate, urine output, capillary refill, and perfusion would provide additional information regarding the hemodynamics of each subject. As this population is dependent on low pulmonary vascular resistance for pulmonary blood flow, the effect of the hemoglobin level on pulmonary vascular resistance would be interesting to compare. It is unlikely that the liberal group had a clinically relevant elevation in their pulmonary vascular resistance from higher hemoglobin levels, as they did not demonstrate significantly lower Sa_{O_2} or Pa_{O_2} levels.

There was a numeric but not statistically significant increase in length of mechanical ventilation, duration and degree of inotropic support, and length of stay in the restrictive group. As this study was not powered to assess for clinical outcome differences, it is possible that, with larger subject numbers, these differences would become significant. The restrictive group did receive larger volumes of crystalloid infusion compared with the liberal group, which potentially contributed to increased pulmonary edema and duration of mechanical ventilation.

This is the only randomized controlled trial to examine the postoperative transfusion threshold in children with single-ventricle physiology undergoing surgical palliation. There was no selection bias as all subjects presenting for cavopulmonary connection were considered eligible, and 98% of eligible subjects were included. As the exclusion criteria consisted only of inability to obtain consent, no complicating or preexisting clinical condition prevented study participation. As the research protocol was initiated immediately at the time of admission to the PCICU, there was no requirement for patient "stabilization"; therefore, the most severely ill or compromised subjects were included. Study findings are further sup-

ported by the fact that there were no protocol violations, there was 100% adherence to the transfusion strategy, and no subjects were lost to follow-up.

Strengths of the study design include the focus on the immediate postoperative period where the potential for low cardiac output syndrome and bleeding complications is the highest, and when RBC transfusions are most likely to be administered. The one other study to examine transfusion thresholds post pediatric cardiac surgery (the TRIPICU subgroup analysis) included subjects within 7 days after pediatric intensive care unit admission (presumably up to 7 days post operation), possibly outside the period of greatest risk for hemodynamic compromise, bleeding, and need for RBC transfusion (20). An additional strength of this study is the frequency at which data were obtained. Hemoglobin concentration was measured every 4 hrs, and all transfusions were initiated within an hour of reaching the transfusion threshold, thus ensuring that liberal group subjects were maintained consistently over the hemoglobin threshold of 13 g/dL.

The major limitation of this study is that the difference in mean hemoglobin between the two treatment groups was not larger. Subjects were admitted to the PCICU with a mean hemoglobin of 12 g/dL, and in the absence of significant bleeding, many restrictive group subjects maintained their hemoglobin well >9 g/dL, decreasing the between-group difference. However, the aim of this study was to test a transfusion strategy, not an intervention, as demonstrated by the fact that several subjects in each group did not receive any RBCs because they did not meet the threshold for transfusion. When this study was designed, the research subject review board would not permit decreasing the transfusion threshold limit further for the restrictive group, but in light of these results, future studies with a lower hemoglobin threshold should be performed.

Although results more distant from surgery would add valuable data, the 48-hr postoperative study period was selected as this is when patients are at greatest risk for low cardiac output states and when RBCs are most commonly transfused. Obtaining study measures further out would require prolonging indwelling catheters for access (limiting patient mobility and increasing risk of catheter-related thrombosis) or using needle-sticks, and the additional blood sampling might lead to larger phlebotomy losses that would affect hemoglobin values. Furthermore, postoperatively patients typically raise their hemoglobin concentration over several weeks to months, especially in the presence of cyanosis. Therefore, hemoglobin differences between groups would lessen over time until the two groups would not be significantly different and, thus, not allow for between-group comparison.

This study would have been stronger had it been powered to assess BDG and Fontan subjects separately, as significant differences in postoperative physiology exist for each procedure. Children with variations of single-ventricle physiology were chosen as they are cyanotic on presentation and have the unique limitation in their ability to increase their cardiac output and oxygen delivery. Because subject numbers are limited, all patients with single-ventricle physiology undergoing cavopulmonary connection were included. Future studies with larger subject numbers would allow each group to be analyzed separately. This study would be of greater interest if it included neonates with single-ventricle physiology undergoing initial palliation, as these subjects have a greater degree of cyanosis and pulmonary vascular reactivity. In light of our results,we are initiating a prospective randomized trial comparing transfusion thresholds in neonates with single-ventricle physiology undergoing first stage surgical palliation.

Had study measures been followed longer or more subjects studied, additional clinical outcomes measures (e.g., sepsis, mediastinitis, thrombosis) would have been interesting to compare. Testing of cognitive and behavioral development and function at distant time points could provide documentation of longer-term neurodevelopmental outcomes and might add important information. Future studies, including markers of inflammation, could add valuable information regarding each subject's degree of inflammation and immunomodulation in response to blood transfusions.

CONCLUSIONS

It seems that a lower hemoglobin level can be maintained in children with single-ventricle physiology post cavopulmonary connection without effecting arterial lactate levels, measurable end points of tissue oxygenation, and/or clinical outcomes. These results strongly suggest that the practice of aggressively maintaining high hemoglobin concentrations postoperatively in children with single-ventricle physiology post cavopulmonary connection be reexamined. Achieving this unproven therapeutic goal comes at the cost of increased transfusions without proven benefits. Larger studies utilizing clinical outcome measures might reflect improved outcomes in subjects managed with a restrictive RBC transfusion strategy. These results might be extrapolated to neonates and other children with complex congenital heart disease who undergo palliative procedures. Further work is necessary to explore whether our results can be generalized to these populations.

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