A randomized controlled pilot study of adherence to transfusion strategies in cardiac surgery

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BACKGROUND: It is important to determine the optimal hemoglobin (Hb) concentration for red blood cell (RBC) transfusion for patients undergoing cardiac surgery because increased mortality has been associated with the severity of anemia and exposure to RBCs. Because a definitive trial will require thousands of patients, and because there is variability in transfusion practices, a pilot study was undertaken to determine adherence to proposed strategies.

STUDY DESIGN AND METHODS: A single-center parallel randomized controlled pilot trial was conducted in high-risk cardiac patients to assess adherence to two transfusion strategies. Fifty patients were randomly assigned either to a "restrictive" transfusion strategy (RBCs if their Hb concentration was 70 g/L or less intraoperatively during cardiopulmonary bypass [CPB] and 75 g/L or less postoperatively) or a "liberal" transfusion strategy (RBCs if their Hb concentration was 95 g/L or less during CPB and less than 100 g/L postoperatively).

RESULTS: The percentage of adherence overall was 84% in the restrictive arm and 41% in the liberal arm. Twenty-two (88%) patients were transfused 99 units of RBCs in the liberal group compared to 13 patients who were transfused 50 units in the restrictive group ($p < 0.01$). There were no significant differences in individual adverse outcomes; however, more adverse events occurred in the restrictive group (38 vs. 15, $p < 0.01$).

CONCLUSION: Adherence to the evaluated interventions is vital to all randomized controlled trials as it has the potential to affect outcomes. Further pilot studies are required to optimize enrollment and transfusion adherence before a definitive study is conducted.

Red blood cell (RBC) transfusion rates are high in cardiac surgery, in part due to the question of whether these patients require a higher transfusion threshold. However, there is little direct evidence to support this assumption. To date no randomized controlled trial has assessed the optimal transfusion threshold or determined the crossover point at which the risk of acute anemia exceeds that of RBC transfusion in cardiac surgical patients.

In a retrospective study of seven Canadian centers, which included 11,812 cardiac surgical patients,[1] 44% of patients received one or more RBC units, and the range of patients transfused was 28% to 60%. In a recent study in

ABBREVIATIONS: CARE = Cardiac Anesthesia Risk Score; CPB = cardiopulmonary bypass; IQR = interquartile range; TRACS = Transfusion Requirements after Cardiac Surgery.

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the United States, in 100, 000 patients undergoing primary elective coronary artery bypass graft surgery (CABG) the frequency of RBC transfusion rates ranged from 7.8% to 92.8%.[2] Because morbidity and mortality may be dependent on the severity of anemia and exposure to transfusions,[3-8] it is essential to determine the optimal threshold hemoglobin (Hb) concentration at which physicians should be transfusing these patients, to reduce morbidity and mortality. This is particularly important because the efficacy of liberal transfusion has not been established in cardiac surgical patients and RBC transfusion has been associated with an increased risk of renal failure (odds ratio [OR], 2.1; 95% confidence interval [CI], 1.9-2.3), cardiac complications (OR, 1.6; 95% CI, 1.5-1.6), neurologic events (OR, 1.4; 95% CI, 1.3-1.4), and mortality (OR, 1.8; 95% CI, 1.7-1.9).[8]

Despite the large number of published clinical studies which have attempted to determine the optimal Hb concentration at which to transfuse cardiac surgical patients, no clear consensus has emerged to guide clinical practice. Retrospective analyses have demonstrated increased morbidity and mortality near preoperative Hb values less than 120 g/L[5,9] and at intraoperative Hb values ranging from 50 to 80 g/L.[10,11] Furthermore, patients having cardiovascular surgery with postoperative hematocrit (Hct) values of 34% (Hb concentrations of 110 g/L) or higher appeared to have an increase in morbidity.[12] The OR for myocardial infarction for the group with a Hct of 34% or higher was 2.2 (95% CI, 1.04-4.76) compared to the group with a Hct of 24% or less.[12] Yet, low Hb concentrations have also been associated with adverse outcomes. Of 27 patients undergoing infrainguinal arterial bypass surgery,[13] six patients who had symptomatic cardiac events had a Hct level below 28% (a Hb concentration of approximately 93 g/L).

Because there is a wide range of Hb concentrations for transfusion, and because anemia and transfusions are independently associated with morbidity and mortality, a definitive study is needed to determine the effect of anemia. However, barriers to recruitment and adherence need to be identified so they can be addressed before a larger definitive study.[14] Clinical uncertainty resulting from 1) apprehension about transfusion, 2) concern that the transfusion thresholds are not consistent with clinical practice, 3) not knowing which treatment is best, and 4) the concern that the doctor–patient relationship could be adversely affected by trial participation have been shown to be deterrents in previous randomized controlled trials.[15,16] Therefore, a pilot study is required to determine the acceptability and feasibility of the transfusion strategies by physicians and patients because it is anticipated that enrollment and adherence will be low. The objective of this study was to determine enrollment and adherence with a protocol for Hb transfusion strategies in patients having cardiac surgery.

MATERIALS AND METHODS

Study design

A single-center open-labeled parallel randomized controlled pilot trial of two transfusion strategies in patients having elective cardiac surgery was conducted to determine enrollment and adherence to Hb concentrations used for transfusion triggers. The randomization sequence was created using permuted blocks of four stratified by age and the Cardiac Anesthesia Risk Score (CARE) score.[17] Opaque sequential sealed envelopes were used and opened at the start of surgery. The allocation sequence was generated by an independent statistician at the Ottawa Methods Centre of the Ottawa Hospital Research Institute. The research coordinator enrolled participants and assigned participants to the transfusion strategies. The study was approved by the research ethics board at St Michael's Hospital and written informed consent was obtained from all patients before randomization.

Eligible participants were identified in the preoperative clinic or hospital ward at St Michael's Hospital (Toronto, Ontario, Canada) from 2007 to 2010. St Michael's Hospital is a university-affiliated tertiary care center with approximately 1000 cardiac surgeries conducted yearly.

Patients were allocated to one of two transfusion strategies. Patients allocated to a "restrictive" transfusion strategy received RBC transfusions if their Hb was 70 g/L or less during cardiopulmonary bypass (CPB) and 75 g/L or less postoperatively after bypass. Patients allocated to a "liberal" transfusion strategy received RBC transfusions if their Hb concentration was 95 g/L or less during and less than 100 g/L after bypass. A lower Hb concentration for transfusion was used during CPB because metabolic demands are reduced during anesthesia and CPB. When a threshold was reached, each group was to receive 1 unit of RBCs administered at a time followed by determination of the Hb concentration. The transfusion protocols were to be adhered to from beginning of surgery until discharge from hospital. Patients who had rapid blood loss were transfused at the discretion of the attending physician. All other aspects of patient care were left to the discretion of the attending physicians.

All outcomes were prespecified. The primary objective was to assess the enrollment rate and overall adherence to the transfusion strategies. We defined successful adherence as adherence to the transfusion strategies in 90% of patients in more than 90% of their days in hospital. Adherence was defined as transfusion of RBCs according to the Hb threshold.

Secondary outcomes included RBC transfusions, clinical outcomes, and physiologic indicators of hypoxemia (mixed venous oxygen saturation). Clinical outcomes were defined as 1) in-hospital all-cause mortality;

2) a composite score of morbidity consisting of a) neurologic events defined as a new focal neurologic deficit lasting more than 24 hours or irreversible encephalopathy, b) dialysis-dependent renal failure or greater than 50% increase in creatinine, c) prolonged low cardiac output state (i.e., need for two or more inotropes for 24 hours or more, intraaortic balloon pump or ventricular assist device for greater than 48 h), and/or myocardial infarction, defined as troponin I level greater than 2.5 μg/L and new Q waves on electrocardiogram or a clinical diagnosis; and 3) hospital lengths of stay. We assembled an independent data safety monitoring board consisting of a cardiac anesthesiologist and a hematologist who reviewed the data after 20 patients were recruited.

Study population

Eligible participants were adults patients undergoing cardiac surgery with a CARE score (a score for cardiac surgery patients used to predict morbidity and mortality) of 3 or 4,[17] or patients of advanced age defined as greater than or equal to 80 years on the day of screening were included. A CARE score of 3 is defined as patients with uncontrolled medical problems such as unstable angina treated with intravenous heparin or nitroglycerin, use of a preoperative intraaortic balloon pump, heart failure with pulmonary or peripheral edema, uncontrolled hypertension, renal insufficiency (creatinine level greater than 140 μmol/L), debilitating systemic diseases, or patients in whom a complex surgery is undertaken (i.e., reoperation, combined valve and coronary artery surgery, multiple valve surgery, left ventricular aneurysmectomy, repair of ventricular septal defect after myocardial infarction, or CABG of diffuse or heavily calcified vessels). A CARE score of 4 is defined as patients with any uncontrolled medical problem and in whom a complex surgery is undertaken.[17] These patients were selected as transfusion rates in these individuals are high (e.g., reoperation, combined valve and coronary artery surgery,[18-20] renal insufficiency[18,21,22]). Patients were excluded if they refused participation, were unable to receive or refused blood products, or were involved in the autologous predonation program.

Anesthesia and surgical management

All patients remained on their preoperative medications as directed until the surgical date. Patients were anesthetized using a narcotic (1-2 μg/kg sufentanil or 10-20 μg/kg fentanyl), a benzodiazepine (0.1-0.15 mg/kg midazolam), 0.2% to 1.5% isoflurane, and/or 50-100 μg/kg/min propofol, with muscle relaxation provided from 0.6 to 1.0 mg/kg rocuronium or 0.15 mg/kg pancuronium. Heparin was given to maintain an activated clotting time of more than 420 seconds during CPB. Bypass management included nonpulsatile pump flow of 2.4 × body surface area, mean arterial pressure 55 to 85 mmHg, temperature 33 to 35°C, and blood sugar 4 to 10 mmol/L. Myocardial protection was achieved with cold blood crystalloid cardioplegia, and a "hot-shot" (250 to 500 mL) was delivered just before the removal of the aortic cross-clamp. After separation from CPB, heparin was reversed with protamine (approx. 10 mg/1000 units of heparin) to normalize the activated clotting time. Postoperatively, patients were managed in a specialized cardiovascular intensive care unit with standardized protocols for early extubation (2-4 hr). Intraoperative use of antifibrinolytic agents and cell salvage are routinely used at the study site and were used at the discretion of the surgical team.

Statistical analysis

Continuous variables were described as mean (standard deviation [SD]) or medians (with interquartile range [IQR]) if the data were not normally distributed. Categorical variables were described as numbers and percentages. We analyzed adherence rates and also examined the effect of the transfusion strategies on the clinical outcomes using univariate analysis, t test, and Mann-Whitney U test for continuous variables and chi-square test for categorical variables (or the Fisher's exact test if the expected number in any cell was less than 5). The significance level was set at a p value of less than 0.05 for all statistical analyses. All analyses were conducted on an intent-to-treat basis.

A total sample size of 50 patients was estimated to produce a 97.5% CI equal to the sample adherence prevalence plus or minus 8% when the true prevalence of adherence was hypothesized to be 90%. Therefore, 25 patients were randomized to the restrictive group and 25 patients were randomized to the liberal group. We estimated our sample size using computer software (PASS 2002, NCSS, Kaysville, UT).

RESULTS

A flow diagram for the 50 patients recruited in this study demonstrated that a high percentage of individuals were not eligible and a considerable proportion declined participation in the study (Fig. 1). Enrollment rate was less than 1%.

The characteristics of the patients according to allocation group are listed in Table 1. There were no significant differences between the groups with regard to age, height, weight, and comorbid illnesses. Intraoperatively, the duration of CPB and cross-clamping were similar for both groups as were the volume of estimated intraoperative blood loss and the number of attempts to separate from CPB. Seventy-two percent of patients in the restrictive group and 68% of patients in the liberal group were using antiplatelet (PLT) medications before surgery. Anti-PLT medications tended to be discontinued earlier in the

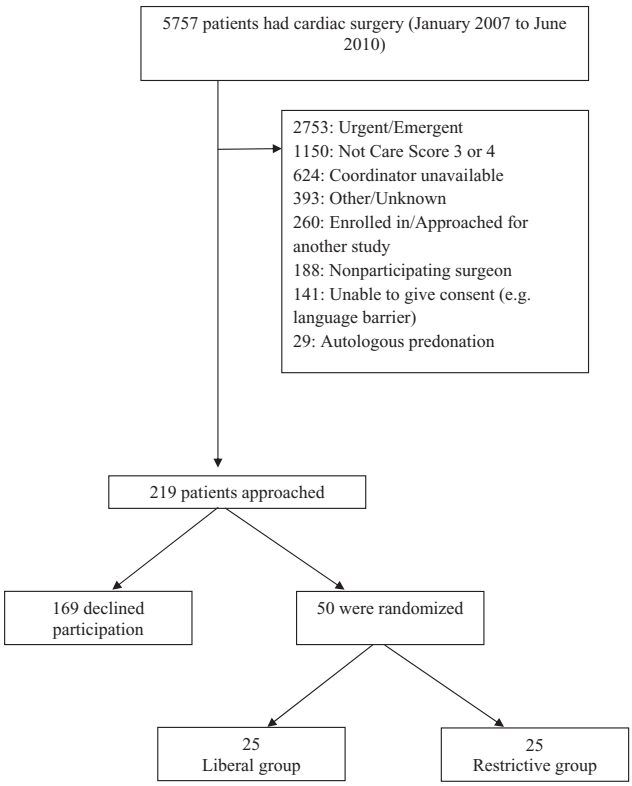

Fig. 1. Flow diagram for inclusion and exclusion of patients.

TABLE 1. Characteristics of patients according to allocation group*

Characteristic	Restrictive strategy (n = 25)	Liberal strategy (n = 25)
Age (years)	67.2 ± 11.2	68.8 ± 9.2
Male : female	17:8	20:5
Weight (kg)	88.2 ± 15.3	85.5 ± 17.5
Height (cm)	171.2 ± 8.3	170.9 ± 10.8
Surgical procedure		
CABG	13 (52)	15 (60)
Valve	5 (20)	1 (4)
Combined CABG and valve	7 (28)	9 (36)
Unstable angina	6 (24)	8 (32)
Angina	9 (36)	10 (40)
Myocardial infarction	9 (36)	9 (36)
Valvular heart disease	11 (44)	9 (36)
Hypertension	25 (100)	23 (92)
Creatinine > 140 μmol/L	2 (8)	3 (12)
Congestive heart failure	4 (16)	3 (12)
Chronic obstructive pulmonary disease	2 (8)	4 (16)
Cerebrovascular accident	3 (12)	7 (28)
Diabetes mellitus	9 (36)	12 (48)
CARE score 3	17 (68)	15 (60)
CARE score 4	3 (12)	5 (20)
Age > 80 years	5 (20)	5 (20)
Duration of CPB (min)	98.8 ± 44.6	96.8 ± 41.5
Duration of cross-clamp (min)	74.6 ± 40.3	74.2 ± 33.1
Estimated intraoperative blood loss (mL)	710.5 ± 165.5	646.2 ± 277.9
More than one attempt to separate from CPB	1 (4)	2 (8)
Pre-CPB Hct	36.6 ± 5.8	37 ± 5
Lowest Hct on CPB	25.5 ± 2.8	24.8 ± 3.7

* Data are reported as number (%) or mean ± SD. There were no significant differences between the groups.

restrictive group than the liberal group but this difference did not achieve significance (median 5 days, IQR 6 days vs. median 1 day, IQR 7 days; p = 0.9). Twenty-eight percent of patients in the restrictive group and 32% of patients in the liberal group were taking anticoagulants preoperatively. All patients received antifibrinolytics except one patient in the restrictive group. Two patients in the restrictive group received aprotinin.

Overall, 13 patients were transfused 50 units in the restrictive group compared to 22 (88%) patients who were transfused 99 units of RBCs in the liberal group ($p < 0.01$ for the number of units transfused). Intraoperatively, 14 RBC units were transfused to the restrictive group compared to 48 units of RBCs administered to the liberal group ($p < 0.01$) (Fig. 3). Table 2 illustrates the proportion of patients transfused RBCs, plasma, and PLTs.

Table 3 illustrates the adherence data. The median number of days of adherence to the transfusion strategy was 8 days (IQR, 12 days) in the restrictive arm and 6 days (IQR, 3 days) in the liberal arm (p = 0.04). Adherence was calculated as the proportion of triggers that resulted in transfusions administered according to the transfusion strategy (i.e., below the Hb transfusion threshold attained and patient was transfused/transfusion threshold attained for all patients). RBC units transfused for excessive bleeding were not included in the calculation of adherence data as the protocol was suspended if a patient was rapidly bleeding. If 2 units of RBCs were transfused after one Hb measurement, the first unit was considered adherent if the Hb threshold was attained; however, the second unit was not considered adherent because only one RBC unit was to be transfused for each trigger attained. The adherence table (Table 3) also does not include data for units transfused in the absence of a known Hb concentration. For patients allocated to the restrictive strategy, adherence was 69% in the operating room, 82% in the intensive care unit, and 100% on the ward. For the liberal group, adherence was 40% in the operating room, 69% in the intensive care unit, and 14% on the ward. There were 10 RBC units in the restrictive group and 3 units in the liberal group that were transfused in the absence of a Hb transfusion threshold being attained. Thus adherence overall was 84% in the restrictive group and 41% in the liberal group. Reasons for nonadherence included patient refusal, the use of hemoconcentration, hemorrhage, the Hct and not the Hb concentration being used to transfuse the patient,

confusion about the transfusion strategy and whether it was to be applied on the ward, hyperkalemia, the physician planning to repeat the complete blood count before transfusing the patient, and the perfusionist being occupied. The rationale for nonadherence was not well described for the remainder of the transfusions.

The mean Hb concentrations were similar preoperatively but after surgery the Hb concentrations began to diverge (Fig. 2). The differences in Hb concentration increased as the hospital stay increased ($p < 0.01$). The mean Hb concentration on Day 6 for the restrictive group was 91.1 g/L and for the liberal group 107.0 g/L ($p = 0.0004$).

The mixed venous oxygen saturation was measured in some patients (11 patients in the liberal group and four patients in the restrictive group) with a pulmonary artery catheter as a sign of tissue hypoxia (Fig. 4). There were no differences in the mixed venous oxygen saturation before or after RBC transfusion in the restrictive or liberal group.

We did not detect significant differences in any of the adverse outcomes (Table 4); however, the total number of adverse events was 38 (including death) in the restrictive strategy group compared to 15 in the liberal strategy (OR, 6.4; 95% CI, 2.8-14.9). There were four deaths in the restrictive group and one in the liberal group. In the restrictive strategy, one patient died of respiratory failure secondary to pneumonia, pulmonary embolism, and pulmonary edema; two patients died from septic shock; and one patient had a cerebrovascular accident. The cause of death of the patient in the liberal group was cardiogenic shock.

TABLE 2. Proportion of patients transfused blood products and recombinant factor VIIa*

Blood product	Restrictive (n = 25)	Liberal (n = 25)
Intraoperative		
RBCs	6 (24)	15 (60)
PLTs	3 (12)	4 (16)
Plasma	3 (12)	3 (12)
Cryoprecipitate	2 (8)	0
Factor VIIa	0	0
Postoperatively†		
RBCs		
Intensive care unit	11 (44)	17 (68)
Ward	3 (12)	4 (16)
PLTs	1 (4)	9 (36)
Plasma	2 (8)	8 (32)
Cryoprecipitate	0	1 (4)
Factor VIIa	0	0

* Data are reported as number (%).
† There were no plasma or PLT transfusions administered on the ward. All of these transfusions were administered in the intensive care unit.
$p = 0.01$ for postoperative PLT transfusion. There were no other significant differences.

DISCUSSION

This is the first randomized controlled trial in patients undergoing cardiac surgery to focus on adherence rates to transfusion strategies in a patient population where there is variability in transfusion practice and clinical equipoise in selecting transfusion thresholds. The trend for reduced adherence in the liberal group suggests an unproven bias that cardiac surgery patients require lower thresholds which may have the potential to influence practice and study outcomes. The importance of the determination of adherence rates to transfusion strategies cannot be understated because adherence rates can affect outcomes if a considerable proportion of patients do not receive a transfusion according to their transfusion strategy. Experimental data can be difficult to interpret if a high proportion of patients do not receive transfusion according to the transfusion threshold or if patients only receive a transfusion during presumed critical periods of reduced oxygen supply, that is, intraoperatively and in the intensive care unit. Adherence to transfusion strategies should occur throughout the entire hospital stay since changes in transfusion practice may impact patient outcomes regardless of when the transfusion was received in the perioperative period. There is evidence that preoperative and intraoperative anemia and transfusion are associated with increased adverse events and length of stay, and adverse events are increased by the number of RBC transfusions.[6,23,24]

The recently published single-center Transfusion Requirements after Cardiac Surgery study (TRACS; a randomized controlled trial of two transfusion strategies in cardiac surgery patients) highlights the need for recruitment strategies to increase the general-

TABLE 3. Adherence data

	Restrictive			Liberal		
Hb level	Operating room	Intensive care unit	Ward	Operating room	Intensive care unit	Ward
Hb below threshold						
Patient transfused	9	18	2	33	39	3
Patient not transfused	4	4	0	51	17	18
Hb above threshold						
Patient not transfused	141	127	96	75	100	105
Patient transfused	9	2	0	2	0	0

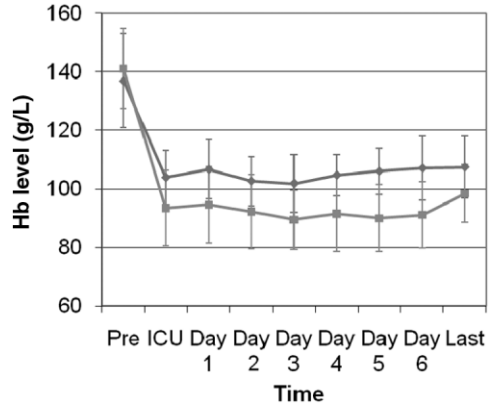

Fig. 2. Mean Hb concentrations during hospitalization according to the transfusion strategy. (◆) Liberal; (■) restrictive.

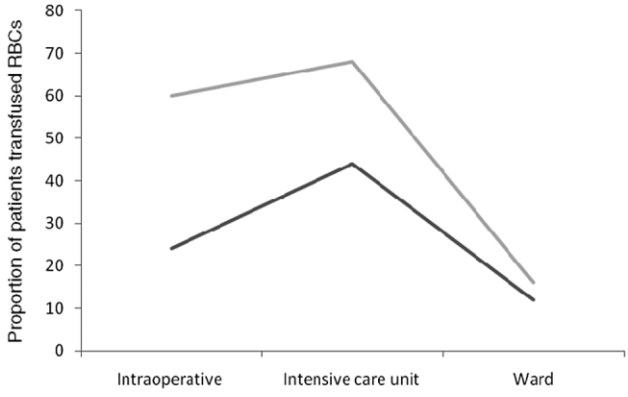

Fig. 3. Proportion of patients transfused RBCs according to the transfusion strategy. (——) Restrictive; (——) liberal.

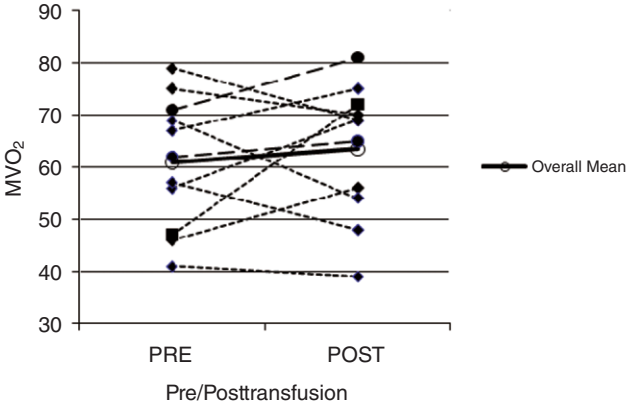

Fig. 4. Mixed venous oxygen saturation (MVO_2) levels pre- and posttransfusion in a subset of patients in the cardiovascular intensive care unit.

izability of results.[25] Only a minority of patients are included in randomized controlled trials—28% of patients assessed in TRACS were included in that study.[26]

For both strategies there was a lower than accepted adherence rate. The low proportion of adherence on the ward in the liberal group could confound a study of transfusion. The lack of adherence likely reflects the preference for a restrictive transfusion strategy at our hospital and patient preference due to educational information administered to them about the risks of transfusion during hospitalization. These adherence rates are lower than we had anticipated and reflects the challenges of conducting studies in transfusion medicine in this patient population that need to be surmounted. For example, as a result of this study we will revise our consent form to highlight the potential risk of not receiving a transfusion and the uncertainty for the need of transfusion. In addition, the lack of adherence also reflects how adherence is defined and calculated.

Although not our primary outcome, patients allocated to a lower Hb concentration experienced more adverse events. This occurred despite a lack of significant difference in the mixed venous oxygen saturation. It has been well established that reduction in mixed venous oxygen saturation is a poor surrogate of focal tissue hypoxia as focal reductions in vital organs have been demonstrated in the absence of changes in venous saturation.[27] In addition, the pilot study was not powered to detect a difference in the mixed venous oxygen saturation. Nonetheless, the higher frequency of adverse events potentially related to tissue oxygen delivery suggests that further research is needed to determine if patients with high-risk features may benefit from higher Hb concentrations for transfusion.

Although the TRACS study did not find a significant difference in mortality between a Hb concentration of 80 g/L compared to 100 g/L, the trial was not powered to do so. Because mortality rates in cardiac surgery are low, thousands of patients would need to be recruited for mortality as a primary outcome.[25] TRACS did find a trend to an increased risk of cardiogenic shock in patients randomized to a Hb concentration of 80 g/L. There was also a suggestion that mortality may be increased in the restrictive group because the hazard ratio for mortality, although not significant, was 1.28 (95% CI, 0.60-2.73); and the mortality rate from Day 18 to Day 28 was approximately 3% for the liberal strategy but 5% for the restrictive strategy, which would be a clinically important difference.[25]

There are a few limitations to this study. The enrollment rate was low; however, considering that patients are sensitized to the risk of transfusion before surgery and there were several competing studies, these results are not unexpected. Future studies need to stress the importance of determining the transfusion thresholds and the lack of scientific evidence to support institutional transfusion thresholds in this population. The adherence rates on the ward were lower than anticipated, likely due to the perception that most adverse events secondary to hypoxia would be anticipated to occur in the operating room or in the intensive care unit. This study was a pilot study and the

TABLE 4. Postoperative complications*

Adverse event	Restrictive (n = 25)	Liberal (n = 25)
Transfusion reaction	0	0
Hemorrhage	1 (4)	2 (8)
Pneumonia	4 (16)	0
Use of inotropes for more than 24 hr	4 (16)	2 (8)
Sepsis	3 (12)	0
Postoperative myocardial infarction	1 (4)	0
Greater than 50% increase in serum creatinine	6 (28)	5 (20)
Dialysis	0	1 (4)
Stroke	3 (12)	0
Pulmonary embolism/deep venous thrombosis	1 (4)	0
Multiorgan failure	1 (4)	0
Reintubation	4 (16)	1 (4)
Intubation more than 48 hr	5 (20)	2 (8)
Hospital stay more than 11 days	9 (36)	5 (20)
More than 4 days in the intensive care unit	6 (24)	3 (12)
Death	4 (16)	1 (4)
Composite score†	14 (48)	8 (32)
Length of hospital stay (days)	9 ± 12	7 ± 4

* Data are reported as number (%) or median ± IQR. There were no statistically significant differences between the groups.
† Composite score = neurologic events, dialysis dependent renal failure or greater than 50% increase in creatinine, prolonged low output state, and myocardial infarction.

resultant low adherence data can direct investigators in future trials to provide appropriate education materials to all individuals who participate in transfusion of these patients to ensure adherence to transfusion strategies. This study included patients with high-risk features and therefore cannot be applied to all patients. The rationale for the selection of this population was that this population would more likely receive a transfusion because of a higher risk of organ injury and because they are a group that would most likely derive a benefit from the transfusion. Selecting a homogenous population potentially also ensures comparability.[28] The choice of triggers and range of Hb concentrations selected reflect 1) the values studied in the transfusion triggers in critical care trial;[29] 2) the need to have a sufficient range difference between strategies so as to have the potential to influence outcomes; 3) representative values within the margin of clinical practice as established by surveys, variation studies, and clinical guidelines;[30] 4) ranges perceived to be safe by the investigators and experts in the field;[31,32] and 5) the clinical uncertainty of optimum Hb concentrations for transfusion.[33-37]

Future studies of transfusion thresholds should include detailed information about enrollment and adherence rates. Adherence rates and the proportion of individuals satisfying these adherence rates should be reported for the entire hospitalization. An 80% adherence rate is acceptable as previous reports have attained this adherence rate,[27,30] albeit not for the entire hospitalization. By achieving this adherence rate a definitive study that will require at least 2000 patients can be completed and used to guide clinical practice.

This study identified barriers to enrollment and recruitment so that methods to overcome these barriers can be incorporated in future studies to improve enrollment and recruitment rates. By addressing uncertainty surrounding transfusion thresholds and overtransfusion, future studies may be completed in a timely fashion. However, additional pilot studies need to be conducted to ensure enrollment and adherence before a definitive randomized controlled trial is conducted.

This pilot study demonstrated that there are physician and patient biases for transfusion thresholds and that there is a need for knowledge translation. The pilot study also demonstrated that the adherence rates were sufficient in the operating room and intensive care unit to separate Hb concentrations. Studies assessing transfusion strategies should report adherence rates because adherence reflects the proportion of patients transfused according to the transfusion strategy and therefore compliance. Adherence will affect the interpretation of outcomes if a high proportion of patients are not transfused according to the strategy. This study and the TRACS study highlight the need for a large multicentered collaborative study to address transfusion requirements in this patient population.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest relevant to the manuscript submitted to **TRANSFUSION**.

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