The Effect of Preoperative Anemia on Patients Undergoing Cardiac Surgery: A Propensity-Matched Analysis

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It is unknown if anemia in the absence of transfusions is an independent risk factor for adverse outcomes in cardiac surgery, and if correction to higher hemoglobin targets impacts these outcomes. This is a retrospective review of 3848 cardiac surgery patients. Propensity matching was completed using 41 covariates. Intraoperative Anemia Analysis matched patients with or without anemia who did not receive intraoperative transfusions (n = 392/group), while Intraoperative Transfusion Analysis matched anemic patients treated conventionally with intraoperative transfusions to end cardiopulmonary bypass hemoglobin greater or less than 95 g/L (n = 261/group). Outcomes of death, renal failure, and 2 composite outcomes were assessed using paired analysis techniques. Study composite 1 consisted of prolonged ventilation, renal failure, myocardial infarction, stroke, or deep sternal wound infection, while composite 2 was the TRICS-III composite.

In the Intraoperative Anemia Analysis, anemia was associated with mortality ($P = 0.034$), stroke ($P = 0.021$), renal failure ($P = 0.015$), and a significant increase in the composite measure (control 8.7% vs anemia 16.1%, $P = 0.002$). These findings were unchanged in patients who did not receive any postoperative transfusions. The Intraoperative Transfusion Analysis showed no difference in mortality or the composite outcome between groups. There was a significant increase in low cardiac output in the lower threshold group ($P = 0.001$). There were no differences in outcomes between those who did and did not receive postoperative transfusions ($P > 0.05$). Preoperative anemia in the absence of transfusions is a risk factor for morbidity and mortality after cardiac surgery, and there is no evidence that transfusion to higher end cardiopulmonary bypass hemoglobin levels impacted this risk.

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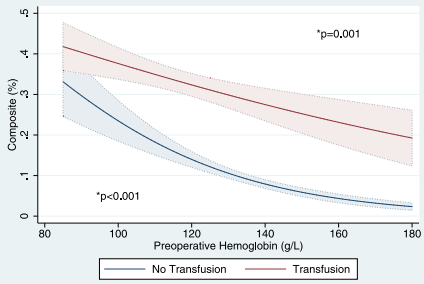

Lower Hb was significantly associated with the composite outcome in all patients.

Central Message

Preoperative anemia in the absence of transfusions is a risk factor for morbidity and mortality postcardiac surgery, with postoperative transfusions not ameliorating these risks.

Perspective Statement

Preoperative anemia is associated with increased risk of morbidity and mortality after cardiac surgery. This study demonstrated that anemia in the absence of perioperative transfusions is associated with an increased risk of death, renal failure, and stroke; additionally, transfusion to a higher hemoglobin threshold at the end of CPB does not reverse these risks.

Abbreviations: PTCA, previous percutaneous transluminal catheter angioplasty; PVD, peripheral vascular disease; DM, diabetes mellitus; CARE, Cardiac Anesthesia Risk Evaluation Score; CABG, coronary artery bypass grafting; MVR, mitral valve replacement/repair; AVR, aortic valve replacement; OHT, orthotopic heart transplant; ETOH, alcohol use; LMWH, low molecular weight heparin; CCS, Canadian Cardiovascular Society; NYHA, New York Heart Association; RAP, retrograde autologous priming

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INTRODUCTION

Much attention has been paid to the impact of preoperative anemia on postoperative outcomes in cardiac surgery, as up to one-third of all patients present with low hemoglobin levels.[1−3] Previous studies have suggested that preoperative anemia is associated with increased postoperative morbidity and mortality after cardiac surgery,[1,2,4−7] with the magnitude of these risks increasing with the degree of anemia.[1,2,8,9] However, these studies have been confounded by not excluding perioperative red blood cell (RBC) transfusions, which themselves have been linked to adverse outcomes.[2,10,11] Previous randomized controlled trials evaluating the effect of transfusions in cardiac surgery, have also excluded those with preoperative anemia,[12] while others have not clearly differentiated the effect of intraoperative vs postoperative anemia, since different physiology may exist in terms of anemia tolerance during and after cardiopulmonary bypass (CPB).[13] Thus, the independent effect of anemia during CPB has not been quantified, and the ideal perioperative transfusion management of patients with anemia remains unknown.

The objectives of this study were 2-fold: (1) to delineate the association between preoperative anemia and adverse outcomes in patients without intraoperative transfusion and (2) to determine whether low or high transfusion thresholds in anemic patients impact these outcomes. We hypothesized that (1) preoperative anemia increases postoperative morbidity and mortality, however (2) high intraoperative transfusion thresholds in anemic patients will not lower these risks.

PATIENTS AND METHODS

Patient Population and Data

The institutional ethics board provided approval to analyze the data used in this study and individual patient consent was waived. The study population consisted of all patients (>18 years of age) undergoing cardiac surgery utilizing CPB between January 2010 and December 2012 at the Ottawa Heart Institute. Patients undergoing off-pump surgery and transcatheter aortic valve replacement were excluded. Prospective clinical data is routinely collected during surgical admission and forms part of the Cardiac Surgery and Cardiac Anesthesia databases. Hospital records of patients who did not receive intraoperative transfusions were reviewed and all postoperative transfusions (intensive care to discharge) were recorded.

Conduct of Surgery and Transfusion Practice

Narcotic-based anesthesia was used for all patients who also received 1 g tranexamic acid as a bolus at induction followed by an infusion of 2.0 mg/kg/h for the duration of surgery. Patients were heparinized to an activated clotting time of >400 seconds. CPB was conducted with a roller pump, a hollow-fiber oxygenator (Inspire 8 [LivaNova Canada, Markham, ON] or Capiox FX25 [Terumo Canada, Mississauga, ON]) with a 43 μm arterial filter and an open venous reservoir. Pumps were primed with 800 mL Ringers Lactate. Flows were maintained at 2.4−3.2 L/min/m^2. Hearts were arrested with antegrade or retrograde cold blood cardioplegia (16:1 blood:crystalloid) at the surgeon's discretion. During cardiac anoxia, body temperature was allowed to drift to a minimum of 34°C with re-warming to a maximal nasopharyngeal temperature of 37°C when weaning from CPB.

Retrograde autologous priming was utilized at the discretion of the cardiac anesthetist. Cell salvage was utilized at the discretion of the cardiac surgeon. In all cases where postoperative chest tube drainage exceeded 1000 mL in 6 hours, cell salvage was routinely used to process the shed blood. The perioperative team includes a group of 15 anesthesiologists who have a uniform transfusion practice. The CPB circuit was primed with homologous blood for patients with a preoperative hematocrit of less than 24%. The target hematocrit on CPB was 24% with a transfusion threshold hemoglobin of 85 g/L after chest closure and in the ICU. Higher hemoglobin levels (90−100 g/L) were maintained for patients who were actively bleeding or who had increased need for oxygen carrying capacity.

Study Definitions and Measurement of Outcomes

Preoperative anemia was defined as less than 130 g/L and less than 120 g/L in men and women, respectively.[14] Smoking designation included active or ex-smoker. Recent myocardial infarction (MI) refers to MI less than 6 weeks before surgery. Prolonged ventilation was defined as the requirement for intubation exceeding 24 hours. The degree of kidney injury was classified according the Acute Kidney Injury Network classification system, using the ratio of the highest postoperative creatinine to the baseline creatine and the RIFLE criteria as follows: risk (R)—ratio 1.5−2, injury (I)—ratio 2−3, failure (F)—ratio >3 or highest postoperative creatinine minus baseline >44.2 μmol/L if preoperative creatinine >354 μmol/L or loss(L)—need for continuous venovenous hemofiltration or new onset dialysis. Extended (E) need for dialysis was not available from the database. Renal failure was defined as the presence of injury, failure, or loss.[15] Deep sternal wound infection (DSWI) was diagnosed using Center for Disease Control criteria.[16] Perioperative MI was diagnosed using a combination of electrocardiographic (new Q waves or a new left bundle branch block), biochemical (elevations of CK-MB mass >60 ug/L) and echocardiographic (presence of new wall motion abnormalities) findings. Stroke was defined as a new "central" neurologic deficit with focal or lateralizing signs on physical examination, confirmed by computer tomographic or magnetic resonance imagining. Low-cardiac output was defined as a cardiac index (CI) <1.8 L/min/m^2 for a period >24 hours.

The primary outcomes included (a) the incidence of in-hospital death and (b) the incidence of a composite morbidity of 1 of the 5 following complications: prolonged ventilation, renal failure, perioperative MI, stroke, or DSWI. The secondary outcomes included: hours ventilated and the individual incidences of renal failure, stroke, prolonged ventilation, low cardiac output syndrome, DSWI, and the TRICS III-composite of death, perioperative MI, or new-onset dialysis.[17]

Statistical Analysis and Propensity Matching

Continuous variables were reported as mean ± standard deviation or median (interquartile range [IQR]) for non-normally-distributed variables. Categorical variables were reported as counts and percentages. Student's *t*-tests or Wilcoxon rank-sum tests were used to compare continuous variables between gender groups while chi-square tests were used for categorical variables. Propensity scores were calculated using a logistic regression model in which the group indicator was the dependent variable. Two strategies were utilized: (a) Intraoperative Anemia Analysis (IAA): patients who did not receive any intraoperative transfusion, matched using presence or absence of anemia as the dependent variable and (b) Intraoperative Transfusion Analysis (ITA): patients who may or may not have received intraoperative transfusion, matched based on a hemoglobin target above or below 95 g/L at the end of CPB[17] as the dependent variable. Thirty-nine demographic and perioperative covariates entered in the model as independent variables in the IAA with the addition of preoperative hemoglobin and lowest hematocrit on CPB in the ITA. Treated observations were matched in a 1:1 ratio using the nearest neighbor method with a caliper width of 0.2 of the SD of the propensity score logit.

Lists of the variables used in the propensity score calculation and the standardized differences after matching are presented in Tables 1 and 2 (Supplemental). Figures 2 and 3 (Supplemental) display the graphical summary of the covariate imbalances and propensity score histograms before and after matching. McNemar's chi-squared was calculated to compare proportions in the propensity-matched groups.[18] Logistic regression models for the risk of the composite outcome, and renal failure vs preoperative hemoglobin were derived in the whole population and in the IAA, with determination of predicted margins. A P value <0.05 was considered significant. All statistical analyses and plots were performed with Stata version 14.1 (College Station, TX).

RESULTS

Clinical Characteristics

A total of 3859 patients undergoing surgery between January 2010 and December 2012 were included in this study. The flow of patients in the 2 strategies is presented in Figure 1 (Supplemental). Marginal effects of the preoperative hemoglobin level to the risk of the composite outcome and renal failure in all entire cohort (regardless of transfusion or preoperative anemia status) are presented in Figure 1a and b.

Propensity-Matched Intraoperative Anemia Analysis

Demographics of the variables in the propensity-matched groups are presented in Table 1 (Supplemental). The preoperative hemoglobin in the control group was 143 ± 1 g/L and in the anemia group, 119 ± 1 g/L (P <0.001). Figure 2a illustrates the changes in hemoglobin level related to surgery in the 2 groups of the IAA. Table 1 presents the details of the

Table 1. Intraoperative Anemia Analysis: Propensity-Matched Cohort Results for Primary and Secondary Outcomes

Variables	Control (n = 392)	Anemia (n = 392)	*P*
In-hospital death (n %)	1 (0.3)	7 (1.8)	0.034
Composite outcome (n %)	34 (8.7)	63 (16.1)	0.002
Kidney (n %)			
Risk	29 (7.4)	42 (10.7)	0.10
Injury	12 (3.1)	24 (6.1)	0.046
Failure	3 (0.8)	6 (1.5)	0.32
Loss	9 (2.3)	16 (4.1)	0.14
Renal failure (n %)	18 (4.6)	35 (8.9)	0.015
Perioperative MI (n %)	1 (0.3)	2 (0.5)	0.56
Prolonged ventilation (n %)	20 (5.1)	31 (7.9)	0.11
Hours ventilated (h [IQR])	6.0 (4.3, 10.1)	6.4 (4.5, 12.8)	0.13
DSWI (n %)	3 (0.8)	7 (1.8)	0.21
Stroke (n %)	2 (0.5)	10 (2.6)	0.021
Postop low CO (n %)	90 (23.0)	63 (16.1)	0.017
Reopening (n %)	15 (3.8)	14 (3.6)	0.84
Cell saver use (n %)	2 (0.5)	5 (1.3)	0.26

Composite outcome (prolonged ventilation, stroke, renal failure, DSWI, perioperative MI). Renal failure (any of injury, failure or loss).
Abbreviations: CO, cardiac output; DSWI, deep sternal wound infection; IQR, interquartile range; MI, myocardial infarction.

Table 2. Intraoperative Transfusion Analysis: Propensity Matched Cohort Results for Primary and Secondary Outcomes

Variables	Low Threshold (n = 261)	High Threshold (n = 261)	*P*
In-hospital death (n %)	13 (5.0)	10 (3.8)	0.19
Composite outcome (n %)	73 (28.0)	62 (23.8)	0.57
Kidney (n %)			
Risk	40 (15.3)	42 (16.1)	0.32
Injury	18 (6.9)	16 (6.1)	0.30
Failure	12 (4.6)	11 (4.2)	0.62
Loss	28 (10.7)	25 (9.6)	0.56
Renal failure (n %)	41 (15.7)	40 (15.3)	0.66
Perioperative MI (n %)	2 (0.8)	3 (1.2)	0.66
Prolonged ventilation (n %)	49 (18.8)	38 (14.6)	0.30
Hours ventilated (h [IQR])	9.0 (5.3, 23.1)	8.5 (4.8, 21.5)	0.15
DSWI (n %)	3 (1.2)	9 (3.5)	0.09
Stroke (n %)	6 (2.3)	6 (2.3)	0.72
Postop low CO (n %)	72 (27.6)	49 (18.8)	0.00
Reopening (n %)	17 (6.5)	22 (8.4)	0.51
Cell saver use (n %)	6 (2.3)	5 (1.9)	0.64

Composite outcome (prolonged ventilation, stroke, renal failure, DSWI, perioperative MI). Renal failure (any of injury, failure or loss).
Abbreviations: CO, cardiac output; DSWI, deep sternal wound infection; IQR, interquartile range; MI, myocardial infarction.

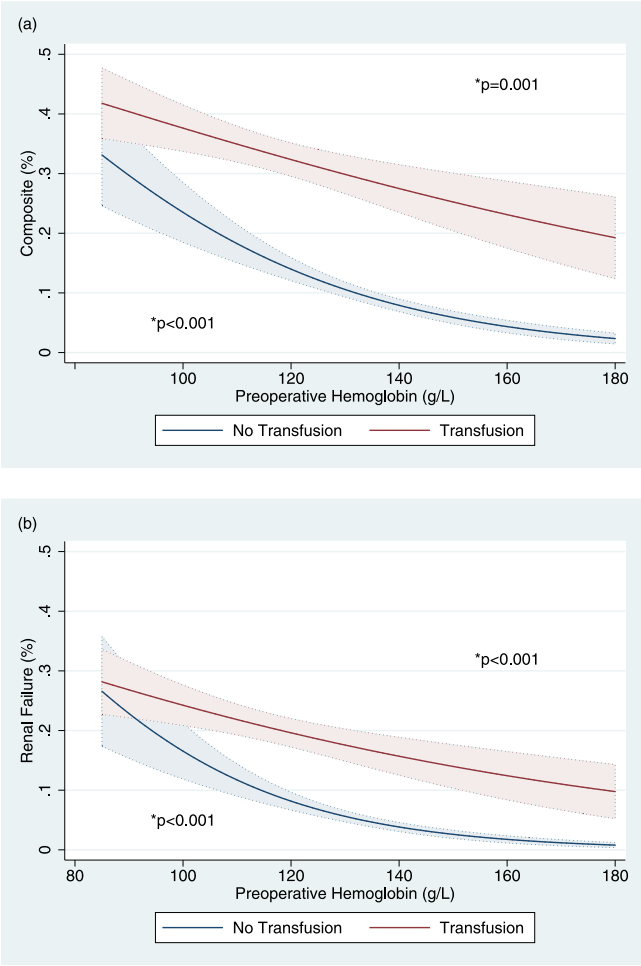

Figure 1. Marginal predictions with 95% CI of the incidence of the composite outcome (a) and renal failure (b) in the entire cohort prior to matching, related to the preoperative hemoglobin. Lowering hemoglobin was significantly associated with the composite outcome and renal failure in both the intraoperative nontransfused (blue) and intraoperative transfused (pink) patients. (Color version of figure is available online.)

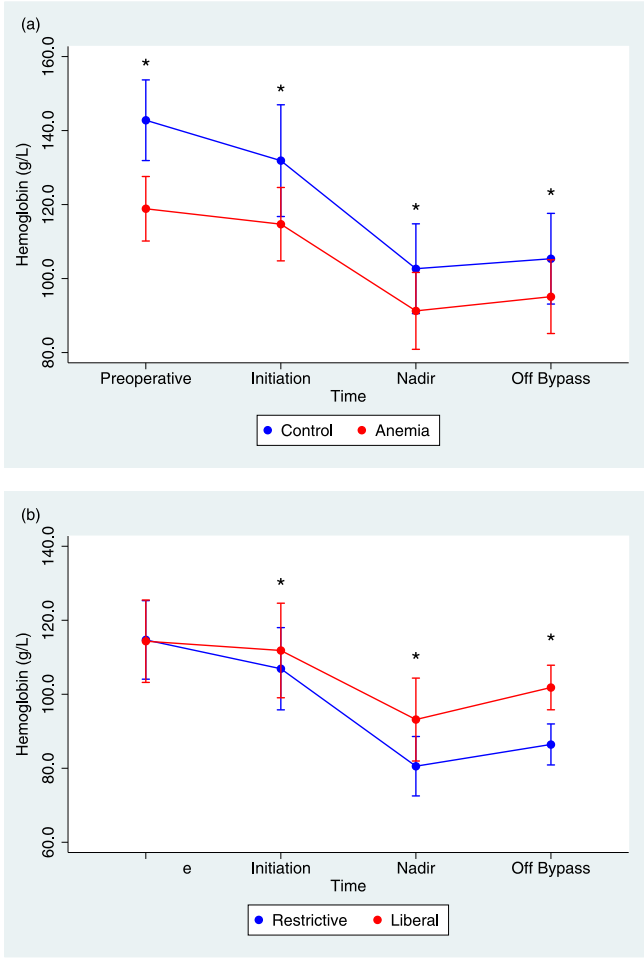

Figure 2. Intraoperative hemoglobin levels (g/L) in the IAA (a) and ITA (b) analyses. * indicates P <0.05.

differences in the primary and secondary outcomes between the groups. Anemia was associated with an increased risk of death ($P = 0.034$) and the composite outcome ($P = 0.002$). It was also associated with an increase in stroke ($P = 0.021$), kidney injury ($P = 0.046$), and renal failure ($P = 0.015$). Nonanemia was associated with an increased risk of low cardiac output syndrome ($P = 0.017$). Anemia was significantly associated with the TRICS III-composite (odds ratio [OR] 0.967 95% CI [0.944, 0.991] $P = 0.008$). Figure 3a and b illustrates the associations between the composite outcome and renal failure on preoperative hemoglobin level in the IAA (P <0.001 and $P = 0.002$ respectively). Postoperative RBC transfusions occurred in 345 patients in the IAA (124 [31.6%] patients in the nonanemic group vs 221 [56.5%] in the anemic group, P <0.001). Table 3 shows the breakdown of all postoperative transfusions in the anemia analysis. RBC transfusions were significantly increased in the preoperative anemic group (P <0.001). When examining patients who had received no postoperative RBC transfusions, preoperative anemia was associated with a significant increase in the composite outcome (OR 0.647, 95% CI [0.490, 0.854], $P = 0.002$). This relationship was not significant when examining patients who had received postoperative RBC transfusions (OR 0.888, 95% CI [0.740, 1.064], $P = 0.19$).

Propensity-Matched Intraoperative Transfusion Analysis

Demographics of the variables in the propensity-matched groups are presented in Table 2 (Supplemental). Figure 2b illustrates the changes in hemoglobin level related to surgery in the 2 groups of the ITA. Table 2 presents the details of the differences in the primary and secondary outcomes between the groups. Patients in the lower threshold group received more red cell transfusion (1 IQR [0, 2] vs 0 IQR [0, 2] $P = 0.046$). There was no difference in the incidence of death between groups ($P = 0.19$) nor in the composite outcome ($P = 0.57$). There was no difference in renal failure ($P = 0.62$) or in any of

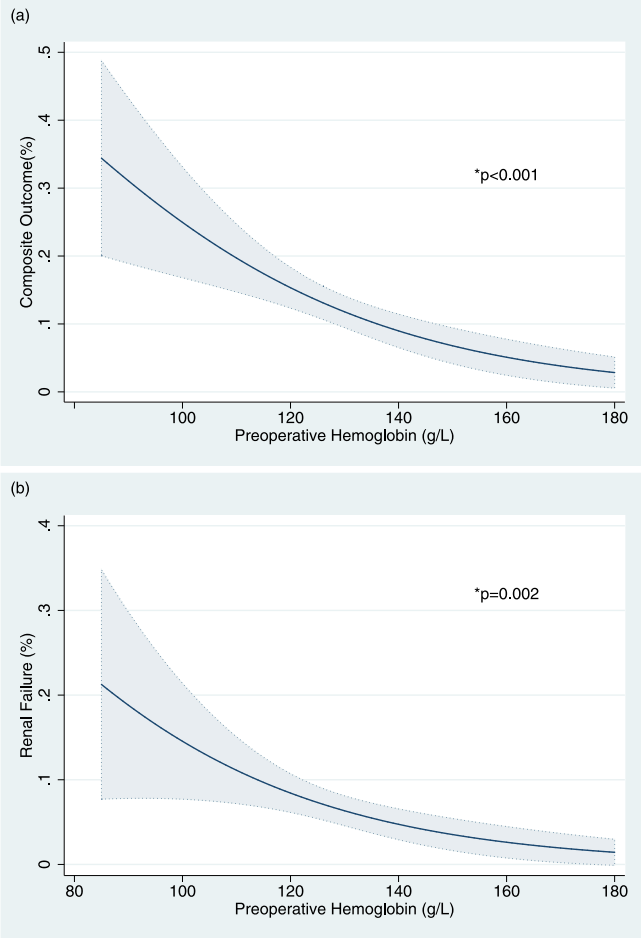

Figure 3. Marginal predictions with 95% CI of the incidence of the composite outcome (a) and renal failure (b) in the IAA related to the preoperative hemoglobin. * indicates P <0.001. IAA, Intraoperative Anemia Analysis.

the component RIFLE outcomes. There was a significant increase in incidence of low cardiac output in the lower threshold group ($P = 0.001$). There was no difference in the TRICS III-composite outcome between groups (OR 0.902 [0.540, 1.508] $P = 0.69$).

In the ITA, a total of 364 patients received RBC transfusions (189 [52.1%] patients in the low threshold group vs 174 [47.9%] patients in the high threshold group, $P = 0.15$). There was no difference in both postoperative transfusion rates or the number of units between groups however the higher threshold group did receive more red cells intraoperatively (Table 3). Postoperative transfusions also had no effect on the incidence of the composite outcome ($P = 0.11$ in the nontransfused and $P = 0.87$ in the transfused). Similarly, there was no difference in the TRICS III-composite outcome between groups when compared to patients that were transfused (OR 0.926, 95% CI [0.519, 1.653], $P = 0.79$) and not transfused (OR 0.963, 95% CI [0.308, 3.004], $P = 0.95$).

DISCUSSION

Preoperative anemia was a prevalent condition in our study, accounting for 22% of the study population. In the IAA, anemia was associated with an increased risk of death, renal failure, stroke, and the composite outcome in patients who did not receive an intraoperative transfusion. The risk of the composite outcome and renal failure increased with lowering hemoglobin levels in nontransfused patients. This relationship remained when further restricting to those that also did not receive postoperative transfusions. In patients that received postoperative transfusions, there was no longer a significant difference in the composite between groups, however the overall complication rate was significantly increased in both groups, which may be secondary to the effects of the transfusions, or some unseen bias. In the ITA, there was no difference in the incidence of the primary outcome, or their individual indices, in higher hemoglobin thresholds as opposed to lower

Table 3. Intraoperative and Postoperative Transfusions for both Propensity-Matched Analyses

Transfusion Type	Intraoperative Anemia Analysis			Intraoperative Transfusion Analysis		
	Control (n = 392)	Anemia (n = 392)	P	Low Threshold (n = 261)	High Threshold (n = 261)	P
Intraoperative						
RBC (U)	–	–		1 (0,2)	0 (0,2)	0.046
FFP (U)	–	–		0 (0,0)	0 (0,0)	0.61
Platelets (U)	–	–		0 (0,4)	0 (0,4)	0.79
Cryoprecipitate (U)	–	–		0 (0,0)	0 (0,0)	0.35
Factor 7a (mg)	–	–		8	6	0.27
Postoperative						
RBC (U)	0 (0,1)	0 (0,2)	<0.001	2 (0,5)	2 (0,4)	0.28
FFP (U)	0 (0,0)	0 (0,0)	0.64	0 (0,0)	0 (0,1)	0.68
Platelets (U)	0 (0,0)	0 (0,0)	0.45	0 (0,1)	0 (0,1)	0.43
Cryoprecipitate (U)	0 (0,0)	0 (0,0)	0.54	0 (0,0)	0 (0,0)	0.08
Factor 7a (mg)	2	2	1.00	7	6	0.77

Blood products presented as median (IQR). Abbreviations: FFP, fresh frozen plasma; RBC, red blood cells; U, units.

hemoglobin thresholds. There was also no difference in our composite outcome or the TRICS-composite outcome between groups in the ITA. Postoperative transfusions also had no effect on any of the outcomes seen in the ITA.

Numerous studies have identified preoperative anemia as an independent risk factor for adverse outcomes after cardiac surgery.[2,9,19] In a study of 3500 patients undergoing cardiac surgery, Karkouti et al demonstrated preoperative anemia to be independently associated with a composite adverse outcome (in-hospital death, stroke, and AKI), after controlling for important confounders (OR 2.0, 95% CI [1.4−2.8], P <0.0001).[2] The results of our study are consistent with the aforementioned study, and strengthen our current understating of this association, as ours is the first study to control for the potential effects of perioperative transfusions on postoperative outcomes in anemic patients undergoing cardiac surgery.

Renal dysfunction postcardiac surgery is a common occurrence, with previous studies reporting postoperative stage 1 AKI in 22% of patients.[3] In a study of 1214 patients undergoing cardiac surgery, De Santo et al showed anemia as an independent predictor of AKI (OR 2.06, 95% CI [1.14−3.70]) after CABG.[20] We also demonstrated this in the IAA, with the incidence of renal failure in the anemic group being almost double the control (8.9 % vs nonanemic 4.6%, P = 0.015) and the odds of renal failure increased by 3% for every 1 g/L drop in the hemoglobin levels in nontransfused patients.

Previous work by Karkouti et al has shown that as a patient's hematocrit decreases there are protective affects against AKI in patients placed on cardiopulmonary bypass.[21] These protective effects are most apparent at a nadir hematocrit of moderate hemodilution (21−25%), becoming detrimental to the kidney at either extreme.[21] Ranucci et al also showed that preoperative anemia was an independent risk factor for major morbidity, including AKI, which could be avoided provided the lowest hematocrit on CPB remained above 28%.[22] This finding may account for the higher incidence of AKI seen in the anemic group; secondary to further hemodilution on CPB and subsequent lowering hematocrit, suggesting the key renal insult may occur intraoperatively. Clearly, further studies are needed to determine whether preoperative anemia is a marker for renal impairment or a modifiable risk factor.[3,20]

Anemia in the absence of transfusion was also associated with an increased risk of stroke. These findings are consistent with Karkouti et al,[23] who demonstrated a direct association between the degree of hemodilution and the risk of stroke after CPB, showing a critical nadir hematocrit of 22% to be the tipping point at which the risk of CPB-related stroke increases.[24] The current study contributes in a novel manner, as neither of these earlier studies controlled for the possible effects of intraoperative transfusions.

In the recently published TRICS-III randomized controlled trial, no difference in mortality or the composite outcome in patients treated intraoperatively or postoperatively with either a restrictive or liberal strategy was noted.[17] Subgroup analysis of 1149 anemic patients in this study also demonstrated no difference in the composite outcome, which was consistent with our study when examining the same TRICS-composite. In the IAA, preoperative anemia was significantly associated with the composite if patients were also not transfused postoperatively (11.2% vs 3.6% nonanemic, P = 0.002). When comparing patients who subsequently underwent postoperative transfusion, there was no longer a difference in the composite outcome (19.5% vs nonanemic 17.4%, P = 0.19). However, the overall incidence of the composite is significantly increased in both groups, and may be attributable to the effects of transfusions or some other unseen bias. In the ITA, there was no difference in postoperative transfusion rates or the number of units between groups. There was also no difference in the composite or TRICS-composite outcome when comparing those who did and did not receive postoperative transfusions.

In contrast to the Mazer study, we have matched patients based on intraoperative anemia or hematocrit levels, as opposed to a transfusion threshold that was applied both intraoperatively and postoperatively. We hypothesized that it is during surgery and cardiopulmonary bypass that anemia has its greatest effect. The importance of low hemoglobin levels intraoperatively during cardiac surgery has been extensively studied, and although no safe lower limit for hematocrit during CPB has been identified, hematocrit levels below 20% are associated with major adverse cardiac events.[25,26] In a recent study of patients that did not receive RBC transfusions, Loor et al also demonstrated lower intraoperative hematocrit were associated with worse renal function, increased myocardial injury, longer postoperative ventilator support, longer hospital stay, and higher mortality.[27]

There are several limitations that may impact the current analysis. Data on both morbidity and mortality were limited to the immediate postoperative period and therefore cannot account for the long-term effects of intraoperative anemia. Before matching, significant heterogeneity existed between subpopulations. Demographic and perioperative covariates were utilized in the derivation of propensity scores to ensure equal matching. Specifically, the models included intraoperative covariates, which may be particularly sensitive, to ensure similarity of patients such as CPB and anoxia times and EBL (estimated blood loss). These were utilized to give greater confidence that patients in each group were undergoing surgeries of similar complexity.

CONCLUSION

This study demonstrated that in patients who do not receive intraoperative transfusions, anemia is a significant risk factor for perioperative mortality and morbidity, including renal failure and stroke. In addition, transfusions to more generous hemoglobin levels at the end of CPB do not appear to change the incidence of these adverse events. Since a significant percentage of patients undergoing cardiac surgery suffer from anemia, there is potential for further research to assess whether other strategies to address compromised oxygen carrying capacity in the blood will result in improved outcomes.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.semtcvs.2018.09.015.

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