Association between Intraoperative Blood Transfusion and Mortality and Morbidity in Patients Undergoing Noncardiac Surgery

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ABSTRACT

Background: The impact of intraoperative erythrocyte transfusion on outcomes of anemic patients undergoing noncardiac surgery has not been well characterized. The objective of this study was to examine the association between blood transfusion and mortality and morbidity in patients with severe anemia (hematocrit less than 30%) who are exposed to one or two units of erythrocytes intraoperatively.

Methods: This was a retrospective analysis of the association of blood transfusion and 30-day mortality and 30-day morbidity in 10,100 patients undergoing general, vascular, or orthopedic surgery. We estimated separate multivariate logistic regression models for 30-day mortality and for 30-day complications.

Results: Intraoperative blood transfusion was associated with an increased risk of death (odds ratio [OR], 1.29; 95% CI, 1.03–1.62). Patients receiving an intraoperative transfusion were more likely to have pulmonary, septic, wound, or thromboembolic complications, compared with patients not receiving an intraoperative transfusion. Compared with patients who were not transfused, patients receiving one or two units of erythrocytes were more likely to have pulmonary complications (OR, 1.76; 95% CI, 1.48–2.09), sepsis (OR, 1.43; 95% CI, 1.21–1.68), thromboembolic complications (OR, 1.77; 95% CI, 1.32–2.38), and wound complications (OR, 1.87; 95% CI, 1.47–2.37).

Conclusions: Intraoperative blood transfusion is associated with a higher risk of mortality and morbidity in surgical patients with severe anemia. It is unknown whether this association is due to the adverse effects of blood transfusion or is, instead, the result of increased blood loss in the patients receiving blood.

What We Know about This Topic

- Anemia increases perioperative morbidity and mortality, but whether intraoperative erythrocyte transfusion reduces these adverse events is not known

What New Information This Study Provides

- In more than 10,000 patients undergoing major surgery, intraoperative blood transfusion was associated with a higher risk of mortality and morbidity in surgical patients with severe anemia
- Whether this is due to adverse effects of transfusion or a more critical blood loss is not clear

ANEMIA increases morbidity and mortality in patients undergoing cardiac[1,2] and noncardiac surgery,[3–5] as well as in patients presenting with an acute coronary syndrome.[6] It has long been accepted that blood transfusion will correct the physiologic abnormalities associated with anemia and improve patient outcomes. Blood transfusion remains the cornerstone of the treatment of anemia. Nearly 14 million units of erythrocytes were transfused in 2001.[7] Despite the fact that anemia is associated with worse outcomes, there is increasing evidence that blood transfusion does not improve outcomes and may actually lead to worse outcomes.

◇ This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 9A.

◆ This article is accompanied by an Editorial View. Please see: Spahn DR, Shander A, Hofmann A, Berman MF: More on transfusion and adverse outcome: It's time to change. ANESTHESIOLOGY 2011; 114:234–6

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Most of this evidence is based on retrospective studies. The Transfusion Requirement in Critical Care trial is the only published large, randomized, controlled trial that has evaluated the effect of blood transfusion.[8] This study did not show any benefit in critically ill patients randomly assigned to a liberal transfusion strategy, compared with patients randomly assigned to a restrictive transfusion strategy. Nearly all retrospective studies performed on patients undergoing cardiac surgery,[9–12] patients in the intensive care unit,[13–16] and patients presenting with acute coronary syndromes[17–20] have demonstrated worse outcomes after blood transfusion. The impact of erythrocyte transfusion on outcomes of anemic patients undergoing noncardiac surgery has not been well characterized.

The purpose of our study, based on the American College of Surgery National Surgical Quality Program database, was to determine whether noncardiac surgical patients with baseline hematocrits less than 30% receiving no more than one or two units of erythrocytes intraoperatively are less likely to survive and more likely to experience one of seven major complications, compared with patients receiving no intraoperative transfusion. We limited the study population to patients with severe anemia preoperatively who were exposed to one or two units of erythrocytes intraoperatively to minimize the confounding effect of surgical blood loss on patient outcomes. We assumed that by including only patients with severe baseline anemia who received at most two units of blood intraoperatively, we would minimize the likelihood that the indication for intraoperative transfusion was significant intraoperative blood loss, as opposed to severe baseline anemia.

Materials and Methods

Data Source

This study was conducted using data from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database on patients undergoing noncardiac surgery between 2005 and 2007. This program is a prospective validated outcomes registry designed to provide feedback to member hospitals on 30-day risk-adjusted surgical mortality and complications.[21] The ACS NSQIP database includes deidentified data on patient demographics, functional status, admission source, preoperative risk factors, intraoperative variables, and 30-day postoperative outcomes for patients undergoing major surgery in more than 200 participating hospitals.[21] A systematic sampling strategy is used to avoid bias in case selection and to ensure a diverse surgical case mix.[22] Trained surgical clinical reviewers collect patient data from the medical chart, operative log, anesthesia record, interviews with the surgical attending, and telephone interviews with the patient.[21] Data quality is insured through comprehensive training of the nurse reviewers and through an interrater reliability audit of participating sites.[22]

Study Population and Outcomes

We first identified 19,200 patients who underwent general, vascular, or orthopedic surgery with the use of current procedural terminology codes. We excluded patients who received more than two units of erythrocytes intraoperatively (2,110), patients who underwent emergency surgery (4,301), patients who received more than four units of relative biological effectiveness preoperatively (205) or who received more than four units of erythrocytes postoperatively (149), patients missing information on intraoperative transfusion (1), patients whose baseline hematocrit was drawn more than 14 days before the operation (1,019), patients who received no anesthesia, local anesthesia, or monitored anesthesia care (346), patients who were missing demographic information (365), patients who were mechanically ventilated preoperatively (432), and patients with procedures with work relative value units equal to zero (172).†† The study cohort consisted of 10,100 patients.

The outcomes of interest were 30-day mortality and major 30-day complications: (1) cardiac (acute myocardial infarction or cardiac arrest); (2) pulmonary (pneumonia, ventilatory support for greater than 48 h, or unplanned intubation); (3) renal (progressive renal insufficiency or acute renal failure)‡‡; (4) central nervous system (cerebrovascular accident or coma lasting more than 24 h)§§; (5) sepsis (sepsis or septic shock)‖‖; (6) wound complication (deep incisional surgical site infection, organ or space surgical site infection, or wound dehiscence)##; and (7) thromboembolic (deep venous thrombosis or pulmonary embolism).

Statistical Analysis

We examined the association between intraoperative blood exposure (transfusion of one or two units of erythrocytes) and 30-day mortality and morbidity in patients undergoing major noncardiac surgery. Patients not receiving any erythrocyte transfusion intraoperatively constituted the reference population (no transfusion group).

Separate multivariate logistic regression models for 30-day mortality and for each of the major complications were estimated. Patients not receiving any erythrocyte transfusion intraoperatively constituted the reference population (no transfusion group). Backward stepwise selection was used to select risk factors from the list of potential confounders: age, sex, surgical complexity, admission source, functional status, wound classification, and comorbidities (congestive heart failure, myocardial infarction, previous cardiac surgery, pe-

†† The work relative value unit (workrvu) is used as a measure of surgical complexity.

‡‡ Patients with acute or chronic renal failure preoperatively were excluded from the analysis of renal complications.

§§ Patients with preoperative paraplegia, hemiplegia, quadriplegia, cerebrovascular accident with neurologic deficit, and coma were excluded from the analysis of central nervous system complications.

‖‖ Patients with preoperative sepsis or septic shock were excluded from the analysis of septic complications.

Superficial surgical site infections were not included.

Table 1. Patient Demographics

Patient Risk Factors	Not Transfused (%) (n = 7,940)	Transfused (%) (n = 2,160)	*P* Value
Baseline hematocrit	27.8	27.1	< 0.001
Age, yr	60.2	64.6	< 0.001
Male	56.5	51.3	< 0.001
Admission source			
Home	86.6	83.2	< 0.001
Hospital	7.34	9.81	< 0.001
Chronic care facility	5.21	5.65	0.425
DNR	2.27	2.69	0.257
Dependent functional status	25.6	31.4	< 0.001
Cardiac			
CHF in 30 days prior	3.95	4.03	0.877
MI in 6 months prior	2.17	2.36	0.585
PCI	8.73	10.9	0.002
Previous cardiac surgery	11.9	15.3	< 0.001
Angina hx in 30 days prior	2.03	2.59	0.109
Hypertension	61.7	66.3	< 0.001
Peripheral vascular disease*	17.0	21.3	< 0.001
Rest pain/gangrene	13.3	17.0	< 0.001
Pulmonary			
COPD	7.37	10.1	< 0.001
Pneumonia–current	1.86	1.90	0.917
Dyspnea at rest	3.29	3.84	0.207
Dyspnea on exertion	86.3	82.8	< 0.001
Tobacco use†	22.6	22.4	0.780
Renal			
Mild renal disease	19.0	16.1	< 0.001
Moderate renal disease	42.6	35.3	< 0.001
Severe renal disease	21.9	18.9	< 0.001
Kidney failure	8.98	12.4	< 0.001
Acute renal failure‡	2.22	2.27	0.885
Central nervous system			
Impaired sensorium‡	2.77	3.15	0.350
Coma	0.01	0.05	0.357
Hemiplegia	2.83	3.15	0.440
Paraplegia	1.56	1.57	0.967
Quadriplegia	0.25	0.32	0.566
CVA with neuro deficit	6.18	6.62	0.458
CVA without neuro deficit	4.16	4.03	0.790
TIA	4.56	5.32	0.138
Tumor involving CNS	0.11	0.09	0.796
Hepatobiliary			
Ascites	5.04	7.73	< 0.001
Esophageal varices	0.47	0.51	0.796
Nutrition/endocrine/immune			
Diabetes–oral hypoglycemic	12.4	13.6	0.142
Diabetes–insulin	18.8	20.6	0.069
Alcohol§	2.64	3.15	0.206
Disseminated cancer	5.89	8.70	< 0.001
Steroid use‖	8.85	9.26	0.558
Weight loss#	9.55	13.9	< 0.001
Chemotherapy‖	3.26	4.17	0.042
Radiotherapy**	1.39	1.90	0.083
Systemic infection			
SIRS	13.8	14.6	0.319
Sepsis	7.76	8.84	0.100
Septic shock	0.97	1.16	0.440

(*continued*)

Table 1. Continued

Patient Risk Factors	Not Transfused (%) (n = 7,940)	Transfused (%) (n = 2,160)	*P* Value
Hematology			
Bleeding disorder	15.0	20.6	< 0.001
Previous operation within 30 days	12.6	12.0	0.487
Wound infection	25.4	26.6	0.254

With the exception of age, all numbers are percentages. Statistical analyses were performed using linear regression or logistic regression, as appropriate. Robust variance estimators were used.

* Requiring revascularization, angioplasty, or amputation. † Within 1 yr of surgery. ‡ Within 24 h before surgery. § > 2 drinks/day in 2 weeks before surgery. ‖ Within 30 days before surgery. # > 10% decrease in body weight in 6 months before surgery. ** Within 90 days of surgery.

Angina hx = history of angina; CHF = congestive heart failure; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; DNR = do not resuscitate status; MI = myocardial infarction; PCI = percutaneous coronary intervention; SIRS = systemic inflammatory response state; TIA = transient ischemic attack.

ripheral vascular disease, chronic obstructive pulmonary disease, pneumonia, dyspnea, renal disease, coma, hemiplegia, paraplegia, quadriplegia, stroke, hepatobiliary disease, nutritional status, and systemic infection) (see table 1 for list). Patients were classified by weight categories according to their body mass index: (1) underweight (less than 18.5 kg/m^2); (2) normal (18.5–24.9 kg/m^2); (3) overweight (25–29.9 kg/m^2); (4) obese (30–39.9 kg/m^2); (4) morbid obesity (40–49.9 kg/m^2); and (5) super obesity (greater than 50 kg/m^2). We defined renal dysfunction as follows: (1) mild renal dysfunction: glomerular filtration rate (gfr) 60–89 ml/min per 1.73 m^2; (2) moderate renal dysfunction: 30–59; (3) severe renal dysfunction: 15–29; and (4) kidney failure less than 15 or dialysis.[23]

The intraoperative transfusion status and baseline hematocrit were forced into each model. The ACS NSQIP data identify patients who received greater than four units of erythrocytes during either the pre- or postoperative period, and these patients were excluded from the study sample. The ACS NISQIP data do not include additional information on the number of transfusions received during the pre- and postoperative period. In our analyses, we have assumed that the preoperative hematocrit reflects any blood transfusions given during the preoperative period.*** We were, however, unable to adjust for any blood transfusion received during the postoperative period.

Fractional polynomials were used to examine the linearity of the association between baseline hematocrit and outcome.[24] Risk factors with large effect sizes and nonsignificant *P* values were also considered for inclusion in each model.

We constructed separate models for mortality and cardiac morbidity, with one-way interaction terms between baseline hematocrit and cardiac disease to examine the independent association between outcome and the use of blood transfusion in patients with and without cardiac disease. These interaction terms were found not to be significant and were not included in the final models.

We adjusted for surgical complexity using work relative value units. We also included separate intercept terms for the type of procedure by current procedural terminology code group: (1) intergumentary; (2) musculoskeletal; (3) vascular; (4) hemic and lymphatic system; (5) mouth, palate, salivary glands, pharynx, adenoids, and esophagus; (6) stomach, intestines, appendix and mesentery, rectum and anus, liver, biliary tract, pancreas, abdomen, peritoneum, and omentum (nonhernia); (7) endocrine system; and (8) hernia repair.

Multiple imputation was used to impute missing values[25] for the preoperative serum creatinine (259 patient records had missing values for the preoperative serum creatinine) using the STATA implementation of the MICE method of multiple imputation[26] described by van Buuren *et al.*[27] We specified the imputation model using nonparsimonious linear regression. Simpler approaches for handling missing data (such as deleting observations with missing data or using the missing-indicator method) may produce biased results.[28–30] Rubin rule was used to combine parameter estimates across the five imputed data sets obtained by multiple imputation.[26]

We also conducted a sensitivity analysis in which we used propensity score risk adjustment.[31,32] Nonparsimonious logistic regression was used to estimate a propensity score. The propensity score is the probability that patient will be transfused. The dependent variable is whether a patient received one or two units of erythrocytes *versus* no transfusion. We included all potential confounders as explanatory variables in the regression model: age, sex, surgical complexity, admission source, functional status, wound classification, and comorbidities (congestive heart failure, myocardial infarction, previous cardiac surgery, peripheral vascular disease, chronic obstructive pulmonary disease, pneumonia, dyspnea, renal disease, coma, hemiplegia, paraplegia, quadriplegia, stroke, hepatobiliary disease, nutritional status, and systemic infection) (see table 1 for list). The C statistic for the propensity model was 0.74, indicating acceptable discrimination. All of

*** For the purpose of the analysis, we have assumed that for patients who were transfused preoperatively, the preoperative hematocrit was drawn after all erythrocyte transfusions had been administered.

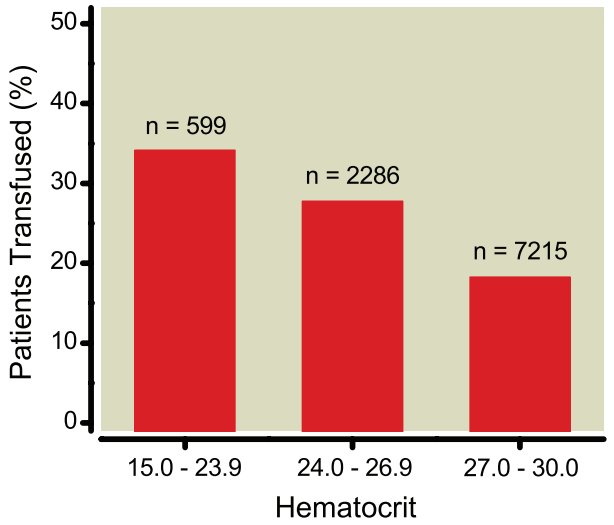

Fig. 1. Proportion of patients receiving one or two units of erythrocytes intraoperatively *versus* baseline hematocrit.

the baseline models were reestimated after adding the propensity score as an explanatory variable to evaluate the impact of blood transfusion on outcome.

Data management and statistical analyses were performed using STATA SE/MP version 11 (STATA Corp., College Station, TX). All statistical tests were two-tailed, and *P* values less than 0.05 were considered significant. We used robust variance estimators to account for the nonindependence of observations within hospitals.[33]

Model discrimination was assessed using the C statistic, and model calibration was assessed using the Hosmer-Lemeshow statistic.

Results

Demographics for patients in the no-transfusion group *versus* patients in the transfusion group are shown in table 1. In comparison with patients who did not receive an intraoperative blood transfusion, patients who received one or two units of erythrocytes intraoperatively were older, more likely to be female, transferred from another hospital, or have dependent functional status. Transfused patients were also more likely to have a history of percutaneous coronary intervention, previous heart surgery, kidney failure, or chronic obstructive pulmonary disease.

Overall, 21.4% of the patients were transfused intraoperatively. The rate of blood transfusion varied as a function of the baseline hematocrit (fig. 1): 34% of patients with a baseline hematocrit between 15% and 23.9% received a transfusion, compared with 18% of the patients with a baseline hematocrit between 27% and 30%.

The risk-adjustment models are shown in table 2. Each of the models exhibited acceptable discrimination. The C statistic for the 30-day mortality model was 0.81. The C statistic for the 30-day morbidity models ranged between 0.71 and 0.77. All of the models exhibited acceptable calibration based on the Hosmer–Lemeshow statistic ($P > 0.05$), with the exception of the cardiac model ($P > 0.039$), which had a marginally acceptable Hosmer–Lemeshow statistic.

Effect of Intraoperative Transfusion on 30-Day Mortality and 30-Day Complications

The 30-day mortality rate for patients who were transfused was 6.44 *versus* 4.26% for patients who were not transfused (table 2). In the multivariate analyses, blood transfusion was associated with an increased risk of death (odds ratio [OR], 1.29; 95% CI, 1.03–1.62). Patients receiving an intraoperative transfusion were more likely to have four of the seven major complications, compared with patients not receiving an intraoperative transfusion. Compared with patients who were not transfused, patients receiving one or two units of erythrocytes were more likely to have pulmonary complications (OR, 1.76; 95% CI, 1.48–2.09), sepsis (OR, 1.43; 95% CI, 1.21–1.68), thromboembolic complications (OR, 1.77; 95% CI, 1.32–2.38), and wound complications (OR, 1.87; 95% CI, 1.47–2.37) (table 3). The interaction between transfusion therapy and cardiac disease was not statistically significant for either mortality and cardiac morbidity. In our sensitivity analysis, in which a propensity score was included in the multivariate models, we found qualitatively very similar results (table 3). However, using the propensity-based technique, blood transfusion was marginally associated with higher mortality (OR 1.21; 95% CI 0.96, 1.52).

Discussion

In this study, we found that blood transfusion in the setting of noncardiac surgery is associated with increased risk of 30-day mortality and pulmonary, septic, wound, and thromboembolic complications. The increased risk of mortality and morbidity associated with blood transfusion was present after adjusting for patient demographics, functional status, comorbidities, and surgical complexity. Blood transfusion did not appear to be protective in patients with cardiovascular disease.

The magnitude of the increase in the risk of mortality and morbidity associated with intraoperative transfusion is important. In particular, patients who received one or two units of erythrocytes had a 29% increased odds of death and a 40–90% increased odds of pulmonary, sepsis, wound, or thromboembolic complications.

One of the most important limitations of this observational study was that we had information only on the baseline hematocrit and not on the hematocrit immediately before transfusion. Blood transfusion may be a marker for surgical bleeding. It is possible that surgical bleeding, and not the blood transfusion itself, may be responsible for worse outcomes in the transfusion cohort.[34] Information on the transfusion trigger during noncardiac surgery is frequently not available retrospectively, because the decision to transfuse is often a decision dictated by clinical circumstances. In design-

Table 2. Risk Models for the Association between Intraoperative Blood Transfusion and 30-Day Mortality and 30-Day Morbidity

		Morbidity						
Patient Risk Factors	Mortality	Cardiac	Pulm	Renal	CNS	Sepsis	Wound	Thromb
Transfusion	1.29*	1.40†	1.76‡	1.32	0.84	1.43‡	1.87‡	1.77‡
Age	1.04‡	1.03‡	1.01‡	—	—	—	—	1.01*
Male	—	—	—	—	—	1.18*	—	—
Work RVU	—	—	1.02‡	1.02*	—	1.03‡	1.04‡	1.03‡
Admission source								
Home	Ref	—	Ref	Ref	Ref	Ref	—	Ref
Chronic care facility	—	—	—	—	—	1.28†	—	—
Hospital	1.27	—	1.29*	0.48†	2.69§	1.35§	—	1.54*
DNR	2.26‡	—	—	—	1.87	—	—	—
Dependent functional status	1.90‡	—	1.64‡	—	—	1.60‡	1.21	—
Baseline hematocrit								
15.0–23.9	1.27	1.06	0.89	1.10	1.27	0.89	1.14	0.77
24.0–26.9	1.34*	1.05	1.08	1.34	1.80†	1.04	1.11	1.08
27.0–30.0	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Weight								
Underweight	1.82‡	—	—	—	—	—	1.60§	—
Overweight	—	—	—	—	—	—	—	—
Obese	0.72*	—	—	1.81‡	—	—	—	—
Morbid obesity	1.62†	1.99*	—	1.91†	—	—	—	—
Super obesity	2.59§	1.45	1.87*	—	—	—	—	—
ASA Class								
I	—	—	Ref	Ref	—	Ref	Ref	—
II	—	—	—	—	—	1.31	2.45	—
III	—	—	2.06‡	—	—	2.16†	2.24	—
IV or V	—	—	3.46‡	1.65§	—	3.42§	3.03	—
Cardiac								
CHF in 30 days before	1.84‡	2.02§	1.40*	—	—	—	1.42	—
MI in 6 months before	—	2.35§	—	1.93†	4.33§	—	—	—
Previous cardiac surgery	1.26†	1.56*	—	—	2.06*	—	—	—
Angina history in 30 days before	—	—	—	2.05*	—	1.46†	—	2.17*
Hypertension	—	1.39	—	—	—	—	—	—
Peripheral vascular disease	—	—	—	—	—	1.23	1.74§	—
Pulmonary								
COPD	—	—	—	—	—	1.23†	—	—
Pneumonia–current	1.62*	2.21*	—	—	—	1.36	—	—
Dyspnea on exertion	—	—	—	—	2.44§	—	—	—
Dyspnea at rest	2.00‡	2.17§	1.89‡	2.76‡	—	—	—	—
Tobacco use	—	—	1.28*	—	—	1.21*	1.34*	—
Renal								
Mild renal dysfunction	—	—	—	1.45	2.31*	—	—	—
Moderate renal dysfunction	1.14	1.47	—	3.23‡	1.98†	—	—	—
Severe renal dysfunction	1.63§	2.69‡	—	8.30‡	—	—	—	—
Chronic renal failure	2.71‡	3.61‡	1.22‖†	NA	—	—	—	—
Acute renal failure	—	1.64		NA	—	—	—	—
Central nervous system								
Impaired sensorium	2.15‡	1.63	1.55*	2.07*	2.39			1.70†
Quadriplegia	—	—	—	—	NA	3.67§	—	3.12†
Tumor involving CNS	—	—	—	4.96	—	—	4.67	—
Hepatobiliary								
Ascites	2.09‡	1.79*	1.69‡	2.09§	—	1.26†	—	—
Esophageal varices	1.87	—	—	—	2.94	2.18*	—	—
Nutrition/endocrine/immune								
Diabetes–insulin	—	1.60*	—	—	—	1.18†	—	—
Disseminated cancer	3.39‡	—	—	—	1.95	1.43§	—	2.05‡
Steroid use	1.44*	—	1.31*	—	—	1.34§	1.48*	1.80§
Weight loss	1.41*	—	—	—	—	—	—	—
Chemotherapy	1.61*	—	—	—	—	—	1.54†	—
Radiotherpay	—	—	—	—	—	—	—	1.95†

(*continued*)

Table 2. Continued

Patient Risk Factors	Mortality	Morbidity						
		Cardiac	Pulm	Renal	CNS	Sepsis	Wound	Thromb
Systemic infection								
SIRS	1.57‡	—	1.65‡	1.45†	—	1.98‡	1.40*	1.51*
Sepsis	—	—	1.34*	—	—	NA	1.82§	1.79§
Septic shock	2.36§	—	3.20‡	2.03	—	NA	1.45	—
Hematology								
Bleeding disorder	—	—	—	—	2.04*	—	1.35†	—
Previous operation within 30 days	—	—	—	—	—	1.27*	1.65§	1.75§
Wound infection	—	1.38†	1.25*	1.52*	—	1.66‡	NA	—
C statistic	0.81	0.77	0.74	0.76	0.74	0.72	0.71	0.73
Hosmer-Lemeshow statistic	7.48	16.2	11.3	4.23	2.56	12.5	8.33	9.60

The estimated odds ratios for the intercept terms for surgery CPT groups are not shown. — represents explanatory variables that were not included in the final model(s).

* *P* value ≤0.05. † *P* value ≤0.100. ‡ *P* value ≤0.001. § *P* value ≤0.01. ‖ Severe renal dysfunction and chronic renal failure were combined in the pulmonary morbidity model.

Angina hx = history of angina; ASA = American Society of Anesthesiologists; CHF = congestive heart failure; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; CPT = current procedural terminology; DNR = do not resuscitate; MI = myocardial infarction; NA = not applicable; Pulm = pulmonary; RUV = work relative value unit; SIRS = systemic inflammatory response state; thromb = thromboembolic.

ing this study, we assumed that limiting the transfusion group to patients with severe baseline anemia who received one or two units of blood intraoperatively would minimize the likelihood that the indication for intraoperative transfusion was significant intraoperative blood loss, as opposed to severe baseline anemia. We also limited the study cohort to patients undergoing nonemergent surgery, because we assumed that patients undergoing emergency surgery would be more likely to have significant intraoperative bleeding, compared with patients undergoing nonemergent surgery. These important assumptions cannot be tested empirically using our data.

Our results confirm the findings of previous studies based on patients undergoing cardiac surgery. In a single-center study of 11,963 patients undergoing isolated coronary artery bypass grafting, Koch and colleagues[9] at the Cleveland Clinic demonstrated that erythrocyte transfusion was associated with increased risk of mortality and postoperative complications. This study also controlled for the baseline hematocrit, but not for the hematocrit before transfusion. Murphy and colleagues, using a United Kingdom population registry, showed that patients undergoing cardiac surgery who received erythrocyte transfusion were more likely to have ischemic or infectious complications and were less likely to survive.[12] In a study from the Northern New England Cardiovascular Study Group, cardiac surgical patients who received one or two units of erythrocytes had a 16% higher increased long-term risk of death.[11] A recent study by Bernard *et al.*, also based on the ACS NSQIP database, found that intraoperative transfusion is associated with increased mortality and morbidity.[48] However, this study was not limited to patients with severe baseline anemia. It is therefore likely that most of the patients in this study who received blood transfusion had significant intraoperative blood loss,

Table 3. Impact of Intraoperative Transfusion on 30-Day Mortality and 30-Day Complications

Outcome	Transfusion Group, Outcome Rate (%)	No Transfusion Group, Outcome Rate (%)	Unadj OR Txf *vs.* No Txf (95% CI)	Adj OR Txf *vs.* No Txf (95% CI)	Adj OR Txf *vs.* No Txf (PS Method) (95% CI)
Mortality	6.44	4.26	1.55 (1.24, 1.90)	1.29 (1.03, 1.62)	1.21 (0.96, 1.52)
Cardiac complications	2.08	1.40	1.50 (1.06, 2.12)	1.40 (0.97, 2.03)	1.31 (0.88, 1.95)
Pulmonary complications	12.6	6.03	2.24 (1.92, 2.63)	1.76 (1.48, 2.09)	1.75 (1.47, 2.08)
Renal complications	2.69	1.85	1.46 (1.08, 1.99)	1.32 (0.93, 1.88)	1.29 (0.91, 1.84)
CNS complications	0.69	0.58	1.20 (0.67, 2.15)	0.84 (0.43, 1.64)	0.68 (0.34, 1.38)
Sepsis complications	16.4	9.81	1.81 (1.58, 2.07)	1.43 (1.21, 1.68)	1.46 (1.24, 1.72)
Wound complications	9.17	4.65	2.07 (1.73, 2.48)	1.87 (1.47, 2.37)	1.89 (1.49, 2.41)
Thromboembolic complicatioins	4.07	1.89	2.20 (1.69, 2.88)	1.77 (1.32, 2.38)	1.81 (1.34, 2.45)

Adj = adjusted; CI = confidence interval; CNS = central nervous system; OR = odds ratio; PS method = propensity score method; Txf = transfusion; Unadj = unadjusted.

making it difficult to separate out the adverse effects of transfusion *versus* blood loss on postoperative outcomes.

Carson and colleagues[35] conducted a retrospective analysis of 8,787 patients who underwent surgical repair of hip fractures. Blood transfusion during either the pre- or postoperative period was not associated with differences in mortality after adjusting for the nadir hematocrit. Most recently, the National Heart, Lung, and Blood Institute funded a randomized, controlled trial to examine whether higher blood transfusion triggers improve mortality, cardiac outcomes, functional outcomes, and morbidity in postoperative patients with cardiovascular disease who have undergone surgical repair of hip fractures.[36] Patients were randomly assigned to a transfusion threshold of 10 g/dl or to be transfused if they became symptomatic and their hemoglobin fell less than 8 g/dl. Results published in abstract form reveal that the symptomatic transfusion strategy yielded similar mortality and functional outcomes to the 10-g/dl transfusion approach.[37] Information on other outcomes from the Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) trial is not yet available.

The only other large, randomized, controlled trial to examine the impact of blood transfusion[38] (Transfusion Requirement in Critical Care Trial) was performed using critically ill patients and found no survival benefit after blood transfusion,[8] even for the subset of patients with cardiovascular disease.[39] There was, however, a trend toward improved survival in patients with severe ischemic heart disease.[39] Patients were randomly assigned to a restrictive transfusion strategy (patients were transfused if their hemoglobin dropped to less than 7.0 g/dl) *versus* a liberal transfusion strategy (patients were transfused if their hemoglobin dropped to less than 10 g/dl). There was no significant difference in 30-day mortality across the two groups. However, there was a trend toward lower survival in the liberal transfusion group. Further, subgroup analysis revealed decreased survival in the liberal transfusion group for patients younger than 55 and for less critically ill patients (Acute Physiology and Chronic Health Evaluation II score $\leq$ 20). The Transfusion Requirement in Critical Care Trial has been criticized for applying fixed treatment protocols to heterogeneous patient populations (with and without cardiovascular disease) whose response to treatment would have been expected, *a priori*, to differ.[40] Two retrospective studies in critically ill patients have also failed to demonstrate a survival advantage with blood transfusion.[13,15] Most,[18–20] but not all,[17] studies in patients presenting with acute coronary syndromes show that blood transfusion is associated with higher mortality. Finally, a recent meta-analysis of 45 retrospective studies, based on 272,596 patients, suggests that erythrocyte transfusion is associated with increased morbidity and mortality.[16]

The findings from the Transfusion Requirement in Critical Care and FOCUS trials, as well as from most observational studies, suggest that blood transfusion may have a narrow therapeutic window, even in critically ill patient populations that would be expected to benefit most from blood transfusion. Despite the fact that anemia has been consistently shown to worsen patient outcomes, the majority of studies do not demonstrate improved outcomes after blood transfusion. The benefits of blood transfusion may be offset by its adverse effects. The mechanism by which blood transfusion worsens outcomes is unknown. Erythrocyte transfusion results in transfusion-induced immunomodulation (TRIM) because of the infusion of cytokines, lipids, and other soluble bioactive substances, most likely because of allogenic leukocytes.[41,42] Immunomodulation may lead to immune activation, resulting in transfusion-related lung injury or immune suppression, increasing susceptibility to infectious complications.[41] Leukoreduction is associated with decreased mortality, but is not associated with changes in the incidence of serious nosocomial infections.[43] Erythrocyte storage leads to decreases in cellular deformability and increased adhesion to the vascular endothelium,[44] resulting in impaired microvascular flow and decreased oxygen delivery.[41,45] Recent work by Koch *et al.* shows that cardiac surgical patients receiving erythrocytes that had been stored for more than 2 weeks have a higher risk of in-hospital mortality and postoperative complications.[46] These clinical findings suggest possible strategies for reducing the adverse effects associated with erythrocyte transfusion.

Our study has major limitations. As described earlier, we were unable to control for the exact transfusion trigger that led to the transfusion. We also did not have information on the number of units transfused during the postoperative period. Patients could have received up to four units of erythrocytes postoperatively; patients receiving more than four units of erythrocytes postoperatively were identified in the database and were excluded from the study cohort. This could have led to two potential biases. First, if patients in the no-transfusion group received blood postoperatively, then our study would have been biased toward the null, leading us to underestimate the effect of blood transfusion on outcomes. This form of bias would have been important only if we were not able to detect a significant difference between the transfusion and the no-transfusion group. Second, patients in the transfusion group could have received up to four units of blood postoperatively. In this case, our assumption that significant bleeding was not a cause of the outcome difference across the two groups is less likely to be valid.

Another potential limitation of this study was that we were unable to control for hospital effects owing to the absence of hospital identifiers in our data. There may have been variability in hospital quality and variability in hospital transfusion strategies—transfusion triggers, use of leuko-reduced blood, and blood storage—which may have potentially confounded the association between blood transfusion and outcome. Finally, the possibility of omitted variable bias is always present in observational studies. An editorial by Carson and Klein elegantly summarized the problem of uncontrolled

confounding: "blood transfusion is more frequently administered to sick patients and sick patients more frequently develop infections and die."[38] The corollary to this is that surgical patients with significant intraoperative bleeding are more likely to receive blood transfusions, and patients who bleed are also more likely to have worse outcomes.

Conclusion

This multicenter observational study suggests that intraoperative blood transfusion is associated with a higher risk of mortality and morbidity. It is unknown whether this association is due to the adverse effects of blood transfusion or is, instead, the result of increased blood loss in the patients receiving blood. There is increasing evidence that blood transfusion does not lead to improved outcomes, despite the finding that anemia is associated with decreased survival. The Transfusion Requirement in Critical Care and FOCUS trials provide evidence supporting a restrictive transfusion strategy in intensive care unit patients and in postoperative surgical patients, respectively. Current guidelines recommend blood transfusion when the hemoglobin concentration is less than 6 g/dl and the avoidance of blood administration when the hemoglobin concentration is greater than 10 g/dl.[47] These recommendations do not address the need for intraoperative transfusion in the large group of surgical patients where the hemoglobin concentration is between 6 and 10 g/dl. Given the potentially large difference in outcome attributable to intraoperative blood transfusion in this patient population, we believe that our findings should lead to consideration of a randomized, controlled trial comparing a restrictive intraoperative transfusion strategy to a liberal one in patients undergoing noncardiac surgery.

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