The Association of Perioperative Red Blood Cell Transfusions and Decreased Long-Term Survival After Cardiac Surgery

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BACKGROUND: Exposure to red blood cell (RBC) transfusions has been associated with increased mortality after cardiac surgery. We examined long-term survival for cardiac surgical patients who received one or two RBC units during index hospitalization.

METHODS: Nine thousand seventy-nine consecutive patients undergoing coronary artery bypass graft, valve, or coronary artery bypass graft/valve surgery at eight centers in northern New England during 2001–2004 were examined after exclusions. A probabilistic match between the regional registry and the Social Security Administration's Death Master File determined mortality through June 30, 2006. Cox Proportional Hazard and propensity methods were used to calculate adjusted hazard ratios.

RESULTS: Thirty-six percent of patients ($n = 3254$) were exposed to one or two RBC units. Forty-three percent of RBCs were given intraoperatively, 56% in the postoperative period and 1% were preoperative. Patients transfused were more likely to be anemic, older, smaller, female and with more comorbid illness. Survival was significantly decreased for all patients exposed to 1 or 2 U of RBCs during hospitalization for cardiac surgery compared with those who received none ($P < 0.001$). After adjustment for patient and disease characteristics, patients exposed to 1 or 2 U of RBCs had a 16% higher long-term mortality risk (adjusted hazard ratios = 1.16, 95% CI: 1.01–1.34, $P = 0.035$).

CONCLUSIONS: Exposure to 1 or 2 U of RBCs was associated with a 16% increased hazard of decreased survival after cardiac surgery.

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There is growing evidence that transfusion of allogeneic red blood cells (RBCs) during management of cardiac surgical patients is associated with increased in-hospital morbidity and mortality.[1] Additionally, two groups have observed that patients exposed to RBC transfusion experienced decreased long-term survival after coronary artery bypass graft (CABG) surgery.[2,3] Similar observations of dose-dependent decreased long-term survival after RBC

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transfusion have been previously made among general hospitalized patients.[4]

The association of RBC transfusion and in-hospital adverse events may be causally explained by increased rates of infection among patients exposed to RBCs.[5–8] This proposed cause and effect is logical temporally, as the adverse outcomes occur within a reasonable time after the exposure. However, this same mechanism is more difficult to accept as an explanation for decreased long-term survival after exposure to RBC transfusions when the adverse events, i.e., deaths, are occurring so long after the exposure. In fact, several authors have opined that observations of reduced survival after RBC transfusion are explained by RBC transfusion acting as a marker for some other conditions that limit survival, such as patient characteristics (e.g., age or coexisting disease) or medical indications (e.g., perioperative hemorrhage).[9–11]

The association of long-term survival and perioperative RBC transfusion during cardiac surgery has not been fully characterized. The studies by Engoren et al.[3] and Koch et al.[2] used rigorous multivariate and propensity analysis to demonstrate that differences inpatient characteristics do not explain significant reductions in survival, as was previously suggested. However, the cohorts of cardiac surgical patients in both studies contained patients who received large doses of RBC transfusions. Among such patients, RBC transfusion could be a marker for a medical indication that limits survival, such as perioperative hemorrhage or worse cardiopulmonary function.

The current study was designed to limit the potential impact of such confounding medical indications on our observation of survival by restricting the analysis to only those patients exposed to small quantities of RBC transfusions (1 or 2 U) compared with those with no exposure during their index cardiac surgery admission. This analysis is focused on patients who were transfused as treatment for stable perioperative anemia.

METHODS

The Northern New England Cardiovascular Disease Study Group (NNECDSG) is a voluntary research consortium composed of eight medical centers in Vermont, New Hampshire, and Maine. The intent of the group is to foster continuous improvement in the quality of care of patients with cardiovascular disease. Registries containing data on all CABG procedures performed in the region since 1987 and all valve procedures performed since 1989 are maintained and regularly validated.

This prospective observational study examined 15,512 consecutive patients undergoing first-time CABG, valve or CABG/valve surgery in northern New England from 2001 to 2004 at all eight centers. Excluded were patients with additional surgical procedures ($n = 1459$), prior CABG or valve surgery ($n = 923$), emergency procedures ($n = 847$), patients who returned to the operating room for reexploration ($n = 383$), and patients who received three or more units of RBCs ($n = 2821$). After exclusions, the analysis dataset included 9079 cardiac surgery procedures performed by 37 surgeons at all eight centers during the 4-yr period from 2001 to 2004. There were 964 off-pump procedures included in the analysis. Complete data regarding RBC transfusion exposure during index hospitalization was available for all procedures. Timing of transfusion (preoperative, intraoperative, or postoperative) and number of units transfused was collected. The decision to transfuse was at the discretion of the patient care team.

The participating medical centers received internal review board approval for participation in the registry, data from which were used for this study. We had full access to the data and take responsibility for its integrity.

Data were collected on patient demographics, procedure characteristics, and RBC use. Data fields and definitions are available at www.NNECDSG.org. The NNECDSG conducts regular validation of its registries to verify capture of all procedures and vital status at discharge from the index hospitalization by determining the concordance between hospital discharge data and NNECDSG registry data.

The outcome measure for this analysis was all-cause mortality over a 5-yr period. A probabilistic match between the regional registry and the Social Security Administration's Death Master File (SSA), United States Department of Commerce Technology Administration, determined mortality through June 30, 2006. Linkage was made using a combination of first name, last name, date of birth, date last known alive, last known state of residence, and Social Security number. The sensitivity of the SSA (92.2%) is comparable with the National Death Index among American-born individuals (87%–98%). Schisterman et al.[12] reported a decrease of nearly 10% in the sensitivity of the SSA file among foreign-born individuals.

Kaplan-Meier survival curves were plotted by extent of RBC exposure (zero units versus 1 or 2 U of RBCs). The log-rank test and Cox Proportional Hazards modeling were used for univariate and multivariate tests of statistical significance, respectively. In addition, a propensity-adjusted analysis was performed and results were compared with those from the multivariate Cox model. All of the analyses were performed using Stata release 9.1 software.[13]

RESULTS

There were 9079 patients in this cohort after the exclusions. Thirty-six percent of patients ($n = 3254$) were exposed to RBCs. Fifty-six percent of these transfusions were postoperative ($n = 1136$ receiving 1

Table 1. Patient and Disease Characteristics by Red Blood Cell Use

Variable	Red blood cell use: No blood	1–2 units	*P*
Number of procedures	5825 (64.2%)	3254 (35.8%)	—
Age, (yr) % by group			
<60	40.7	20.3	<0.001
60–69	32.3	29.9	
70–79	22.7	37.7	
≥80	4.3	12.2	
Female sex, %	14.0	42.2	<0.001
Body surface area (m^2), %			
<1.70	3.8	15.4	<0.001
1.70–1.99	32.6	48.9	
≥2.00	63.6	35.7	
Preoperative hematocrit (%), % by group			
<36	8.1	31.5	<0.001
36–39	24.8	34.4	
40–42	31.4	20.6	
≥43	35.7	13.6	
Comorbid disease, % yes			
Vascular disease	15.5	23.3	<0.001
Diabetes	28.6	34.7	<0.001
COPD	8.7	12.0	<0.001
CHF	12.3	21.4	<0.001
Dialysis	0.4	1.2	<0.001
Creatinine (mg/dL)			
<1.0	41.6	41.7	<0.001
1.0–1.4	52.6	48.1	
1.5–1.9	4.5	6.5	
≥2.0	1.3	3.8	
White blood cell ≥12,000	5.3	6.4	0.028
Ejection fraction <40 (%), % yes	10.1	13.9	<0.001
Coronary disease			
Left main stenosis, % yes			
none	76.1	74.9	0.370
50%–89%	20.8	22.0	
≥90%	3.1	3.1	
Three-vessel disease, % yes	39.5	41.8	0.038
MI within 7 days, % yes	14.0	17.2	<0.001
Preoperative LOS (days), % yes			
0	39.1	32.3	<0.001
1	19.7	20.0	
2	12.3	12.1	
≥3	28.9	35.6	
Preoperative IABP, % yes	2.6	4.2	<0.001
Urgent at surgery, % yes	60.4	66.2	<0.001

* *P* value from χ^2 test.

COPD = chronic obstructive pulmonary disease; CHF = congestive heart failure; MI = myocardial infarction; IABP = intraaortic balloon pump; LOS = length of stay.

Table 2. Intraoperative and Treatment Variables

Variable	Red blood cell use: No blood	Blood 1–2 units	*P**
Number of procedures	5825 (64.2%)	3254 (35.8%)	—
Procedure			
CABG	82.2	74.7	<0.001
Valve	11.6	12.3	
CABG/valve	6.2	12.9	
OPCAB, % yes	11.4	9.3	0.002
Pumptime, % by group			
<70 min	20.4	16.6	<0.001
70–89 min	25.2	23.9	
90–109 min	24.9	23.6	
≥110 min	29.5	35.9	
Antifibrinolytic use, %			
None	7.0	5.3	<0.001
Amicar/tranexamic acid	71.0	62.8	
Aprotinin	22.0	31.9	
Intra/postoperative IABP, % yes	0.7	1.5	<0.001
Use of IMA, % yes	86.0	83.0	<0.001
Lowest core temperature, %			
<33.0°C	19.8	29.5	<0.001
33.0°–33.9°C	19.3	19.5	
34.0°–34.9°C	36.4	31.8	
≥35.0°C	24.4	19.3	
Nadir HCT (%), %			
<21	5.6	28.1	<0.001
21–23	24.1	39.5	
24–25	25.3	18.2	
≥26	45.0	14.3	

* *P* value from χ^2 test.

OPCAB = off-pump coronary artery bypass; IABP = intaaortic balloon pump; IMA = internal mammary artery; HCT = hematocrit; CABG = coronary artery bypass graft surgery.

U; *n* = 808 receiving 2 U), 43% were intraoperative (*n* = 650 with 1 U; *n* = 848 with 2 U), and 1% were preoperative. Sixty-three percent of women received RBCs compared with only 27% of men.

Patient and Disease Characteristics

There were significant differences in preoperative factors between patients who did and did not receive blood (Table 1). Patients receiving small quantities of blood were much more likely to be female with a smaller body surface area and a lower preoperative hematocrit (Hct). They were also older and more likely to have a comorbid illness, such as peripheral vascular disease (PVD), diabetes, chronic obstructive pulmonary disease (COPD), renal disease or congestive heart failure (CHF). Those receiving blood were somewhat more likely to have a depressed ejection fraction (EF <40) or to have suffered a myocardial infarction within 7 days. They had somewhat longer preoperative lengths of stay, and had a greater likelihood of having a preoperative intraaortic balloon pump (IABP) and to present urgently for surgery. Although the rate of three-vessel coronary disease was slightly higher in the blood group, there was no difference between the groups in the rate of left main coronary stenosis.

Procedural Characteristics

There were also differences in procedural characteristics between patients who did and did not receive blood (Table 2). Patients who received 1 or 2 U of RBCs were more likely to have had a CABG/valve procedure and less likely to have had an off-pump

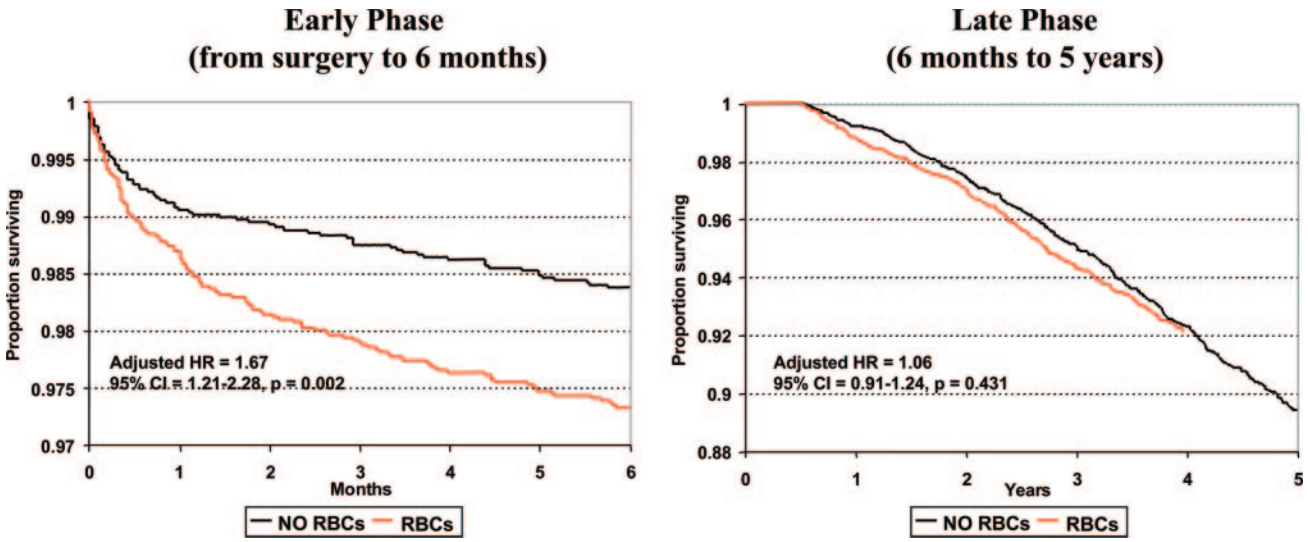

Figure 1. Adjusted survival by red blood cell use.

coronary artery bypass than those who did not. Patients in the blood group had slightly longer pump runs and were more likely to have received aprotinin. Rates of intra- or postoperative IABP were higher in the blood group although rates were low for all patients. Internal mammary artery (IMA) use was similar between groups. More of the patients who received blood had lower core temperatures and many more patients who were transfused had nadir Hcts below 24 (68% in blood group versus 30% in no blood group). Although tests comparing the two groups were all statistically significant, with the exception of nadir Hct, most differences were not large.

Survival Analysis

Among the 9079 patients, median follow-up time was 4.4 years. The overall annual incidence rate of death was 2.7% per 100 person years.

The overall crude hazard ratio (HR) for blood versus no blood was 1.94 (95% CI = 1.71–2.20; $P < 0.001$). Significant independent predictors of long-term mortality ($P < 0.05$) included age, diabetes, PVD, CHF, COPD, dialysis, preoperative creatinine, preoperative white blood cell count, preoperative Hct, EF < 40, preoperative length of stay, preoperative IABP placement, and priority at surgery. After adjustment for preoperative characteristics, there was still a 16% increased hazard of death with RBC use (HR = 1.16; 95% CI: 1.01–1.33; $P = 0.035$). Two distinct survival phases were noted, early (surgery to 6 mo) and late (6 mo to 5 yr) (Fig. 1). During the early time period, exposure to 1 or 2 U of RBCs was associated with a 67% increased hazard of death (HR = 1.67; CI 1.21–2.28; $P = 0.002$) after adjustment for patient and disease characteristics. During the late phase (6 mo to 5 yr), there was no significant association of exposure to blood and survival (HR = 1.06; 95% CI = 0.91–1.24, $P = 0.431$) (Table 3).

When procedural variables were added to preoperative variables in the adjusted Cox model, the effect remained the same (adjusted HR with preoperative variables = 1.16, 95% CI = 1.01–1.33, $P = 0.035$; adjusted HR with preoperative and intraoperative variables = 1.16, 95% CI = 1.01–1.34, $P = 0.038$).

Table 3. Adjusted[a] Hazard Ratios (HR) for Red Blood Cell (RBC) Transfusion vs No RBC Transfusion

	All patients		
Time period	Adjusted HR	95% CI	*P*
Surgery to 6 mo	1.67	1.21–2.28	0.002
6 mo to 5 yr	1.06	0.91–1.24	0.431
Overall	1.16	1.01–1.33	0.035

[a] Adjusted for age, diabetes, peripheral vascular disease, congestive heart failure, chronic obstructive pulmonary disease, preoperative dialysis, preoperative creatinine, preoperative white blood cell count, preoperative hematocrit, ejection fraction, preoperative length of stay, preoperative intraaortic balloon pump, priority at surgery.

Propensity Analysis

Adjusted HRs were also calculated using a propensity model that included significant predictors of RBC usage (CABG/valve procedure, age, sex, body surface area, preoperative HCT, diabetes, PVD, preoperative creatinine, EF, three-vessel coronary disease, preoperative IABP). Patients were matched within strata of the propensity score. Within strata, mean propensity scores for blood versus no blood patients were required to balance, and values for each covariate were required to match within certain limits. Propensity score strata were then used in an adjusted Cox model. The adjusted HR using this methodology was 1.16 (95% CI = 1.00–1.34; $P = 0.043$), results that are nearly identical to the previously described covariate adjustment.

DISCUSSION

Exposure to limited RBC transfusions (1 or 2 U) during admission for cardiac surgery was associated with a 16% increased adjusted risk of 5-yr mortality in this regional cohort of cardiac surgical patients. The

impact on survival was most pronounced in the first 6 mo after surgery, with a 67% increased adjusted risk. This adverse impact on survival after exposure to RBC transfusion was not explained by differences among patients who received blood or by procedural characteristics. This was confirmed using propensity score analysis. Furthermore, because we excluded patients who were exposed to larger amounts of RBC transfusions, it is unlikely that the decreased survival observed with RBC transfusion exposure is a marker for some other condition that limits survival, such as perioperative hemorrhagic shock, as suggested by other authors.[4,9–11]

These findings are important for three reasons. First, among eight cardiac surgical programs in our region, the majority of patients who receive RBCs are exposed to only 1 or 2 U of RBCs (3254 of 6075 patients transfused). For anesthesiologists and cardiac surgeons, transfusion of just 1 or 2 U of RBCs is often viewed as a minor and routine decision as we manage cardiac surgical patients. These data strongly suggest that the decision to transfuse RBCs places this majority group of patients at significant risk. Based on these findings, we are suggesting that any physician or health care provider in our region who currently views RBC transfusion decisions as innocuous or unimportant to reassess their approach to the management of anemia. Although we would always support consideration of RBC transfusion in the presence of active hemorrhage, these data, together with our prior analysis, seriously question the treatment of stable anemia with RBC transfusion to "top off" the patient's hemoglobin.[14]

Second, when the high volume of cardiac surgical procedures performed internationally is considered, there is an even larger population of cardiac surgical patients exposed to small doses of RBC transfusions worldwide each year. Clinicians in our region are actively rethinking how to approach the management of anemia. Our observations, combined with those by Engoren et al. and Koch et al.,[2,3] strongly suggest that all cardiac surgical programs should examine their practice of RBC transfusion.

Third, huge variation in RBC transfusion practice has been documented among cardiac surgeons for many years.[15,16] This variation continues to persist despite the introduction of practice guidelines, improved blood conservation techniques, a randomized trial and differences inpatient disease burden, or differences in procedural factors. The majority of the variation depends on who is the provider. In other words, providers approach the decision to transfuse RBCs differently. On the basis of these observations of variation, we believe that a large number of these 1 or 2 U transfusions may be avoidable. If the majority of patients were managed as if they were Jehovah's Witnesses, using readily available and relatively simple blood conservation techniques, the development of perioperative anemia could be largely avoided. Furthermore, the only randomized controlled trial of blood transfusion by Hebert et al.[17] suggests that a conservative strategy for blood transfusion is just as effective as a more liberal strategy. Although that trial was not focused on cardiac surgical patients, a conservative strategy may be appropriate for cardiac surgical patients who are not experiencing active myocardial ischemia. Adopting a conservative RBC strategy in combination with efforts to prevent anemia could dramatically reduce the need for small dose RBC transfusions.

These data confirm and supplement the observations of Engoren et al. and Koch et al.,[2,3] who concluded that exposure to any quantity of RBC transfusions was associated with decreased survival after coronary artery surgery. In those prior analyses, patients who needed to return to the operating room for postoperative bleeding or were emergency patients (who are at increased risk for bleeding) were not excluded, and in Koch et al.'s study there was marked increase in risk of mortality for patients exposed to three or more units of blood compared with those exposed to 1 or 2 U of blood. Patients exposed to three or more units of blood may experience not only the risks directly related to the RBC transfusions but also risks from the perioperative events that necessitated the need for blood administration. In our study, we used restrictive exclusion (excluded patients exposed to three or more units or RBCs) criteria to ensure that patients who experienced active hemorrhage were removed from our analysis and the observation of reduced survival after RBC transfusion remained significant even when only 1 or 2 U transfusions were considered. The Engoren et al. data set is from 1994 to 1997, and the Koch et al. data set is from 1995 to 2002. The current dataset is from 2001 to 2004, providing the most current dataset available for a long-term analysis. We considered both patient characteristics and procedural variables to determine whether the association between RBC transfusion and decreased survival was explained by other factors. Using conservative methods, we confirmed the observations of Engoren et al. and Koch et al., that exposure to even small amounts of RBC transfusion adversely impacts survival after cardiac surgery.

The magnitude of the impact of RBC transfusion on survival we report is clinically important, especially when compared with other important risk factors. Many factors, such as age, diabetes, CHF, and COPD, have a more significant impact on survival but, for the most part, are not notifiable. Maximizing the use of IMA conduit has been known to provide a benefit on survival for many years.[18] More recently the use of both IMAs was associated with a 19% improvement in survival after coronary bypass surgery.[19] Based on our analysis, eliminating nonessential low-volume transfusion would also provide a benefit of survival.

We, similar to Engoren et al. and Koch et al., observed two distinct phases of survival after 1 or 2 U of RBCs. We report an initial decrease in survival among those exposed to transfusion that is dramatic during the first 6 mo after surgery. For those patients who survive 6 mo, there was not a significant difference in survival among patients exposed to blood after adjustment for patient and disease characteristics.

This study did not evaluate cause and effect for the observed findings. We did not have data about the mode of death for each of the patients reported in the SSAs Death Master File. However, the work of other authors may provide plausible mechanisms of action. One possible mechanism is postoperative infectious processes.[5–8] These infections may be related to suppression of immune function as a result of the exposure to RBC transfusion. Another possible mechanism is damage or congestion of the microcirculation resulting from transfused RBCs that have abnormal morphology.[20]

Although rare, ABO incompatibility is another important risk related to RBC transfusion. Another hypothesis is that RBC transfusions may exert a long-lasting alteration upon the recipient's immune function, thereby impacting long-term survival.[21]

There are other limitations that are notable. First, we are not able to differentiate the use of leukoreduced transfusions. During the time period that was investigated, however, most of the centers in this analysis transitioned to the use of leukoreduced RBC units. We did not collect this information at a patient level; therefore, we were unable to include leukoreduction as a part of our analysis. Second, we did not measure exposure to platelets, fresh frozen plasma, or cryoprecipitate. Third, observational studies are subject to confounding. We have identified all patients and disease characteristics that are collected in the NNECDSG database that are important predictors of mortality, but failure to identify one or more key confounding variables could alter the observations of this analysis. There are statistically significant differences for several of these patient and disease characteristics (Table 1). Appropriately, we addressed these confounders through risk adjustment and restriction. Clearly, a prospective, randomized trial of intraoperative RBC transfusions during cardiac surgery would contribute to confirmation of this and other observations regarding long-term survival after coronary artery bypass surgery.

Summary

Exposure to 1 or 2 U of transfused RBCs is associated with decreased long-term survival after cardiac surgery. These data support blood conservation and avoidance of unwarranted RBC transfusions to reduce a patient's risk of short- and long-term mortality.

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