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Is Transfusion Associated With Graft Occlusion After Cardiac Operations?

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Background. **Packed red blood cell (RBC) transfusions are associated with increased mortality after coronary artery bypass grafting (CABG) but not after cardiac valve operations. Transfusions are associated with increased strokes and deep venous thromboses after cardiac operations as well as increased peripheral vascular graft thrombosis. The purpose of this study was to determine if RBC transfusions were associated with a greater hazard of an occluded graft developing after CABG.**

Methods. **Patients who underwent symptom-driven coronary artery angiography after CABG were analyzed using Cox models and propensity scoring to compare outcomes based on the RBC transfusion status during their index CABG hospitalization.**

Results. **We analyzed 940 patients. We found that patients who received transfusions were more likely to have occluded grafts on angiography (hazard ratio [HR], 1.24; 95% confidence interval [CI], 1.03–1.50; $p = 0.02$). After adjusting for other factors, we found that RBC transfusion was associated with about a 20% increased hazard of graft occlusion (HR, 1.21; 95% CI,1.07–1.37; $p = 0.003$).**

Conclusions. **Perioperative RBC transfusion is associated with graft occlusion after CABG at both the patient and graft levels. These results add to the growing body of evidence that homologous RBC transfusion is not risk free but is associated with a variety of adverse effects including midterm graft failure.**

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Patients exposed to red blood cell (RBC) transfusions are at increased risk of morbidity and long-term mortality. Interestingly, this effect is most pronounced among patients undergoing isolated coronary artery bypass grafting (CABG). Previous reports have found limited risk associated with transfusions among patients undergoing isolated valve operations, suggesting that intrinsic factors unique to CABG (relative to valve operations) may in part explain the role of transfusion in this setting [1–5]. Because the studies showing an association between transfusion and late mortality have not shown a cause-and-effect relationship, investigators have inferred a number of mechanisms to explain the apparent association between RBC transfusions and mortality; these include immunomodulation or microcirculatory injury from transfused RBCs [2–4]. However, the lack of a similar mortality association in patients not undergoing CABG suggests that the mechanism of RBC transfusion causing death is not generalizable to all types of surgical procedures but instead may be specific to CABG [1–5].

Such reasoning is appealing because CABG frequently produces endothelial disruption and injury to the graft conduits, leading to localized inflammation and coagulation abnormalities [6–8], which may be exacerbated by the additional detrimental effect of homologous RBC exposure, eg, an enhanced inflammatory state and thrombogenesis. In patients with gastrointestinal hemorrhage, RBC transfusion attenuates the hypercoagulable state and is associated with increased repeated bleeding; however, its effects on the vascular system may differ [9, 10]. Indeed, studies have shown that transfusion is associated with increased graft thrombosis in infrainguinal vascular operations, deep venous thrombosis after cardiac operations, and stroke after CABG [11–13].

Studies that evaluated markers of CABG graft occlusion found several patient-level factors, such as age, sex, left ventricular function, fibrinogen, and creatinine to be associated with graft occlusion [14, 15]. However, to our knowledge, no study has evaluated the effect of RBC transfusion on graft occlusion in CABG. Given these findings, we undertook a single-center observational study to investigate the association of RBC transfusions on graft patency in the setting of isolated CABG. Specifically, we hypothesized that perioperative RBC transfusion is associated with earlier graft closure.

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Secondarily, we hypothesized that antiinflammatory agents, specifically ketorolac, might reduce the apparent impact of RBC transfusions on graft occlusion [16].

Material and Methods

After institutional review board approval, which waived patient consent because the data were deidentified, we examined the institutional Society of Thoracic Surgeons National Adult Cardiac Surgery Database consisting of demographics, comorbidities, perioperative factors, processes of care, medications, and coronary angiograms [16]. The index operation was performed as previously described [17]. Post-CABG coronary angiograms were obtained at the discretion of the patients' cardiologists based on the development of symptoms suggestive of myocardial ischemia. Angiographic results, based exclusively on the cardiologists' interpretations, were entered into the institutional database. For patients who had more than 1 angiogram, only the first was used. Adult patients were included if they underwent CABG between January 3, 1997 and April 24, 2007 and had coronary angiography by April 24, 2007. Graft failure was defined as complete closure of the graft (FitzGibbon class O).

Statistics

Patients who had 1 or more graft closures were compared with patients with no graft failure, using the Student's t test, Mann-Whitney test, χ^2 test, and Fisher's exact test. Multivariable analyses were performed at both patient and graft levels (Table 1). First, using Cox models, the hazard ratio (HR) of transfusion-associated graft closure was determined, adjusting for demographics, comorbidities, and preoperative medication (Table 2) and for the number and type of grafts (internal mammary, radial, or saphenous). RBC transfusions given perioperatively during the index hospitalization were treated as a dichotomous variable. Transfusions and transfusion-ketorolac interaction were forced initially to be in the model (model 1). Subsequently, the interaction term was removed and the model was recalculated with the remaining factors from that model (model 2).

Second, propensity methods were used to adjust for variables that were associated with transfusion. Using nonparsimonious logistic regression with transfusion as the dependent variable and demographics, comorbidities, and preoperative medicines as independent variables (Table 2), propensity-to-be-transfused scores were calculated. Cox models were created using propensity scores, transfusion status, ketorolac use, and number and type of grafts, with patients with and without graft occlusion as the dependent variable (model 3). To evaluate the effects at a graft level and not just a patient level, patients pairs, who differed on transfusion status, were created with identical type and number of grafts (model 4). (Models are summarized in Table 1.) For example, in model 4, a transfused patient with 1 internal mammary artery, 1 radial artery, and 2 vein grafts was matched to a nontransfused patient with 1 internal mammary artery, 1 radial artery, and 2 vein grafts. Because we had previously used part of this database to evaluate the effect of ketorolac on graft occlusion and found an association between postoperative ketorolac use and delayed graft occlusion [16], we further required that both members of each pair also be matched on use or nonuse of ketorolac. Finally, we used propensity scores, calculated as described earlier, to adjust for the other factors that were possibly associated with transfusion. For all models, 95% confidence intervals (CIs) that excluded 1 denoted statistical significance. Statistics were performed using R (R Foundation, Vienna, Austria).

Table 1. Summary of the Different Models

Model 1—patient level: All variables included with transfusion and transfusion; ketorolac interaction forced to remain in the model
Model 2—patient level: Factors of model 1 with the interaction term removed and no variables forced
Model 3—patient level: Propensity (to be transfused) score included in the model
Model 4—graft level: Patients identically matched on the number and type of grafts and use or nonuse of ketorolac

Power Analysis

With 1,051 patients and a transfusion rate of 33% and a 70% match, assuming 2.5 grafts per matched patient and 1,200 grafts in the propensity-matched groups, the study would have 90% power with an alpha equal to 0.05 to detect a difference in graft occlusion of 10% (65% versus 55%).

Results

Of the 3,843 patients who underwent isolated CABG, 940 patients (24%) with 3 ± 1 (mean ± standard deviation) grafts were studied 2.4 ± 2.0 years after CABG for symptoms suggestive of myocardial ischemia. Five hundred thirty-nine of patients (57%) studied had 1 or more occluded grafts. Saphenous grafts had a 42% occlusion rate (240 of 542 grafts in transfused patients versus 369 of 917 in nontransfused patients; $p = 0.78$), radial grafts had a 34% occlusion rate (51 of 141 grafts in transfused patients versus 131 of 401 in nontransfused patients; $p = 0.47$), and internal mammary grafts had an 8% occlusion rate (27 of 264 grafts versus 45 of 618 grafts in nontransfused patients; $p = 0.29$). By univariate analysis, patients with occluded grafts were more likely to have received blood transfusions (35% versus 26%; $p = 0.004$). They also had more diseased vessels and more grafts and required longer cardiopulmonary bypass and cross-clamp times. They were less likely to have had strokes and congestive heart failure and to have received ketorolac (Table 2). After adjusting for other factors that were associated with transfusion (model 1), we found that there was a trend toward earlier graft closure (HR, 1.22; 95% CI, 0.96–1.55; $p = 0.11$) associated with transfusion with a small nonsignificant transfusion-ketorolac interaction (HR, 1.05; 95% CI, 0.73–1.52; $p = 0.80$) (Table 3, top; Fig 1) With the interaction term removed (model 2), use of

Table 2. Patient Characteristics and Processes of Care

	No Occlusions n = 401		≥ 1 Occluded Conduit n = 539		
Factor	No	%	No	%	*p* Value
Male sex	260	65	340	63	0.584
Family coronary artery disease	265	66	376	70	0.257
Comorbidities					
Smoker	277	69	355	66	0.325
Diabetes mellitus	144	36	204	38	0.585
Hyperlipidemia	283	71	393	73	0.463
Renal failure	14	4	11	2	0.219
Hypertension	332	83	442	82	0.796
CVA	39	10	33	6	0.047
COPD	83	21	120	22	0.576
Peripheral vascular disease	66	17	74	14	0.267
Cerebrovascular disease	99	25	105	20	0.066
Stable angina	225	56	285	53	0.354
Unstable angina	154	38	205	38	0.946
Myocardial infarction	214	53	291	54	0.895
≤ 24 h	11	3	13	2	0.835
1–7 d	74	19	103	19	0.866
8–21 d	12	3	8	2	0.169
> 21 d	117	29	167	31	0.566
Congestive heart failure	52	13	38	7	0.003
New York Heart Association classification					
I	14	4	22	4	0.732
II	120	30	156	29	0.852
III	181	45	260	48	0.356
IV	146	36	179	33	0.332
Arrhythmia	25	6	29	5	0.575
Previous cardiac intervention					
Any	158	39	206	38	0.735
Cardiac surgery	28	7	30	6	0.412
Coronary artery bypass	21	5	28	5	0.999
Preoperative medication					
Digitalis	26	7	14	3	0.005
Beta-blocker	241	60	359	67	0.047
Intravenous nitrate	123	31	166	31	0.999
Anticoagulation	160	40	216	40	0.999
Diuretic agent	98	24	109	20	0.131
Inotropic agent	7	2	5	1	0.379
Corticosteroid	17	4	9	2	0.025
Aspirin	294	73	421	78	0.09
Coronary anatomy (no. diseased vessels)					
1	39	10	25	5	0.003
2	113	28	110	20	0.007
3	249	62	403	75	<0.001
Left main coronary artery disease	83	21	93	17	0.205
Surgery status					
Elective	130	32	183	34	0.626
Urgent	243	61	333	62	0.735
Emergent	28	7	23	4	0.081
Off pump	55	14	38	7	0.001

(*Continued*)

Table 2. Continued

Factor	No Occlusions n = 401		≥ 1 Occluded Conduit n = 539		*p* Value
	No	%	No	%	
Processes of care					
Internal mammary artery, only	42	11	8	2	<0.001
Internal mammary artery, any	362	90	490	91	0.736
Saphenous vein, only	24	6	26	5	0.464
Saphenous vein, any	292	73	475	88	<0.001
Radial artery, only	9	2	5	1	0.110
Radial artery, any	160	40	262	49	0.008
Blood transfusion	104	26	188	35	0.003
Ketorolac use	228	57	248	46	0.001
Factor	Mean	SD	Mean	SD	*p* Value
Age (y)	62	11	62	11	0.347
Weight (kg)	87	17	88	18	0.641
Height (cm)	171	10	171	10	0.729
Creatinine (μmol/L)	97	62	97	79	0.548
Body mass index (kg/m^{-2})	30	6	30	6	0.872
Body surface area (m^2)	2.0	0.2	2.0	0.2	0.647
Number of diseased vessels	2.5	0.7	2.7	0.6	<0.001
Ejection fraction	49	11	50	10	0.524
Perfusion time (min)	63	35	79	35	<0.001
Cross-clamp time (min)	37	23	48	23	<0 .001
Number of grafts	2.8	1.1	3.3	0.9	<0.001
Distal arterial grafts	1.4	0.8	1.6	0.8	0.027
Distal vein grafts	1.3	1.0	1.7	0.9	<0.001
Postoperative length of stay	6	4	6	5	0.209

COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; SD = standard deviation.

transfusion was statistically significantly associated with graft closure (HR, 1.24; 95% CI, 1.03–1.50; $p = 0.02$) (Table 3, bottom).

To further determine the patient-level effect of transfusion, we created 273 matched pairs of patients who differed by transfusion status. Three hundred thirty-four (61%) of these 546 matched patients had at least 1 occluded graft at catheterization. After adjusting for other variables (model 3), blood transfusion was associated with patients having an increased hazard of graft occlusion (HR, 1.21; 95% CI, 1.07–1.37; $p = 0.003$) (Table 4). Receiving more grafts was associated with an increased hazard of patients having 1 or more occluded grafts, whereas receiving ketorolac was associated with a lower hazard. The propensity score to transfuse blood, which is the combined factor representing patient factors that might affect the decision to transfuse or not transfuse, was not associated with graft occlusion.

When we used propensity scores to analyze on a graft level and matched exactly for ketorolac use and number and type of grafts (model 4), we found that transfusion was associated with a 21% increased hazard of graft occlusion (HR, 1.21; 95% CI, 1.07–1.37; $p = 0.003$) (Table 5).

Comment

Graft occlusion after CABG is an ominous outcome because it may cause myocardial ischemia and is also a marker of future cardiac events, such as repeated coronary revascularization, myocardial infarction, and death [18, 19]. We found that RBC transfusion was associated with graft occlusion in a population of patients who underwent CABG and had symptom-driven post-CABG coronary angiography. This association was present at both the patient and graft levels. At the patient level, our models (models 1 and 2) showed that in addition to transfusion, and not unexpectedly, a greater number of grafts was associated with a higher number of failed grafts. Although this might be expected, a greater number of grafts typically entails longer cardiopulmonary bypass time and greater potential for hemodilution and possibly greater blood loss resulting in lower hematocrit values, which in turn lead to an increased likelihood of transfusion. To control for this, we analyzed the data on the graft level by comparing only patients with identical numbers and types of grafts (models 3 and 4) and found that transfusion remained associated with graft occlusion. Thus our results should be viewed as hypothesis-generating research of a potential mechanism behind

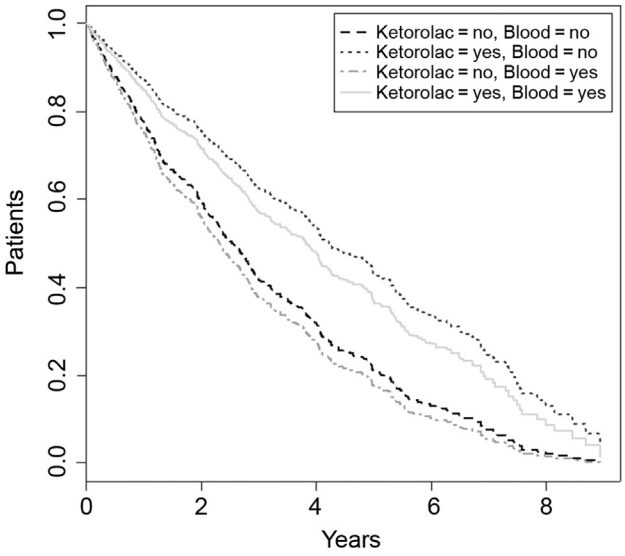

Figure 1. Cox hazard curves for graft occlusion in all patients. Transfusion is associated with 0.17 years (in patients without ketorolac) and 0.42 years (in patients with ketorolac) earlier graft occlusion at time that 50% of patients would be expected to have 1 or more graft occlusions, after adjusting for other factors including demography, comorbidities, and number and type of grafts.

the well-established association of homologous blood transfusion and diminished long-term survival after CABG.

Although previous studies have shown an association between RBC transfusion and increased late mortality, these studies lacked a causative mechanism to underpin their findings [2–4]. By evaluating patients who had coronary angiography for symptoms of cardiac ischemia after CABG, our study is able to suggest that the association between transfusion and late mortality may be mediated by transfusion promoting graft occlusion. Studies have shown that transfusion of banked blood induces a prothrombotic state. Platelets release CD40 ligand (CD40L) in response to blood transfusion. The interaction between CD40L and the CD40 antigen on macrophages promotes tissue factor expression and reduces fibrinolytic activity [20]. By also binding to vascular endothelium, CD40L stimulates metalloproteinase expression, which degrades matrix and promotes plaque rupture [20].

Levels of plasminogen activator inhibitor 1 (PAI-1), which can act as a direct procoagulant [21], increase severalfold in a time-dependent manner in banked blood [22]. PAI-1 also contributes to the shedding of microparticles with a high concentration of phosphatidyl-L-serine, which is a strong promoter of factor VIIa activation and thrombin production [23]. Transfusion of homologous blood produced higher circulating levels of PAI-1 in postoperative orthopedic patients than did the transfusion of autologous blood [24].

Nitric oxide, a potent vasodilator and inhibitor of platelet activation, is inactively transported by the heme molecule in RBCs. In areas of tissue hypoxia, nitric oxide is normally released by the cell to promote vasodilation [25]. As part of the storage lesion, transfused cells are deficient in nitric oxide and will scavenge nitric oxide released by normal endogenous RBCs, thus promoting platelet aggregation [26]. Furthermore, damaged transfused RBCs release adenosine diphosphate, which in the setting of coronary vessel injury may provoke platelet-mediated thrombosis [27].

Some of our patients received ketorolac, predominantly a COX-1 inhibitor that has been shown to be associated with improved short- and long-term outcomes after CABG [16, 28, 29]. In our patient-level analyses, we adjusted for ketorolac's nonrandom use, and in our graft-level analysis, we matched exactly on ketorolac use. Given that ketorolac has been associated with better

Table 3. Patient-Level Cox Model Between Factors and Graft Occlusion

Factor	Hazard Ratio	95% Confidence Interval	*p* Value
With ketorolac, transfusion interaction (model 1)			
Cerebrovascular disease	0.77	0.62–0.96	0.022
Digoxin use	0.43	0.25–0.73	0.002
Age (y)	0.99	0.98–0.998	0.013
No. of grafts	1.18	1.06–1.31	0.003
Perfusion time (min)	1.21	0.99–1.47	0.056
Blood transfusion	1.22	0.96–1.55	0.109
Ketorolac use	0.54	0.44–0.68	<0.001
Ketorolac-transfusion interaction	1.05	0.73–1.52	0.802
Without ketorolac (model 2)			
Cerebrovascular disease	0.77	0.62–0.96	0.022
Digoxin use	0.43	0.25–0.73	0.002
Age (y)	0.99	0.98–0.998	0.013
No. of grafts	1.18	1.06–1.31	0.003
Perfusion time (min)	1.21	0.99–1.47	0.056
Blood transfusion	1.24	1.03–1.50	0.024
Ketorolac use	0.55	0.46–0.67	<0.001

Table 4. Cox Model Showing Association of Transfusion and Graft Occlusion at a Patient Level With Propensity Score Included in Model 3

Factor	Hazard Ratio	95% Confidence Interval	*p* Value
Transfusion	1.29	1.06–1.57	0.010
Propensity score	0.64	0.37–1.09	0.098
Ketorolac use	0.60	0.50–0.71	<0.001
No. of internal mammary artery grafts	1.24	0.96–1.59	0.094
No. of radial artery grafts	1.23	1.10–1.38	<0.001
No. of vein grafts	1.33	1.20–1.46	<0.001

outcomes and that the harmful effects of transfusion may be from an induced hypercoagulable state, we investigated whether ketorolac achieved its benefit by mitigating the transfusion-associated graft failure. We found that ketorolac did not affect the association of RBC transfusion and long-term mortality (model 1) (Table 3), suggesting that the beneficial association of ketorolac and the deleterious association of transfusion with long-term survival are independent of each other.

A limitation of this study is the inability to determine the specific timing of graft occlusion. Although the postoperative coronary angiograms were symptom driven, grafts may have become occluded early postoperatively but the patients did not become symptomatic until later. Alternatively, if graft occlusion happened later, and transfused RBCs have a lifespan less than 3 months and the chemical constituents in transfused blood (such as CD40L, PAI-1, and microparticles) have an even shorter lifespan, transfused blood may not have caused immediate graft thrombosis but rather small nonocclusive areas of thrombosis that provided a nidus for future atherosclerosis. Finally, despite leukoreduction, transfused white blood cells may have persisted for years, producing a low level of graft-versus-host disease, which may contribute to atherosclerosis [30]. Our data do not permit us to assess the chronology of graft occlusion.

There are several other limitations to this study. First, postoperative coronary angiograms were obtained based on the development of symptoms suggestive of recurrent coronary artery disease. Patients who died without undergoing coronary angiography may have died for reasons related or unrelated to either graft occlusion or transfusion. Other patients may have had graft occlusion without the development of ischemic symptoms or may have declined coronary angiography. These patients may have biased our results in unknown ways. Second, transfusion may be a marker of another factor that is the actual cause of both transfusion and graft occlusion. Third, although all patients were discharged on aspirin and statins, unless they were contraindicated, we have no way of ensuring that patients took these medicines as prescribed. Patients who underwent transfusion may have been less likely to have taken patency-enhancing medicines. Finally, given the close association of anemia and transfusion, it is challenging to ascribe a specific effect to either 1 or the other of these codependent factors. Because we did not control for the degree of anemia in our analysis, it is conceivable, although less likely, that anemia may be the ultimate culprit in graft occlusion after CABG.

Table 5. Full-Fit Cox Model of the Identically Matched 273 Pairs of Patients (Model 4)

Factor	Hazard Ratio	95% Confidence Interval	*p* Value
Transfusion	1.21	1.07–1.37	0.003
Propensity score	0.91	0.64–1.29	0.595

Although it would be interesting to determine if the transfusion-occlusion association had similar HRs for vein, radial artery, and internal mammary grafts, we do not have sufficient numbers of patients to achieve adequate power to study this.

Our study is unique in finding a possible mechanism between perioperative transfusion and late mortality and provides a basis for further studies to investigate the effects of transfusion on outcomes. By providing a possible mechanism, our study may also permit the investigation of potential therapies that block transfusion-associated graft failure. Although short-term perioperative administration of ketorolac did not provide benefit by blocking transfusion-associated graft failure, other antithrombotic and anticoagulant agents may provide a benefit and should be studied.

In conclusion, we found perioperative transfusion to be associated with graft occlusion after CABG at both patient and graft levels through both traditional multivariable analysis and propensity analysis. This consistency of our results strengthens our findings that RBC transfusion is associated with graft occlusion and thus adds to the growing body of evidence that homologous RBC transfusion is not risk free but is associated with a variety of adverse effects. Given the preliminary nature of our study and its hypothesis-generating findings, further analysis is warranted, especially in light of the wide range of postoperative transfusion practice patterns in cardiac operations.

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