The Independent Effects of Anemia and Transfusion on Mortality After Coronary Artery Bypass

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Background. Both anemia and transfusions (Tx) are associated with mortality after cardiac operations. However, the relative contributions of anemia and Tx and their interaction on late mortality have not been determined.

Methods. 922 patients who underwent isolated coronary artery bypass grafting (CABG) were retrospectively studied. Anemia (A+) was defined as hemoglobin <12 g/dL for men and <11 g/dL for women. Patients who received (Tx+) and did not receive (Tx-) transfusions were compared; patient characteristics were controlled for by the use of Cox analysis and then by matching Tx+ to Tx- patients based on identical hemoglobin levels at admission and by propensity matching.

Results. 5.3% of Tx- patients died, compared with 11% of Tx+ patients ($p = 0.001$). The interaction of anemia and Tx was associated with a greater hazard of dying. In particular, A+Tx+ (anemic, received transfusion) patients had a threefold hazard of death (2.918, 95% confidence interval = 1.512–5.633, $p = 0.001$) compared with A−Tx− (nonanemic, no transfusion) patients. A+Tx+ patients had twice the hazard of dying as did A+Tx− (anemic, no transfusion) (hazard ratio = 2.087, 95% confidence interval = 1.004–4.336, $p = 0.049$). In populations matched by preoperative hemoglobin levels or by propensity scores, similar results were seen: a significant interaction between anemia and transfusion of red blood cells. A+Tx+ patients fared significantly worse than did the other three groups. Although there was no difference in mortality between A− patients who did or did not receive transfusions, A+T+ patients had triple the risk as A+T- patients, whereas A+Tx− patients had a similar risk of late mortality as A−Tx− patients.

Conclusions. The anemia–transfusion interaction was associated with an increased hazard of late mortality.

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Anemia is common in patients undergoing cardiac operations; besides its distinct detrimental effects on outcomes, is also important because it is the driving force behind transfusions of red blood cells (RBC) [1–3]. Low preoperative hemoglobin levels are common in patients undergoing cardiac operations and are often caused by hospital acquired blood loss, iron-deficiency anemia, and anemia of chronic disease that are unrelated to the operative procedure [4]. Determinants of perioperative anemia related to surgical procedures include phlebotomy, intraoperative blood loss, and the hemodilution inherent to the use of the cardiopulmonary bypass. The resultant intraoperative or postoperative anemia is frequently treated by RBC transfusions. Although traditional dogma holds that although the immediate effects of a transfusion may be an increase in oxygen delivery and amelioration of organ ischemia, there are data suggesting that RBC transfusions may be associated with significant short-term and long-term harmful effects that need to be carefully weighed in current transfusion practices. Several studies have found that perioperative RBC transfusion is associated with lower long-term survival in patients undergoing coronary artery bypass grafting (CABG) [5–8].

Some have argued that it is preoperative anemia (rather than RBC transfusion itself) that is harmful, and RBC transfusion may merely be a marker of an anemic patient [9, 10]. Preoperative anemia is a recognized risk factor for major morbidity and perioperative mortality after cardiac operations [3, 10]. However, an association of anemia with long-term outcomes is less well defined. A recent report has found an association between anemia and long-term mortality [9]. However, these studies neglected to control for RBC transfusions—an important confounder, given the increased likelihood of this treatment among anemic patients. Furthermore, studies to date have neglected to adequately address the interaction of preoperative anemia and RBC transfusions on late mortality.

We undertook a historical cohort study at a single center to test whether preoperative anemia would

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significantly interact with RBC transfusions whereby transfusions would either provide a protective or a pernicious effect on a patient's risk of late mortality.

Material and Methods

Using prospectively collected data, we undertook an Institutional Review Board (IRB) (Mercy St. Vincent Medical Center) approved historical cohort study. The IRB waived informed consent, given our use of deidentified data.

Patients

Patients (n = 999) who underwent isolated CABG between October 1, 2006, and July 30, 2010, at Mercy St. Vincent Medical Center were studied. Patients were excluded for having any missing hemoglobin values (n = 60) or for operative mortality (n = 17), defined as death within 30 days of the operation or later if still hospitalized after the operation.

Perioperative Management

During this time, we had a restrictive RBC transfusion practice with RBC transfusion based on hemoglobin level; the threshold was approximately 6.0 g/dL during cardiopulmonary bypass and 7.0 g/dL at other times or in any patient with evidence of end-organ ischemia in the setting of optimized hemodynamics. Transfusion was a physician's decision reflective of these institutional norms. In our practice, CABG is typically performed by using normothermic cardiopulmonary bypass, with the goal of obtaining complete revascularization. We routinely used internal mammary arteries and discharged patients with recommended medicines including aspirin, statins, β-blockers, clopidogrel, and angiotensin converting enzyme inhibitors.

Data Collection and Definitions

Data were obtained from our institutional cardiac surgery database, which contains preoperative demographics, comorbidities, operative details, blood transfusions, and mortality. These variables were defined according to the Society of Thoracic Surgeons definitions (http://www.sts.org/) (Table 1). Our institutional database had been last updated with all mortalities through November 30, 2011, by use of the Social Security Death Index. Hemoglobin was measured at several protocol-driven times in the perioperative period: Admit (first in-hospital value if an inpatient, from preadmission testing if an elective case), immediate preoperative (obtained in the operating room from arterial line insertion), nadir intraoperative (lowest value obtained between induction and discharge from the operating room), nadir postoperative (lowest value in the intensive care unit or stepdown unit), and discharge (last value before hospital discharge). Changes in hemoglobin value from admit to the lowest intraoperative or postoperative value (ΔHb) were calculated and included in the database. Preoperative creatinine was entered into the database as the last value before the procedure.

Analysis

We divided all patients into groups based on presence (A+) or absence (A−) of anemia, as hemoglobin <12 g/dL for men and <11 g/dL for women and receipt (Tx+) or absence (Tx−) of RBC transfusion. This interaction of anemia and RBC transfusion produced four groups of patients for the analyses: anemic patients who received RBC transfusion (A+Tx+), anemic patients who did not receive RBC (A+Tx−), nonanemic patients who received RBC (A−Tx+), and nonanemic patients who did not receive RBC (A−Tx−). We initially analyzed all patients using this four-level interaction variable. In the second analysis, to better define the effect of anemia, using a computer algorithm we matched patients who received RBC transfusions with those who did not receive transfusions 1:1 on the basis of an identical preoperative hemoglobin level. If there was more than one potential match of patients not receiving transfusions, one was randomly selected. In the third analysis, we used propensity matching by use of all the variables in Table 1 except anemia, hemoglobin, and transfusion with calipers = 0.001 and all standardized differences <10% to match patients not receiving transfusions with those not receiving transfusions on the basis of their likelihood or propensity to receiving transfusions.

Statistics

Patients who survived were univariably compared with those who died by use of Student's t test, Wilcoxon rank sum, χ^2, and Fisher's exact test, as appropriate. Normally distributed data are presented as mean ± standard deviation and nonparametric data as median (intraquartile range). Cox modeling, used to determine the independent effect of anemia and transfusion on survival, was done by entering all preoperative patient characteristics and processes of care that were univariably associated ($p < 0.2$) with survival in stepwise models. For the propensity-matched population, Cox models contained only anemia, preoperative hemoglobin, transfusion, and anemia–transfusion interaction. Final models included variables found to be significant based on a p value <0.05 and 95% confidence intervals that did not overlap with 1. Predictive discrimination of the Cox models is presented as Harrell's c and its standard deviation as modified Kendall τ, and presented as mean ± standard deviation [11, 12]. Cox plots were created by a method of direct adjustment of the observed conditional probability of survival at the time of each event [13]. Binary logistic regression was used to find the association between hemoglobin levels and RBC transfusion. Its ability to accurately discriminate between patients receiving and not receiving transfusions was determined by the area under the receiver operator characteristic curve and expressed as the c statistic ± standard error of the mean. All statistics were performed with SPSS 20.0 (SPSS, IBM, Armonk, NY).

Power Analysis

We assumed that 33% of patients would receive transfusions, and we wished to be 90% confident that we could