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Change in Use of Allogeneic Red Blood Cell Transfusions among Surgical Patients Over Time

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Abstract

Background—Although red blood cell (RBC) transfusions can be life-saving, recent evidence suggests that their use is associated with added morbidity/mortality and that a lower transfusion threshold is safe. It is unclear if this new evidence has translated into decreased RBC use among surgical patients. The purpose of this study is to measure the change in use of RBCs over the last decade.

Study Design—We performed a cross-sectional cohort study of all patients who underwent inpatient surgery in the 52 hospitals in Maryland in 1997–1998 and 2004–2005. The primary outcome was whether or not the patient received an allogeneic RBC transfusion. We controlled for confounders related to RBC transfusion, including age, sex, race, type of admission, comorbid conditions, and surgeon case volume.

Results—Patients receiving RBCs were older (63 vs. 52 yrs), were more likely to be admitted through the ED (37% vs 24%) or as a readmission (12% vs. 6.9%), had more Romano-Charlson index comorbidities, and had a higher unadjusted mortality (6.5% vs. 1.1%). Comparing 1997–1998 to 2004–2005, RBC use in surgical patients increased (8.9% vs 14%) while unadjusted mortality decreased (2.0% vs 1.5%). Factors associated with higher adjusted relative risk of transfusion include age >65 (RR 2.45), unscheduled admissions (ED RR 1.32, readmission RR 1.62), Romano-Charlson comorbidities (RR 1.04–2.71), third quartile of surgeon volume (RR 1.10), death (RR 1.24), and having surgery in 2004–2005 (RR 1.42).

Conclusions—Despite evidence supporting more restrictive use of RBC transfusions, RBC use among surgical patients has increased over the last decade.

Keywords

red blood cell; transfusion; time; change; surgical patient

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Introduction

Across the United States, approximately 14 million units of blood are transfused annually.¹ Surgical patients account for two-thirds of the population receiving blood and utilize twice the number of RBC units as medical patients.² Administered with the therapeutic goal of increasing oxygen delivery to tissues, red blood cell (RBC) transfusions can be lifesaving.

Despite the potential benefits of blood products, transfusion practices have been under scrutiny for the last two decades. RBC transfusions have been associated with direct transmission of infectious diseases such as hepatitis B, hepatitis C, and human immunodeficiency virus.^{3,4} In the critically ill, transfusions are independently associated with longer ICU and hospital lengths of stay, as well as higher mortality rates.^{5,6} Among trauma patients, transfusions are associated with increased incidence of ventilator-associated pneumonia, hospital costs,⁷ mortality and LOS.⁸ The immunomodulation effects of RBC transfusions may lead to cancer recurrence,⁹ postoperative bacterial infections,¹¹ transfusion-related acute lung injury,^{12,13} and hemolytic transfusion reactions.¹⁴

Recent evidence suggests that a “restrictive” transfusion strategy in critically ill patients may be associated with similar or better outcomes compared to a “liberal” transfusion strategy. In 1999 Hebert et al published a landmark multicenter, randomized, controlled trial on transfusion requirements. Outcomes among critically ill patients assigned to a restrictive transfusion strategy (transfusion threshold of 7 g/dL and target Hgb of 7–9 g/dL) were similar compared to those assigned to a liberal transfusion strategy (transfusion threshold of 10 g/dL and target Hgb of 10–12 g/dL). In fact, a restrictive transfusion strategy was associated with lower mortality among those less acutely ill (Acute Physiology and Chronic Health Evaluation [APACHE] II score <20 or age <55 years). Even among critically ill patients, a target Hgb of 7–9 g/dL is safe.¹⁵

It is unclear whether ongoing concerns about the adverse effects of transfusion or emerging data supporting lower transfusion thresholds have had an impact on transfusion use. The goal of this study is to determine whether the proportion of surgical patients receiving an allogeneic RBC transfusion has changed in the last decade. We hypothesize that there has been a decrease in allogeneic RBC transfusion. To test this hypothesis, we performed a cross-sectional cohort study of all patients who underwent surgery in the 52 non-federal hospitals in the state of Maryland in 1997–1998 and 2004–2005.

Methods

Study Design

We performed a cross-sectional cohort study of adults who underwent inpatient surgery in Maryland in the years of 1997–1998 (early study group) and 2004–2005 (late study group). These periods represent the two years before publication of literature supporting restrictive transfusion practice¹⁵ and the last two years for which complete data was available. The data for this study was obtained from the Maryland Health Services Cost Review Commission (HSCRC) database. The HSCRC administrative database contains billing and discharge information on all patients treated in the state of Maryland. This study was approved by the Institutional Review Board at Johns Hopkins University School of Medicine.

Data Abstraction

All records from January 1st through December 31st for 1997–1998 and 2004–2005 were obtained. Patient age, sex, race, emergency department or elective admission status, readmission (readmitted within 30 days of hospital discharge) or primary admission status, operating physician, and codes from the International Classification of Diseases, 9th revision,

Clinical Modification (ICD-9-CM) for the primary discharge diagnosis, the principal procedure, and up to 14 secondary diagnostic and procedure codes were abstracted.

Primary Outcome Variable

The primary outcome variable was whether or not the patient received an allogeneic RBC transfusion. Transfusion was determined based upon the secondary procedure codes contained in the HSCRC database. The ability of the secondary procedure codes to determine allogeneic RBC transfusion in the HSCRC database has been previously validated.^{16,17} Data on the number of RBC units transfused per patient, time during hospital course of transfusion, and hemoglobin concentration at time of transfusion was not available.

Predictor Variables

We controlled for multiple potential confounders which are likely related to blood transfusion. We classified patient age into four categories: <18, 18–45, 46–65, >65 years. Race was categorized as white vs. non-white. As a proxy for severity of illness, we classified patients as having been admitted from the emergency department vs. elective admission and readmission vs. primary admission. We classified the principal surgical procedure into 16 categories, as defined by the ICD-9-CM and these categories were included in the multivariate model to control for type of surgery. To account for potential differences in medical coding, we abstracted the number of procedures per patient and included this in the model as well.

To adjust for comorbid diseases that may independently affect the likelihood of an RBC transfusion, we included diseases in the Romano's modification^{18,19} of the Charlson comorbidity index²⁰ for use with ICD-9-CM discharge codes. These comorbid diseases were determined based upon secondary diagnosis and procedure codes and have been previously validated in surgical patients.²¹ Because we also wanted to identify predictors of transfusion, we included each disease in this index as an independent variable, rather than as a single comorbidity index. Prior literature suggests that in surgical patients, the likelihood of receiving a transfusion is related to surgeon case-volume.^{17,22,23} There is also concern that hospital type (tertiary, community, rural) may influence transfusion rates. Although we do not know each hospital's type, we do know the surgical case-volume for each hospital that may be a reasonable surrogate in that higher case volumes are more likely at tertiary care vs. rural hospitals. Therefore, we initially included surgical case volume for each hospital in the adjusted model, but found that it was highly collinear with surgeon case-volume. In order not to over-adjust, we included only surgeon case-volume in our model. To adjust for this, we calculated annual surgeon case-volume for inpatient procedures using the unique surgeon identification number within the HSCRC database. The distribution for annual inpatient surgeon case volume was determined by dividing patients into four equal sized groups based on surgeon case volume. The cut-offs for each group are as follows: <26, 26–62, 63–118, >118 cases/year.

Data Analysis

We performed descriptive analyses of the patient characteristics associated with the primary outcome variable, receipt of an allogeneic RBC transfusion. Tests of bivariate association were done using the chi square test for dichotomous outcomes and student's t-test for continuous outcomes. Logistic regression was used to evaluate the relationship of patient characteristics (age, sex, race, type of admission, and comorbid conditions), period of surgery (early or late study group), and surgeon case-volume with whether or not the patient received an allogeneic RBC transfusion. The multivariate model was created using a step-forward approach with thresholds for addition at $p \leq 0.05$. Collinear covariates (variable inflation factor > 20) were excluded from the model. All patient demographic variables (age, sex, race, all comorbidities), admission status, surgeon case-volume, number of procedures coded, and surgical procedure category ultimately were included in the model. Results of the bivariate and multivariate

analysis are reported as relative risks (RR) and 95% confidence intervals (CI). All tests are two-tailed and the critical region was defined as $\alpha=0.05$. All statistical analysis was performed using *Stata Intercooled Version 8.2 (College Station, Texas)*.

Power Analysis

We considered a 5% absolute reduction in use of allogeneic RBCs as clinically significant. In surgical patients with colorectal cancer, the transfusion rate is approximately 20%.²² Using this as a model and assuming 90% power and a two-sided alpha level of 0.05, we estimated that we would need 2,504 patients to detect a clinically significant difference.

Results

Baseline characteristics of surgical cases in Maryland

There were 691,074 inpatient surgical cases from the 52 non-federal hospitals in the state of Maryland during the 4 years studied (Table 1). Overall, the mean patient age was 53 ± 21 (SD) years. Seventy one percent of the patients were white, 41% were male, and 25% were admitted as an emergency. The overall unadjusted mortality rate of this population was 1.7%. Among all cases, 12% ($n=79,975$) received an allogeneic RBC transfusion.

Comparing transfused patients to those not transfused

When comparing the two groups (Table 1), patients receiving an allogeneic RBC transfusion were older (63 vs. 52 years) and more likely to be admitted through the emergency department (37% vs. 24%) or as a readmission (12% vs. 6.9%). Patients receiving an allogeneic RBC transfusion were more likely to have any of the comorbidities of the Romano-Charlson index. Patients receiving a transfusion were more likely to have surgery of the respiratory (5.4% vs 2.6%), cardiovascular (24% vs 18%), and musculoskeletal (34% vs 24%) systems. Patients receiving a transfusion were most likely to be operated on by surgeons with the extremes of case-volume (highest and lowest quartiles). Patients who received a transfusion had a higher unadjusted mortality than those who did not receive a transfusion (6.5% vs. 1.1%).

Comparing Early vs. Late Study Groups

Comparing 1997–1998 to 2004–2005 (Table 2), patients were of similar age (54 vs. 53 years) and gender (41% vs. 40% male) distribution. While a slightly higher proportion of patients were from an emergency department admission (24% vs. 26%) in 2004–2005, a lower proportion of patients were from readmissions (9.1% vs. 6.2%). There was an increase in the proportion of patients with previous myocardial infarction (4.0% vs. 5.2%), chronic pulmonary disease (11% vs. 15%), mild liver disease (0.5% vs. 0.8%), and mild to moderate diabetes (11% vs. 14%) in 2004–2005 compared to 1997–1998. The proportion of patients having obstetrical surgery increased in 2004–2005 compared to 1997–1998 (9.2% vs. 12%). The unadjusted mortality rate in the late study group decreased (2.0% vs. 1.5%). The proportion of patients receiving an RBC transfusion increased from 8.9% to 14% from the early to late period (Figure 1).

Relative risk of receiving an RBC transfusion for all years

On bivariate analysis (Table 3, unadjusted relative risk), advanced age was associated with higher risk of transfusion, with more than double the relative risk (RR 2.47, 95% CI 2.36–2.58) for those above age 65. Unscheduled admissions (emergency department RR 1.88, 95% CI 1.85–1.91; readmission RR 1.93, 95% CI 1.89–1.98) were associated with an increased risk of receiving a RBC transfusion. Comorbidities of the Romano-Charlson index were all associated with a significantly increased relative risk of transfusion ranging from 1.37–6.36. Severe liver disease was associated with the highest risk (RR 6.36, 95% CI 5.73–7.05). Patients

seen by surgeons with the lowest quartile of surgical case-volume (<26 cases/year) had the highest relative risk of RBC transfusion. Receiving a RBC transfusion was associated with an increased unadjusted risk of death (RR 6.23, 95% CI 6.00–6.46). Patients undergoing surgery in the late study group had more than 50% increased risk of receiving an RBC transfusion (RR 1.64, 95% CI 1.62–1.67) compared to those undergoing surgery in the early study group.

On multivariate analysis (Table 3, adjusted relative risk), most of these associations persisted. However, male sex (RR 0.67, 95% CI 0.65–0.68) became associated with a lower relative risk of RBC transfusion. Additionally, patients operated on by surgeons with the second highest quartile case-volume had the highest risk of receiving an RBC transfusion (RR 1.10, 95% CI 1.07–1.13). The adjusted relative risk of receiving an RBC transfusion in the late period was 1.42 (95% CI 1.40–1.45).

Discussion

In this study evaluating changes in allogeneic RBC use over time, we found that patients undergoing inpatient surgical procedures in 2004–2005 were more likely to receive a RBC transfusion compared to similar patients in 1997–1998. These results are important in light of published data concerning the risks of transfusion and the recent evidence supporting a restrictive transfusion strategy.

Why then, are patients more likely to get RBC transfusions now compared to a decade ago when many of these potential risks were less understood? The most obvious reason is that physicians are moving towards more liberal use of blood products, despite mounting evidence against such practice. This may represent a lack of awareness amongst providers regarding the detrimental effects of transfusions. Additional research is needed to evaluate physician awareness of the emerging literature.

A second reason is that surgeons are performing more complex surgeries (not captured in our model) that require more blood. As we push the envelope of conditions that are amenable to surgery, we may be performing larger and longer surgical procedures. Furthermore, surgeries that were being performed in an inpatient setting a decade ago are being performed in an outpatient setting today. For example, during the late 1990's (ie. the early period of our study), the safety and acceptance of performing a laparoscopic cholecystectomy as an outpatient procedure was debated, and the majority of these procedures were still done on an inpatient setting.^{24,25} However, in the current era (encompassing the late period) outpatient laparoscopic cholecystectomy is well accepted and commonly performed.²⁶ This leaves a more complex set of procedures that are being performed on the inpatient setting. We attempted to capture this in the subgroup analyses of individual surgery types, but we recognize that this approach may not have captured the nuances of surgical complexity.

A third reason that patients may be more likely to receive RBC transfusions is that surgical patients may be more acutely ill today than before. Patients in whom we would not have considered to be surgical candidates a decade ago may be surgical candidates today. We attempted to control for this by adjusting for patient comorbidities, emergency admissions, and readmissions but we recognize that severity of illness may not have been fully accounted for in our model. Other severity of illness measures (ie. APACHE, Multiple Organ Dysfunction Score, Sepsis-related Organ Failure Assessment score, pre-transfusion hemoglobin) may have been useful, but are unavailable in this administrative dataset.

Finally, patients may be more likely to receive RBC transfusions because of changing patterns of medication use. The use of anticoagulant therapy (coumadin) and antiplatelet therapy (aspirin and plavix) may have increased over this time period thus predisposing patients to

bleed more and require more transfusions. The use of erythropoietin may have decreased, leading to more patients being anemic at baseline. Unfortunately, data on specific medication use is not available in this database.

Our findings add to the complex body of literature on changes in RBC use over the last decade. Among patients in the intensive care unit, there has been little change in RBC use.⁶ Among surgical patients, the literature is a bit more complex. At one academic institution, the use of RBC for patients undergoing carotid endarterectomy,²⁷ arthroplasty,²⁸ spinal manipulation,²⁹ and radical retropubic prostatectomy,³⁰ has declined over the last decade. These results may be reflective of an aggressive and successful blood conservation program at this particular institution. Meanwhile, other single-center studies suggest use of RBCs has increased for patients undergoing CABG,^{31,32} trauma,³² and oncology surgery.³² Our results suggest that among 52 hospitals within one state, there has been an increase in RBC across a broad range of surgery types.

Potential Limitations

There were several potential limitations to this study. First, the accuracy of our data was limited by what was coded during discharge, rather than using the medical record to obtain information about patient characteristics. Reviewing the medical records of nearly 700,000 patients would have been logistically impossible. Surgical patients are ideal populations to study with discharge data because specific patient populations are easy to identify and risk adjustment models appear to work relatively well in these patients.³³ Prior research has validated the accuracy of the HSCRC database both in documenting patient comorbidities and transfusion use.^{16,17} Despite the shortcomings of hospital discharge data, its use provides an efficient means to evaluate outcomes for a large number of patients from multiple hospitals.³⁴

Second, we may not have adequately accounted for differences in severity of illness between patients. As discussed above, we attempted to control for severity of illness in our model, but we recognize that it may not have completely accounted for all differences.

Finally, the HSCRC database contains only information regarding whether a patient had a transfusion, rather than the number of units transfused. Furthermore, we do not know at what phase of the hospitalization (emergency department, operating room, intensive care unit, general ward) the transfusion occurred, nor the indication, or what type of provider drove the decision for the transfusion. More detailed information regarding transfusion would allow us to evaluate a dose-response relationship and provide further insight into transfusion practices. Despite these limitations, this study evaluates RBC use over the last decade in a large sample of representative patients for an entire state.

Conclusion

In summary, we found that the RBC transfusion rate in surgical patients has not decreased over the last decade, but in fact has increased. In light of concerns surrounding transfusions and morbidity/mortality, efforts should be directed at understanding why more surgical patients are receiving RBC transfusions compared to a decade ago.

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Figure 1.

Proportion of surgical cases in Maryland receiving an allogeneic red blood cell transfusion, by year. Error bars represent 95% confidence interval of adjusted model. Adjusted model controls for age group, sex, race, admission status, all comorbidities, surgical category, surgeon case-volume, and number of procedures coded.

Table 1

Baseline Characteristics of All Surgical Cases in Maryland Combining Years 1997–1998 and 2004–2005, by Red Blood Cell Transfusion Status

	Received a RBC transfusion n = 79,975	Did not received a RBC transfusion n = 611,099	p Value
Mean age ± SD (y)	63±20	52±20	<0.01
Age group, y			
<18	2.9%	4.2%	
18–45	14%	33%	<0.01
46–65	28%	31%	
>65	55%	32%	
Male	41%	40%	
Caucasian	70%	71%	<0.01
Admission			
Emergency Department	37%	24%	<0.01
Elective	63%	76%	
Readmission	12%	6.9%	<0.01
Primary admission	88%	93%	
Comorbidity			
Previous myocardial infarction	6.1%	4.5%	<0.01
Dementia	2.6%	1.0%	<0.01
Chronic pulmonary disease	19%	13%	<0.01
Liver disease (mild)	1.7%	0.6%	<0.01
Liver disease (moderate to severe)	0.8%	0.1%	<0.01
Diabetes (mild to moderate)	17%	12%	<0.01
Diabetes with complications	6.1%	2.6%	<0.01
Renal disease	3.6%	1.3%	<0.01
Malignancy	6.1%	3.2%	<0.01
Metastases from solid tumor	6.3%	2.6%	<0.01
Surgery type			
Nervous system	2.7%	3.8%	
Endocrine system	0.2%	1.1%	
Eye	0.1%	0.7%	
Ear	0.0%	0.2%	
Nose, mouth, pharynx	0.3%	1.2%	
Respiratory system	5.4%	2.6%	
Cardiovascular system	24%	18%	<0.01
Heme and lymphatic system	2.0%	0.7%	
Digestive system	17%	16%	
Urinary system	3.4%	3.3%	
Male genital organs	1.4%	2.6%	
Female genital organs	4.7%	9.9%	
Obstetrical procedure	1.6%	12%	
Musculoskeletal system	34%	23%	
Integumentary system	3.6%	4.4%	
Mean no. of procedures coded ± (SD)	5.8 ± .013	2.7 ± .0026	<0.01
Surgeon case-volume (cases/y)			
<26	31%	24%	<0.01
26–62	20%	26%	
63–118	23%	25%	
>118	27%	25%	
Mortality %	6.5%	1.1%	<0.01
Year			
1997–1998	35%	47%	<0.01
2004–2005	65%	53%	

Table 2

Baseline Characteristics of All Surgical Cases in Maryland, by Years of Surgery

	Year 1997–1998 (n = 318,404)	Year 2004–2005 (n = 372,670)	p Value
Mean age ± SD (y)	54±21	53±20	<0.01
Age group, y			
<18	4.2%	3.7%	
18–45	31%	30%	
46–65	28%	32%	<0.01
>65	37%	34%	
Male	41%	40%	<0.01
Caucasian	73%	69%	<0.01
Admission			
Emergency Department	24%	26%	
Elective	76%	74%	<0.01
Readmission	9.1%	6.2%	
Primary admission	91%	94%	<0.01
Comorbidities %			
Previous myocardial infarction	4.0%	5.2%	<0.01
Dementia	1.4%	1.0%	<0.01
Chronic pulmonary disease	11%	15%	<0.01
Liver disease (mild)	0.5%	0.8%	<0.01
Liver disease (moderate to severe)	0.2%	0.2%	0.76
Diabetes (mild to moderate)	11%	14%	<0.01
Diabetes with complications	3.1%	2.9%	<0.01
Renal disease	1.4%	1.6%	<0.01
Malignancy	3.6%	3.4%	<0.01
Metastases from solid tumor	3.3%	2.7%	<0.01
Surgery Type			
Nervous system	3.8%	3.6%	
Endocrine system	1.0%	1.1%	
Eye	0.9%	0.4%	
Ear	0.2%	0.1%	
Nose, mouth, pharynx	1.2%	1.0%	
Respiratory system	3.2%	2.8%	
Cardiovascular system	19%	19%	
Heme and lymphatic system	0.9%	0.8%	<0.01
Digestive system	16%	17%	
Urinary system	3.7%	3.0%	
Male genital organs	3.0%	2.1%	
Female genital organs	9.7%	9.0%	
Obstetrical procedure	9.2%	12%	
Musculoskeletal system	23%	26%	
Integumentary system	5.5%	3.3%	
Mean number of procedures coded ± (SD)	2.83 ± .0040	3.26 ± .0044	<0.01
Surgeon case-volume % (cases/y)			
<26	29%	21%	<0.01
26–62	24%	26%	
63–118	24%	26%	
>118	24%	27%	
Mortality	2.0%	1.5%	<0.01
Received RBC transfusion	8.9%	14%	<0.01

Table 3

Relative Risk of Receiving a Red Blood Cell Transfusion in All Surgical Cases in Maryland in Years 1997–1998 and 2004–2005

	Unadjusted RR of receiving a RBC Transfusion (95% CI)	Adjusted RR of receiving a RBC transfusion (95% CI)
Age group, y		
<18	Reference 1.0	Reference 1.0
18–45	0.60 (0.57–0.63)	0.86 (0.81–0.90)
46–65	1.32 (1.26–1.38)	1.18 (1.12–1.24)
>65	2.47 (2.36–2.58)	2.45 (2.33–2.58)
Male	1.04 (1.03–1.06)	0.67 (0.65–0.68)
Caucasian	0.93 (0.92–0.95)	0.80 (0.79–0.82)
Admission		
Emergency Department	1.88 (1.85–1.91)	1.32 (1.29–1.35)
Elective	Reference 1.0	Reference 1.0
Readmission	1.93 (1.89–1.98)	1.62 (1.58–1.67)
Primary admission	Reference 1.0	Reference 1.0
Comorbidities		
Previous myocardial infarction	1.37 (1.33–1.42)	1.09 (1.05–1.13)
Dementia	2.75 (2.62–2.90)	1.90 (1.78–2.02)
Chronic pulmonary disease	1.64 (1.61–1.67)	1.12 (1.10–1.15)
Liver disease (mild)	3.05 (2.87–3.25)	1.56 (1.43–1.69)
Liver disease (moderate to severe)	6.36 (5.73–7.05)	2.71 (2.36–3.11)
Diabetes (mild to moderate)	1.46 (1.43–1.49)	1.04 (1.01–1.06)
Diabetes with complications	2.45 (2.37–2.54)	1.25 (1.20–1.30)
Renal disease	2.92 (2.80–3.05)	1.45 (1.38–1.53)
Malignancy	2.00 (1.93–2.06)	1.40 (1.34–1.46)
Metastases from solid tumor	2.56 (2.48–2.65)	1.38 (1.33–1.44)
Surgeon case-volume (cases/y)		
<26	Reference 1.0	Reference 1.0
26–62	0.61 (0.60–0.62)	0.99 (0.96–1.01)
63–118	0.72 (0.71–0.74)	1.10 (1.07–1.13)
>118	0.84 (0.83–0.86)	0.98 (0.95–1.00)
Mortality %	6.23 (6.00–6.46)	1.24 (1.19–1.30)
Year		
1997–1998	Reference 1.0	Reference 1.0
2004–2005	1.64 (1.62–1.67)	1.42 (1.40–1.45)

Adjusted model controls for age group, sex, race, admission status, all comorbidities, surgical category, surgeon case-volume, and number of procedures coded.