Association Between Venous Thromboembolism and Perioperative Allogeneic Transfusion

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Hypothesis: Perioperative allogeneic blood product transfusion would be associated with venous thromboembolic complications in surgical patients.

Design: Observational study using a state discharge database.


Patients: We obtained data on 14,014 adult patients having a primary diagnosis code for colorectal cancer and a primary procedure code for colorectal resection.

Main Outcome Measures: The primary outcome variable was a discharge diagnosis of venous thromboembolism (VTE).

Results: Venous thromboembolism occurred in 1% of patients and was associated with an adjusted 3.8-fold increase in mortality (odds ratio, 3.8; 95% confidence interval, 2.1-6.8), a 61% increase in mean hospital length of stay, and a 72% increase in mean total hospital charges. Risk factors for VTE after adjustment included transfusion, female sex, age 80 years or older, moderate to severe liver disease vs no liver disease, admission through the emergency department, and low annual surgeon case volume. Transfusion was associated with an increase in the odds of developing VTE in women (odds ratio, 1.8; 95% confidence interval, 1.2-2.6) but not in men (odds ratio, 0.9; 95% confidence interval, 0.5-1.9). In the absence of transfusion, female compared with male sex was not associated with an increased risk of VTE (odds ratio, 1.2; 95% confidence interval, 0.8-1.7).

Conclusions: In this large observational study of patients undergoing colorectal cancer resection, perioperative allogeneic blood transfusion was associated with an increased risk of VTE in women but not in men. Given the substantial morbidity and mortality associated with VTE and the implication that this finding has for postoperative management in women, this association must be confirmed in independent studies.

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Blood product transfusions are routinely administered to patients undergoing surgery. While allogeneic blood product transfusions can be lifesaving for these patients, transfusions carry risks including immunomodulation, transmission of infectious agents, disruption of the normal balance of coagulation factors, and modulation of the inflammatory cascade. Because inflammation and coagulation are tightly coupled, perturbation of the coagulation cascade with blood product transfusions may lead to increased risk of thrombosis during periods of systemic inflammation such as surgery. The purpose of our study was to evaluate the association between blood product transfusion and venous thromboembolism (VTE) in surgical patients. In addition, because the effect of VTE has been incompletely characterized in this patient population, we sought to further define the effect of VTE on total hospital charges, hospital length of stay, rate of admission to the intensive care unit (ICU), and mortality.

See Invited Critique at end of article

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PATIENT DATA

METHODS

After obtaining approval from our institutional review board, we obtained nonconfidential data on patients from the Uniform Health Discharge Data Set maintained by the Maryland Health Services Cost Review Commission. This database contains information on all patients discharged from the 52 nonfederal acute care hospitals in Maryland. We identified all adult patients (aged ≥18 years) who were discharged between January 1, 1994, and December 31, 2000, having an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) primary diagnosis code for colorectal cancer (ICD-9-CM codes: 15.3.x or 15.41) and a primary procedure code for colorectal surgery (ICD-9-CM codes: 45.7.x, 45.8, 48.4.x, 48.5.x, or 48.6.x). These codes accurately identify patients undergoing bowel resection because of colorectal cancer.9,10 Patient age, sex, and race/ethnicity; reason for admission; hospital length of stay; hospital charges; ICU admission; mortality; and ICD-9-CM codes for the primary discharge diagnosis, the principal procedure, and up to 14 secondary diagnostic and procedure codes were abstracted. Because autologous red blood cell transfusion has been associated with a decreased incidence of VTE complications,9,10 38 patients receiving autologous red blood cell transfusion was associated with a decreased incidence of VTE complications.9,10

To adjust for severity of illness, we classified patients according to whether they were admitted because of bowel obstruction (ICD-9-CM codes: 560.89 or 560.90) or bowel perforation (ICD-9-CM codes: 569.83) vs other conditions. These variables have been previously used to account for severity of illness in patients undergoing colorectal cancer surgery.6,16 We also included annual surgeon case volume in our adjusted analyses. Surgeon case volume was classified into quartiles. A Lowess smoother of surgeon case volume vs VTE was used to validate modeling of surgeon case volume.17

PRIMARY OUTCOME MEASURES

The primary outcome variable was whether the patient had a discharge diagnosis of VTE (ICD-9-CM codes: 415.1, 451.2, 451.11, 451.19, 451.81, or 453.8). These codes accurately identify patients with postoperative VTE. Lawthers et al11 found that 90% of surgical patients with a code for VTE had documentation in the medical record to support the diagnosis.98% of surgical patients without the codes had medical record confirmation for the absence of VTE. Secondary outcome variables included in-hospital death, admission to the ICU, hospital length of stay, and total hospital charges. Charges were converted to 2003 dollars using the US Consumer Price Index for health care.12

INDEPENDENT VARIABLES

The primary independent variable was whether the patient received a blood product transfusion vs no transfusion during the hospital stay. Patients were classified as having received a transfusion if they had a secondary diagnosis code for any of the following: autologous packed red blood cells (ICD-9-CM code: 990.4), fresh frozen plasma (ICD-9-CM codes: 990.6 or 990.7), or platelets (ICD-9-CM code: 990.5). The use of hospital discharge data has been previously shown to accurately identify blood product transfusion in surgical patients.13 Data were unavailable for either the number of units transfused or the age of the transfused blood products.

To adjust for preexisting comorbid conditions, we used the Romano modification of the Charlson comorbidity index to identify comorbid conditions that might affect transfusion and complication rates. The Romano-Charlson index has been validated for identifying comorbid conditions in surgical patients.13,14 Because our goal was to identify specific patient characteristics, we evaluated each disease process as a separate variable rather than using a composite comorbidity index.13,15

We performed an unadjusted analysis to determine the relationship between the independent variable and each of the dependent variables. The t test was used to evaluate the relationship between continuous dependent variables and binary independent variables, and the χ² test was used to evaluate the association between categorical dependent and categorical independent variables. Simple logistic regression analysis was used to evaluate the association between continuous independent variables and binary dependent variables.

STATISTICAL ANALYSIS

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RESULTS

PATIENT CHARACTERISTICS

Between January 1, 1994, and December 31, 2000, 14,014 patients underwent colorectal cancer resection at the 52 nonfederal acute-care hospitals in Maryland. A descrip-
Mean (SD) age of the study population was 69 (12.6) years; 79% of the patients were white, and 51% were women. Admission through the ED accounted for 18% of all admissions. Of the operations performed, 81% were colectomies, 7% were abdominoperineal resections, and 13% were other rectal procedures. Patients with congenital bleeding diatheses, such as von Willebrand disease, accounted for less than 0.05% of the study population.

**EFFECT OF VTE**

One hundred thirty-six patients (0.97%) developed VTE while in the hospital for colorectal cancer resection. Development of VTE was associated with a 5.9-fold increase in mortality (OR, 5.9; 95% CI, 3.6-9.6), a 2.5-fold increase in admission to the ICU (OR, 2.5; 95% CI, 1.8-3.5), an 87% increase in mean hospital length of stay, and a 99% increase in mean total hospital charges. After adjustment for predictors of VTE, the development of a thromboembolism was independently associated with a 3.8-fold increase in mortality (OR, 3.8; 95% CI, 2.1-6.8), a 2-fold increase in admission to the ICU (OR, 2.0; 95% CI, 1.3-3.0), a 61% increase in mean hospital length of stay, and a 72% increase in mean total hospital charges.

**INDEPENDENT PREDICTORS OF VTE**

The associations of transfusion, patient characteristics, severity of illness, surgical procedure, comorbid diseases, and surgeon case volume with the primary outcome variable, VTE, are given in Table 2. Factors associated with VTE in the unadjusted analysis include allogeneic blood product transfusion, advanced age, female sex, hospital admission through the ED, bowel perforation, dementia, moderate to severe liver disease, metastatic tumor, and low surgeon volume vs very high surgeon volume.

Factors associated with VTE after adjustment for univariate predictors are given in Table 2. Transfusion was independently associated with a 1.5-fold increased risk of developing a thromboembolism (OR, 1.5; 95% CI, 1.04-2.1). Preoperative risk factors independently associated with an increased risk of development of thromboembolism included age 80 years or older compared with age younger than 60 years (OR, 1.9; 95% CI, 1.0-3.6), female sex (OR, 1.5; 95% CI, 1.0-2.1), hospital admission through the ED (OR, 1.7; 95% CI, 1.1-2.5), and moderate to severe liver disease vs no liver disease (OR, 5.9; 95% CI, 3.6-9.6). Patients with surgeons in the very high-volume quartile had a 2.5-fold lower rate of VTE compared with patients with surgeons in the low-volume quartile (OR, 0.4; 95% CI, 0.3-0.7).

**INTERACTIONS BETWEEN INDEPENDENT PREDICTORS OF VTE AND TRANSFUSION**

To better characterize the association between transfusion and VTE, we evaluated whether each of the demographic, severity of illness surrogates, and comorbid conditions that predicted VTE after adjusted analysis modified its association with transfusion. To that end, we examined whether age older than 80 years, female sex, hos-
hospita admission through the ED, and moderate to severe liver disease modified the association between transfusion and VTE.

After adjusted analysis, the association between transfusion and VTE was not modified by the age of the patient. In the population who received no transfusions, there was a nonstatistically significant association between patient age older than 80 years and VTE (OR, 1.7; 95% CI, 0.7-3.8). Similarly, in the population who received transfusions, there was a nonstatistically significant association between patient age older than 80 years and VTE (OR, 2.2; 95% CI, 0.9-5.4). For the entire study population, age older than 80 years was associated with a 2-fold increased risk of VTE (OR, 1.9; 95% CI, 1.0-3.6; P = .05).

The association between transfusion and VTE was modified by sex. The adjusted association between transfusion and VTE, stratified by sex, is given in Table 3. Transfusion was not associated with an increased incidence of VTE in men (OR, 0.9; 95% CI, 0.5-1.9). Women who received a transfusion were 1.8-fold more likely (OR, 1.8; 95% CI, 1.2-2.6) to develop a VTE than were women who did not receive a transfusion. In the absence of transfusion, female compared with male sex was not associated with an increased risk of thromboembolism (OR, 1.2; 95% CI, 0.8-1.7).

Increased severity of illness, as indicated by hospital admission through the ED, lessened the association between receiving a transfusion and VTE. For patients admitted directly to the hospital, receiving a transfusion was associated with an increased risk of developing VTE (OR, 1.9; 95% CI, 1.3-2.9). There was no association between receiving a transfusion and VTE in patients admitted through the ED (OR, 0.9; 95% CI, 0.6-1.5). This difference is not confounded by sex-specific admitting trends, inasmuch as women were more likely to be admitted through the ED (OR, 1.2; 95% CI, 1.1-1.3).

Only 38 patients with moderate to severe liver disease underwent colorectal cancer resection, and 2 of these developed a VTE. Both patients received a transfusion. Further analysis was precluded by small sample size, as bootstrap estimates of variance suggested overfitting of the data.

### Table 3

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Crude Analysis</th>
<th>Adjusted Analysis†</th>
<th>Adjusted P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y†</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt;60</td>
<td>1.2 (0.7-2.1)</td>
<td>1.2 (0.7-2.2)</td>
<td>.56</td>
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<tr>
<td>60-69</td>
<td>1.5 (0.9-2.5)</td>
<td>1.4 (0.8-2.4)</td>
<td>.25</td>
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<td>≥80</td>
<td>2.4 (1.4-4.0)</td>
<td>1.9 (1.0-3.6)</td>
<td>.05</td>
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<tr>
<td>White race†</td>
<td>1.1 (0.7-1.6)</td>
<td>1.1 (0.7-1.9)</td>
<td>.62</td>
</tr>
<tr>
<td>Female sex†</td>
<td>1.7 (1.2-2.3)</td>
<td>1.5 (1.0-2.1)</td>
<td>.03</td>
</tr>
<tr>
<td>Severity of illness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission through ED‡</td>
<td>2.3 (1.6-3.3)</td>
<td>1.7 (1.1-2.5)</td>
<td>.02</td>
</tr>
<tr>
<td>Bowel perforation‡</td>
<td>2.4 (1.0-5.4)</td>
<td>1.5 (0.7-3.2)</td>
<td>.34</td>
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<tr>
<td>Bowel obstruction‡</td>
<td>1.6 (0.7-3.7)</td>
<td>1.2 (0.5-2.5)</td>
<td>.80</td>
</tr>
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</table>

**COMMENT**

In this study of 14,014 patients undergoing colorectal cancer resection in Maryland, VTE was associated with both an adjusted 4-fold increase in mortality and substantial use of resources. Given the attendant morbidty and mortality associated with VTE, it is crucial that patients at high risk are identified so that optimal VTE prophylaxis can be given. While VTE remains a common problem, occurring in 1% of patients in our study, its pathophysiology remains elusive. In addition, the role of transfusion in the pathogenesis of VTE has been poorly defined. Inasmuch as multiple studies have demonstrated that risk factors often act synergistically to increase the risk of VTE (eg, oral contraceptives and hereditary thrombophilias), we believe it was important to define whether transfusion was associated with VTE and whether it interacted with other independent risk factors to increase risk. In this large retrospective study of patients undergoing colorectal cancer resection at 52 hospitals during a 6-year period, VTE was associated with advanced age,
female sex, perioperative transfusion of allogeneic blood products, admission through the ED, and moderate to severe liver disease, and was inversely associated with increased annual surgeon case volume. The association between transfusion and VTE, however, was modified by both sex and severity of illness surrogate admission through the ED.

Advanced age is a well-defined risk factor for the development of VTE. Our results support previous studies that identify it as a risk factor. There was no statistically significant difference in the risk associated with age 80 or older between the populations who did or did not receive blood transfusions.

The association between female sex and increased risk of VTE has been identified in patients undergoing hip replacement surgery. These trials, however, were small and did not include transfusion status in their adjusted analyses. We also found that women were at increased risk of VTE; however, when we stratified women according to whether they had received a transfusion, we found that female sex only conferred an increased risk of VTE in those who received a blood transfusion.

While transfusion was associated with increased risk of VTE in the study population as a whole (OR, 1.5; 95% CI, 1.04-2.1), stratification by sex revealed that this association existed only in women. Transfusion was associated with a 2-fold increased risk of VTE in women (OR, 1.8; 95% CI, 1.2-2.6); there was no increased risk in men (OR, 0.9; 95% CI, 0.5-1.9). Women not receiving transfusions had the same risk of developing VTE as did men. Our findings suggest that male and female patients undergoing colorectal cancer surgery may respond differently to transfusion. While several small studies have found an association between VTE and transfusion, no study has stratified this association by sex. The most compelling data for the association between VTE and transfusion comes from a small (n = 174), single-center, retrospective analysis of women undergoing resection of gynecologic malignancies. In this study, Abu-Rustum et al found a 3-fold increased incidence of VTE in women receiving allogeneic packed red blood cells and a 7-fold increased risk of VTE in women receiving fresh frozen plasma. While our findings of a sex-specific association between VTE and transfusion were unexpected, they are provocative because there are several plausible biologic explanations.

First, though not addressed by this study, there are inherent differences between men and women insofar as the interdependence of inflammation and coagulation. Although our knowledge is incomplete, inflammation is tightly coupled to coagulation, as highlighted by the success of activated protein C in the treatment of sepsis. Increasingly, sex has been recognized as a modifier of systemic inflammation and has been shown to influence both the incidence of multiorgan system dysfunction and death from sepsis. Few of these studies, however, adjusted for transfusion status, and none of the studies reported the incidence of VTE. One explanation, therefore, is that there is a sex-specific inflammatory response to transfusion that increases the risk of venous thrombosis.

Second, androgens and estrogens have different influences on the pathways that govern thrombosis and thrombolysis. Estrogens have been shown to alter the production of coagulation factors from the liver, accounting, in part, for the increased risk of VTE and myocardial infarction in women receiving hormone therapy. Transfusion, therefore, may affect the balance between thrombosis and thrombolysis differently in women than in men.

Third, rheologic differences between men and women may also account for the sex-specific association of transfusion and VTE. Lower preoperative hematocrit and, therefore, viscosity have been associated with a decreased incidence of VTE. Increased blood viscosity has also been associated with an increased risk of VTE. Blood transfusions alter viscosity both by raising hematocrit and by introducing erythrocytes with altered viscoelastic properties into the circulation. Because hematocrit and blood viscosity tend to be lower in women than in men, women may be more prone to develop VTE after transfusion-induced perturbations in viscosity.

Fourth, there may be a sex-specific difference in the immunologic response to transfused blood. There is a growing body of evidence in the transplantation literature that the sex of both the donor and the recipient influence the incidence of rejection. In addition, HLA sensitization in multiparous donors has been correlated with an increased incidence of transfusion-related acute lung injury. Multiparous women are also likely to have HLA mismatches with transfused blood. This could predispose the multiparous female recipient to red blood cell aggregation and increase the risk of VTE.
Severity of illness at surgery, as inferred by admission through the ED, was an independent predictor of VTE that conferred a 2-fold increased risk (OR, 1.7; 95% CI, 1.1-2.5). Like female sex, increased severity of illness modified the association between transfusion and VTE. Transfusion was not associated with VTE in patients admitted through the ED (OR, 0.9; 95% CI, 0.6-1.5) but was associated with VTE in patients admitted directly to the hospital (OR, 1.9; 95% CI, 1.3-2.9). Two possible explanations account for these findings. First, in a randomized trial by Hebert et al\(^9\) on transfusion requirements in the ICU, there was a trend toward increased mortality in healthier patients with lower Acute Physiology, Age, and Chronic Health Evaluation (APACHE) scores who received transfusions. Our results support their findings because patients admitted directly to the hospital, who were presumably healthier than patients admitted through the ED, were more likely to have a transfusion-associated VTE. Second, severity of illness confounds the need for transfusion. While admission through the ED is a surrogate for severity of illness at admission, transfusion may represent increased severity of illness during the hospital stay. However, such an interpretation seems unlikely, given the sex-specific association between transfusion and VTE. There is no plausible explanation for why transfusion would represent increased severity of illness in women but not men.

The inverse relationship between annual surgeon case volume and complications is well documented.\(^{23}\) We found that patients operated on by surgeons with annual case volume in the highest quartile had a decreased incidence of VTE. Our results support past studies and suggest that surgeon experience is an important determinant of the incidence of VTE.

We have identified several limitations to our study. First, we cannot evaluate the temporal relationship between transfusion and VTE using discharge data. We reviewed hospital discharge data for patients undergoing colorectal cancer resection at our institution and found that 90% of blood product transfusions were given by the first postoperative day. Second, our analysis was based on data from a hospital discharge database rather than medical record review, which limits the information that can be obtained. For example, we were unable to determine whether other confounding factors, such as use of VTE prophylaxis and hormone therapy in women, were present. We also had incomplete data about the technical difficulty of the surgery and the extent of metastatic disease. In addition, information on the number of transfusions received was not available, which limited our ability to evaluate a dose-response relationship. Such review of data for all patients undergoing colorectal cancer resection in Maryland would have been difficult and expensive. In addition, because VTE prophylaxis seems to work equally well in male and female patients, this would not account for the sex-specific risk that we observed. Similarly, sex bias in the practice of VTE prophylaxis would not account for our results because there was no difference in incidence of VTE between men and women who did not receive transfusions. Only women who received transfusions were at increased risk of developing a VTE. Third, the sex-specific association between thromboembolism and transfusion may be a surrogate for another disease process not included in our multivariate model. Comorbidities included in our multivariate model were those disorders previously identified in the Romano-Charlson index, a comorbidity index that has been validated for use with administrative databases. However, it is possible that comorbid illnesses not included in this index (eg, osteoporosis) may have biased our results. Fourth, we studied one surgical disease, which limits our ability to generalize our findings to other surgical disorders. Fifth, a sex-specific association was not included in our original hypothesis and, therefore, our results may reflect chance. There are several reasons why we believe this not to be the case, including the strength of the association (P=.005), a literature precedent for the association between VTE and transfusion in women undergoing resection of gynecologic malignancies, and several plausible biologic explanations for the association. Despite these factors suggesting a potential causal relationship, a sex-specific association was not hypothesized a priori and, therefore, additional studies are warranted.

Our study also has several strengths. First, we used validated methods to identify patients undergoing colorectal surgery, receiving a transfusion, and having postoperative VTE. Second, the large sample size increases our ability to identify associations that could have been missed with smaller studies. Third, the use of hospital discharge data provides an efficient means of analyzing outcomes in patients at multiple hospitals, thereby both minimizing the risk of selection bias that may occur from use of data from a single hospital and generalizing the results.

In this observational study of 14,014 patients undergoing colorectal cancer resection, blood product transfusion was associated with an increased risk of VTE in women but not in men. Given the significant morbidity and mortality associated with VTE, further studies characterizing this association are warranted so that appropriate preventive measures can be instituted.

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REFERENCES


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