Plasma Transfusion Is Associated With Postoperative Infectious Complications Following Esophageal Resection Surgery: A Retrospective Cohort Study

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Objective: **To examine the association between blood component transfusions and the incidence of major postoperative infections in patients undergoing esophageal resection surgery.**

Design: **Retrospective cohort study.**

Setting: **Single academic tertiary referral center.**

Participants: **All patients who underwent esophagectomy from 2005 through 2009.**

Measurements and Main Results: **The primary outcome was the incidence of major postoperative infection, defined as pneumonia, bloodstream infection, and/or a surgical site infection occurring within 30 days postoperatively. In total, 465 patients were evaluated. One hundred thirty-eight patients (29.7%) received a blood transfusion before the onset of a major postoperative infection or during a similar exposure interval in those with no such complications. Univariate analysis showed a significant association between any blood component transfusion and postoperative infection (transfused *v* nontransfused 31.9% *v* 13.2%; odds ratio = 3.1, 95% confidence interval = 1.9-5.0; $p < 0.01$). This association was lost on multivariate analysis. Subgroup analysis with multivariate adjustment identified a significant association between high plasma volume blood component transfusions and postoperative infection (odds ratio = 4.2, 95% confidence interval = 1.2-15.8; $p = 0.03$). With multivariate adjustment, red blood cell administration was no longer associated with major postoperative infectious complications.**

Conclusions: **High plasma volume blood component transfusions were associated with the development of major postoperative infectious complications in patients undergoing esophageal resection surgery. In contrast, red blood cell transfusion was not associated with infectious complications.**

KEY WORDS: blood component transfusion, postoperative wound infection, bloodstream infection, postoperative pneumonia, esophagectomy

ESOPHAGEAL RESECTION SURGERY is a major procedure with the potential for substantial morbidity and mortality. The estimated postoperative morbidity after esophagectomy ranges from 24% to 64%, with an associated mortality of 2.7% to 5.8%.[1,2] Postoperative infectious complications, including pneumonia, surgical site infection (SSI), and bloodstream infection (BSI), contribute significantly to postoperative morbidity[3] and can result in prolonged ventilator requirements, extended stays in the intensive care unit, and increased mortality. Recent estimates have noted the risk of postoperative pneumonia to range from 10% to 20%,[3-7] and this postoperative complication has been associated with a 20% increase in the risk of death.[1] Postoperative SSIs also occur with reasonable frequency, estimated as 6% to 7%.[3,5]

Blood product administration is a common occurrence in patients having esophageal surgery, with a recent estimate suggesting that 38% of patients undergoing this surgical procedure receive a blood transfusion.[5] Importantly, the previous decade has witnessed an increased scrutiny on the efficacy and risk of the once unquestioned therapy of blood transfusion.[8] Examples of transfusion-related risks include allergic reaction,[9,10] transfusion-related acute lung injury,[11-13] transfusion-associated circulatory overload,[14,15] and transfusion-related immune modulation.[16-20]

Although transfusion-transmitted infections long have been a concern with blood product administration, there is a growing body of evidence that suggests blood product administration can increase the risk of more traditional postoperative infectious complications, such as pneumonia, SSI, and BSI.[19,21-26] Although a substantial body of literature supports this association, much of this evidence is biased, with inadequate consideration given to potentially important confounding variables. Moreover, the impact of specific blood component therapies has not been explored adequately. The objective of this investigation was to test the hypothesis that perioperative administration of blood products in patients undergoing esophageal resection surgery increases the risk of postoperative infectious complications. Furthermore, the authors aimed to assess the association among specific blood components administered while controlling for potentially important confounding variables.

METHODS

After institutional review board approval, a retrospective observational cohort study was performed.

This was a single-center investigation that included patients receiving care at a tertiary care, academic medical center. The study population was obtained from an institutional surgical database. This database includes a comprehensive list of all patients undergoing esophageal resection surgery. All adult patients (>18 years of age) who had provided consent for the use of their medical records for research and who underwent open esophageal resection surgery from 2005 through 2009 were included in this analysis. For individuals with more than one esophageal surgery, only the first operative encounter was included. Patients with pre-existing pneumonia or other active infection at the time of the surgical procedure were excluded as were those who denied the use of their medical records for research.

The primary outcome of interest was the development of a major postoperative infectious complication. For this evaluation, a major postoperative infectious complication was defined as postoperative pneumonia, BSI, and/or SSI. Postoperative pneumonia was defined

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using the Clinical Pulmonary Infection Score.[27] This score evaluates 6 readily accessible clinical variables to determine the probability that a patient's clinical findings are due to pneumonia.[28] The Clinical Pulmonary Infection Score was calculated on a rolling basis for every 48-hour window for each patient. The onset of postoperative pneumonia was recorded as the time when the Clinical Pulmonary Infection Score first became higher than 6. The adjudication of postoperative pneumonia was performed by a single physician investigator (A.S.). The documentations of BSI and SSI were obtained from the Mayo Clinic's infectious disease surveillance database. This database contains information on all documented BSIs and SSIs. The BSIs and SSIs included in this database are defined in accordance with Centers for Disease Control and Prevention criteria.[29] Blood cultures were obtained only when clinically indicated and not for surveillance. The date and time of the collection of positive blood cultures were recorded as the time of onset of BSI. Superficial and deep tissue SSIs are included in the infectious disease database and the presence of either was considered evidence for a postoperative SSI in this investigation. SSI onset was recorded as the date and time allocated to the diagnosis of SSI in the infectious disease database. Because the infectious disease surveillance database does not contain data on postoperative pneumonia, it was not used when adjudicating this diagnosis. All patients were evaluated for the development of an outcome of interest from the time of surgery to 30 days postoperatively, death, or time of hospital discharge, whichever occurred first.

The exposure of interest was blood product transfusion. The blood component therapies considered in this evaluation included red blood cells (RBCs), platelets, and fresh frozen plasma (FFP). To account for the high plasma volume contained in single-donor apheresis platelet units (270-290 mL of plasma in each apheresis unit), "high plasma volume products," namely the combination of FFP and platelet units, were evaluated. Cryoprecipitate transfusions were not included in this analysis because of the very small number of units administered in the present cohort. The blood components used during the study period were processed by the Mayo Clinic's blood bank as follows: all RBC units were leukoreduced; all platelet units were collected by apheresis from single donors, resulting in approximately 50 mL of platelets suspended in 270 to 290 mL of plasma; and FFP units were obtained from male and female donors before June 2007 and from male-only donors after June 2007. Transfusions were identified using an institutional database query tool (Database Discovery and Query Builder). This tool is used to perform an automated search of the electronic medical record. To avoid cause-effect inversion, only transfusions administered before the development of a major postoperative infectious complication were included in the analysis. For patients with multiple infectious complications, only the transfusions administered before the first infectious complication were included. To define a comparable exposure interval for patients with no major postoperative infectious complications, the median time to the development of major postoperative infectious complications in the group with these outcomes of interest was used. For patients who underwent transfusion, the date, time, and type (RBC, platelets, or FFP) of transfusion were recorded.

Additional predictor variables abstracted included pertinent baseline demographics, clinical characteristics, potentially confounding exposures, including chemotherapy within 6 months of the operative procedure, immunosuppressive therapy, chronic steroid use, smoking status, and nutritional status. Preoperative albumin concentration was used as a surrogate marker of preoperative nutritional status. The following intraoperative data were extracted: American Society of Anesthesiologists (ASA) physical status, time from antibiotic administration to surgical incision, intraoperative fraction of inspired oxygen (F_IO_2), intraoperative temperature, duration of surgery, and operative estimated blood loss. Duration of surgery was used as a surrogate for procedural complexity. Relevant laboratory data (hemoglobin, platelet count, international normalized ratio [INR], creatinine, and albumin) were recorded. The lowest hemoglobin, lowest platelet count, and highest INR before the development of an infectious complication (or a similar exposure interval in patients with no infectious complications) were used. All preoperative variables were extracted by the study's physician investigators (A.S., A.A., D.J.K.) using the Database Discovery and Query Builder tool. Intraoperative data and ASA physical status were obtained using an electronic data extraction tool that extracts information detailing the operative course (cardiopulmonary data, medications administered, and critical event notations) from the institution's perioperative environment source database (MICS Anesthesia and Monitored Care Reviewer).

Assuming a baseline frequency of major infectious complications of 10% in unexposed patients and a ratio of nontransfused to transfused of 2:1 (based on the data referenced earlier),[5] the estimated power to detect an odds ratio (OR) of 2 for major postoperative infectious complications with exposure to blood products in 465 patients was estimated to be 82% with a 2-sided α value of 0.05. Dichotomous variables are presented as counts with percentages. Continuous data are presented as median with 25th to 75th percentiles. For univariate analyses, comparisons between the 2 groups were performed with the Pearson χ^2 test or Fisher exact test as appropriate for categoric variables. Continuous variables were tested with the Mann-Whitney rank-sum test. In addition to analyzing the association between the transfusion of any blood product and the development of major postoperative infectious complications, subgroup analyses were planned a priori for each specific blood component. Because of the high volume of plasma contained within the platelet components, an analysis of the association between high plasma volume blood components (platelets and FFP combined) and major postoperative infectious complications also was performed.

To control for bias and potential confounding, adjusted analyses evaluating the association between a transfusion and major postoperative infectious complications were performed with multivariate logistic regression. Covariates initially were included in the multivariate model when univariate analyses suggested statistically significant associations with postoperative infectious complications ($p < 0.1$; ASA status, estimated blood loss, duration of the surgical procedure, hemoglobin, platelet count) and/or when a biologic plausibility for a confounding effect was believed present (age, diabetes mellitus, smoking status, preoperative chemotherapy, immunosuppression, intraoperative F_IO_2, intraoperative temperature). Covariates with >15% missing data were not included in the multivariate analyses (preoperative albumin, INR). The model was refined with stepwise elimination. The final model was run with nominal logistic regression analysis. Care was taken to avoid over-fitting the model by ensuring that ≤1 covariate was included for each 10 major infectious complications. Any evidence of colinearity also was evaluated.

RESULTS

In total, 465 patients were identified for inclusion in this study. This sample included all consecutive consenting patients undergoing esophageal resection surgery over the defined interval. Major postoperative infectious complications were identified in 87 patients (18.7%). Forty-five patients (9.7%) developed postoperative pneumonia. Fifty patients (10.8%) developed an SSI and 26 patients (5.6%) developed a BSI. Twenty-six patients (4.5%) developed more than one major postoperative infectious complication. The median time to the first major infectious complication was 7 days (25th-75th percentiles = 4-11). Therefore, 7 days defined the exposure interval in the cohort without infectious complications.