Surgical Outcomes and Transfusion of Minimal Amounts of Blood in the Operating Room

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Objective: To examine outcomes in patients who receive small amounts of intraoperative blood transfusion.

Design: Longitudinal, uncontrolled observational study evaluating results of intraoperative transfusion in patients entered into the American College of Surgeons National Surgical Quality Improvement Program database. We made propensity-matched comparisons between patients who received and did not receive intraoperative transfusion to minimize confounding when estimating the effect of intraoperative transfusion on postoperative outcomes.

Setting: We queried the American College of Surgeons National Surgical Quality Improvement Program database for patients undergoing operations between January 1, 2005, and December 31, 2009.

Patients: A large sample of surgical patients from 173 hospitals throughout the United States.

Main Outcome Measures: Operative mortality and serious perioperative morbidity (≥1 of 20 complications).

Results: After exclusions, 941,496 operations were analyzed in patients from 173 hospitals. Most patients (893,205 patients [94.9%]) did not receive intraoperative transfusions. Patients who received intraoperative infusion of 1 unit of packed red blood cells (15,186 patients [1.6%]) had higher unadjusted rates of mortality and more serious morbidity. These rates further increased with intraoperative transfusion of more than 1 unit of packed red blood cells in a dose-dependent manner. After propensity matching to adjust for multiple preoperative risks, transfusion of a single unit of packed red blood cells increased the multivariate risk of mortality, wound problems, pulmonary complications, postoperative renal dysfunction, systemic sepsis, composite morbidity, and postoperative length of stay compared with propensity-matched patients who did not receive intraoperative transfusion.

Conclusions: There is a dose-dependent adverse effect of intraoperative blood transfusion. It is likely that a small, possibly discretionary amount of intraoperative transfusion leads to increased mortality, morbidity, and resource use, suggesting that caution should be used with intraoperative transfusions for mildly hypovolemic or anemic patients.


Blood transfusion during operative procedures is often the consequence of intraoperative blood loss. Whether intraoperative blood loss warrants blood transfusion is subjective in many cases because triggers for transfusion vary widely among clinicians. Despite guidelines from professional organizations, there are wide variations in blood transfusion practices and no simple transfusion algorithms to which clinicians adhere. Reasons for lack of adherence to blood transfusion practice guidelines are multiple but stem at least in part from lack of agreement with guideline recommendations on the part of clinicians. Because many guideline recommendations are based on low-quality evidence, it may be that clinicians transfuse blood in the operating room for valid reasons dictated by experience and for reasons that are unable to be captured in evidence-based guidelines owing to a lack of relevant published information.

It is difficult to pin down a cause-and-effect relationship between excessive blood transfusion and adverse surgical outcomes, although several authors suggest that such a relationship exists. As many as 80% of the blood products given in the operating room are administered to a minority of high-risk patients with identifiable high-risk characteristics. Adverse surgical outcomes often follow...
transfusion in high-risk patients, especially those who receive excessive amounts of blood products.\textsuperscript{17-19} Conversely, the most common intraoperative transfusion occurrence is not excessive blood product transfusion but rather transfusion of a single donor unit of packed red blood cells (PRBCs).\textsuperscript{1,15,16} It is less certain that transfusion of minimal amounts of intraoperative blood products is associated with adverse surgical outcomes, and surprisingly little evidence exists to support or refute this notion.

To better define the relationship between intraoperative blood transfusion and adverse surgical outcomes, we used a large surgical database to measure surgical outcomes as a function of intraoperative blood transfusion. We hypothesized that if blood transfusion does cause adverse surgical outcomes, then this effect should be dose dependent and transfusion of minimal amounts of blood products should result in significantly worse operative outcomes than in patients who do not receive intraoperative transfusion. Additionally, exploration of the consequences of intraoperative transfusion of small amounts of blood may guide surgeons in their practice behavior, whether experience based or guideline based.

\section*{METHODS}

\subsection*{PATIENT POPULATION}

We used the American College of Surgeons National Surgical Quality Improvement Project (ACS-NSQIP) database to evaluate the effects of intraoperative blood transfusion on patient outcomes. The study group consisted of patients who intraoperatively received only 1 unit of PRBCs. We compared this group with both patients who did not receive intraoperative transfusion and patients who received more than 1 unit of PRBCs. The ACS-NSQIP database contains patient deidentified information that is freely available to all database participants who sign and comply with the ACS-NSQIP Data Use Agreement. The Data Use Agreement implements the data protections of the Health Insurance Portability and Accountability Act of 1996 and the ACS-NSQIP Hospital Participation Agreement. After signing the Data Use Agreement, we obtained and analyzed data from the ACS-NSQIP participant use file containing surgical cases submitted by 173 hospitals throughout the United States from January 1, 2005, to December 31, 2009. This database excludes trauma and pediatric patients. The University of Kentucky Institutional Review Board determined that this study meets federal criteria to qualify as an exempt study. Patients with \textit{Current Procedural Terminology} codes listed as “procedure not otherwise specified” did not enter into the study group because of great variation and uncertainty in the type of procedure performed and because of the lack of associated work relative value units with the unspecified procedure.

\subsection*{ACS-NSQIP MEASURES OF BLOOD TRANSFUSION}

The ACS-NSQIP database variables measure the units of PRBCs transfused in 3 settings: (1) preoperative transfusion of more than 4 units of PRBCs within 48 hours before the operation; (2) intraoperative PRBCs transfused in the operating suite; and (3) postoperative transfusion of more than 4 units of PRBCs within 72 hours of the operation. Our analysis defined comparison groups based on the number of units of PRBCs transfused only in the operating room. Patients who received more than 4 units of PRBCs within 48 hours before the operation and those who received more than 4 units of PRBCs up to 72 hours after the operation were excluded. A small number of patients in the ACS-NSQIP database who had cardiac procedures using cardiopulmonary bypass were also excluded. These patients usually had cardiopulmonary bypass used in an unusual emergency setting and met statistical criteria for outliers with standardized residuals of outcome measures being much greater than 2 SDs from mean outcome values.

\subsection*{OUTCOME MEASURES}

Patient 30-day morbidity (≥1 of 20 complications) and mortality as well as more than 50 demographic and preoperative clinical risk variables are included in the ACS-NSQIP database. Dedicated nurse clinical reviewers at each hospital collected data according to strict ACS-NSQIP definitions on a prospective and systematic sample of patients having major operative procedures. The excellent accuracy and reproducibility of the data are well documented in previous articles.\textsuperscript{20-22} Thirty-day outcomes recorded in the ACS-NSQIP database and used in our analysis include the following: (1) mortality within 30 days of operation or within the same hospitalization; (2) individual morbidities (≥1 of 7 serious adverse events uniformly defined by the ACS-NSQIP); and (3) composite morbidity consisting of any combination of the 7 serious individual morbidities. Serious organ system morbidities included the following: (1) wound complications (deep organ space surgical site infection, deep surgical wound infection, and wound dehiscence); (2) pulmonary complications including pneumonia, unplanned intubation, pulmonary embolism or deep venous thrombosis, and mechanical ventilation for longer than 48 hours; (3) renal complications including acute kidney injury or dialysis; (4) central nervous system complications including new postoperative stroke or coma; (5) cardiac complications including postoperative myocardial infarction or cardiac arrest; (6) sepsis including postoperative septic shock or bloodborne sepsis; and (7) unplanned return to the operating room within 30 days of the initial procedure. The analysis included postoperative length of hospital stay from the day of operation until death or discharge as 1 index of resource use.

\subsection*{STATISTICAL ANALYSIS}

For unadjusted outcome comparisons, χ² test compared categorical variables between the transfused (1 unit of PRBCs) and nontransfused groups. Similarly, t test was used to compare the unadjusted means of continuous variables between patients who received and did not receive intraoperative transfusion. In these and all subsequent analyses, \( P < .05 \) denoted a statistically significant association.

We used propensity score matching to minimize the effects of confounding due to the nonrandomized assignment of transfusion when comparing outcomes between patients who did not receive intraoperative transfusion and those who received 1 unit of intraoperative PRBCs. We chose patients who received 1 unit of PRBCs as the key study group for propensity analysis because transfusion in this group is most likely to be discretionary and is most avoidable without patient harm. Propensity score matching allows for reducing the effect of selection bias in the decision to transfuse small amounts of intraoperative PRBCs and allows balancing of all measured relevant variables between patients who did not receive intraoperative PRBCs and those who received only 1 unit of intraoperative PRBCs. This propensity matching used the methods previously published by Austin et al.\textsuperscript{21-23} We used SPSS ver-
amount of PRBCs is associated with worse unadjusted matching. Invariably, intraoperative transfusion of any fused intraoperatively in all patients before propensity bidity groups) and the number of units of PRBCs trans-
mortality or composite morbidity (any 1 of 7 major mor-
standardized differences were used to assess the balance between covariates in the 2 treatment groups in the propensity score–matched sample. We iteratively modified the propensity model so that all relevant covariates had standardized differences of less than 0.1 to assure accurate matching. The SPSS FUZZY case-matching algorithm accomplished matching between treated patients (ie, those who received 1 unit of PRBCs) and untreated patients (ie, no transfusion) using matching without replacement and a matching tolerance of 0.00001 of the propensity score. McNemar test was used to assess the statistical significance of differences in dichotomous outcomes between treatment groups in the matched sample, while the Wilcoxon rank sum test was used for continuous outcomes.

### Results

#### Patient Population

After patient exclusions, the ACS-NSQIP database generated a study group of 941,496 patients who underwent noncardiac operations. Of the 48,291 patients who received intraoperative PRBCs, 15,186 (31.4%) received a single unit of PRBCs during operation, while the remaining 33,105 patients (68.6%) intraoperatively received more than 1 unit of PRBCs.

#### Relationship Between Unadjusted Outcomes and Intraoperative Blood Transfusion

The Figure depicts the relationship between operative mortality or composite morbidity (any 1 of 7 major morbidity groups) and the number of units of PRBCs transfused intraoperatively in all patients before propensity matching. Invariably, intraoperative transfusion of any amount of PRBCs is associated with worse unadjusted mortality and composite morbidity in this patient cohort (Figure).

**Table 1** outlines unadjusted outcome differences between patients who did not receive intraoperative transfusion and those who received 1 unit of PRBCs. In Table 1, \( \chi^2 \) testing compared rate differences between discrete outcome variables in patients who did and did not receive intraoperative transfusion, while \( t \) test compared differences between continuous variables in these 2 study groups.

### Propensity-Matched Cohorts

Fifty-five preoperative variables were entered into a logistic regression analysis to generate a probability of receiving 1 unit of PRBCs (ie, propensity score). Statistical software (SPSS version 18) matched the untreated cohort (893,205 patients) who did not receive an intraoperative blood transfusion to the treated cohort who received 1 unit of PRBCs (15,186 patients) using an algorithm that required matching on the propensity score to the nearest 0.00001. Of necessity, this matching algorithm resulted in a decreased number of matches between treated and untreated patients but assured a very close match between the 2 final patient groups. **Table 2** compares the values of some of the key preoperative variables in the treated and untreated cohorts after propensity matching and lists the standardized differences between some of the important preoperative variables. All preoperative variables entered into the regression model had a standardized difference of 0.1 or less, indicating a good balance of baseline variables between propensity-matched treated and untreated cohorts.

**Figure.** Unadjusted mortality and composite morbidity rates by number of units of packed red blood cells (PRBCs) received in intraoperative blood transfusion.

![Figure](image_url)
ries a significant risk of increased operative mortality, wound problems, systemic sepsis, pulmonary complications, postoperative renal dysfunction, composite morbidity, and prolonged postoperative length of hospital stay.

**COMMENT**

We found that transfusion of seemingly small and possibly discretionary amounts of intraoperative PRBCs is associated with adverse surgical outcomes. Using propensity matching in conjunction with a large clinical database, we found significantly worse outcomes in patients who received a single unit of PRBCs during their operation. Adverse outcomes included increased operative mortality, pulmonary complications, renal dysfunction, wound problems, sepsis, and prolonged hospitalization. Other investigators reached similar conclusions in patients having cardiac operations, but our study uniquely identifies this relationship in noncardiac operations.

Exploratory observational studies like ours serve to generate hypotheses worth testing in randomized trials. For example, a unique feature of our study is the focus on intraoperative blood transfusion. Other studies reviewed relationships between blood transfusion and pa-
ponent outcomes,\textsuperscript{14,27} but our study is one of the few that emphasizes the intraoperative occurrence of transfusion and surgical outcomes. A reasonable hypothesis based on our results is that small amounts of intraoperative blood transfusion cause adverse outcomes, especially infectious complications. It might be possible to construct a randomized trial where discretionary intraoperative transfusion is tested among surgical patients. To our knowledge, the literature does not have a study of this type.

An important unmeasured variable that may confound our results is the decision tree used to guide transfusion. In a cross-sectional study like ours, no intraoperative transfusion algorithm could be identified. In the ACS-NSQIP database, the decisions about transfusion are not well controlled and this variability provides uncertainty about indications for blood transfusion. Use of transfusion algorithms lessens blood transfusion and decreases perioperative bleeding in certain types of operations.\textsuperscript{1,28-31} Algorithm-driven transfusion using predefined triggers and supplemented with point-of-care tests to monitor adequacy of blood coagulation and clotting is a powerful blood conservation tool.\textsuperscript{1,29,30} Our results suggest that further studies looking at intraoperative transfusion triggers are justified and may help surgeons in their decisions about transfusion.

We found that most of the adverse outcomes associated with intraoperative blood transfusion revolve around infection. Transfusion of 1 unit of PRBCs presaged wound infections, pneumonias, and sepsis in our study. Transfusion is known to be immunosuppressive.\textsuperscript{32-34} A reasonable hypothesis is that transfusion of small amounts of allogeneic blood may limit the immune response, induce inflammatory mediators, and predispose to infectious complications. A corollary is that blood conservation techniques that limit blood transfusion may also limit postoperative infections. Interventions with an evidence base for limiting blood transfusion may have a secondary benefit of limiting surgical infections and systemic inflammatory response. A few studies in the literature support this notion,\textsuperscript{35-37} but others do not.\textsuperscript{38-40} However, no data elements in the ACS-NSQIP database allow direct measurement of inflammatory mediators or molecular markers of inflammation that permit direct inference of the association between blood transfusion and surgical infections. Our results support a relationship between surgical infections and intraoperative blood transfusion and suggest the need for further efforts to investigate the effect of blood transfusion practices on surgical infections.

Retrospective case-control studies like ours have strengths and weaknesses related to both the large size of the database and how variables are measured in the database (Table 4). Because of the large number of patients included in the database, there are some obvious strengths inherent in the analysis, including the large sample size and the broad-based cross section of patients reflecting real-world experience with blood transfusion and surgical outcomes. However, there are also several weaknesses associated with the analysis. For example, one important unmeasured variable is the time from PRBC harvest to transfusion. Data on PRBC storage are not available in the ACS-NSQIP database. Harvested PRBCs close to expiration are associated with worse outcomes than fresher PRBCs more recently donated.\textsuperscript{41-43} In most blood banks, there is selection bias in that high-risk patients are likely to receive the oldest blood in the blood bank. Blood bankers will cross match the oldest blood units in patients having the highest-risk operations because there is a higher likelihood that the blood units will be transfused before they expire compared with lower-risk patients having more routine procedures. It is possible that some of the adverse outcomes associated with blood transfusion are related to transfusion of older PRBCs in higher-risk procedures.

Other weaknesses exist in our analysis (Table 4). Patients get blood transfusions at other hospital sites besides the operating room. Transfusions occurring outside the operating room, especially in the intensive care unit, are associated with worse patient outcomes.\textsuperscript{44} There are peculiarities about how the ACS-NSQIP database records transfusions outside the operating room. Patients who received more than 4 units of PRBCs either before or within 72 hours after operation are identified in the database and were excluded from the study group. This still leaves patients in the database who may receive transfusion of less than 5 units of PRBCs within 72 hours of operation as an extension of intraoperative bleeding. A search of the complete ACS-NSQIP database suggests that patients who received an intraoperative transfusion of 1 unit of PRBCs rarely received more than 4 units of PRBCs in the early
postoperative period. They were no more likely to receive more than 4 units of PRBCs postoperatively than were patients who received no intraoperative transfusion. This suggests that the transfusion of 1 unit of PRBCs was usually an isolated transfusion event that occurred in the operating room. Nonetheless, patients who received fewer than 5 units of PRBCs either before or after the operation are included in the study group, and it is possible that patients who received only 1 unit of PRBCs in the operating room may have received more blood after the operation.

The method of measuring perioperative blood transfusion in the ACS-NSQIP database precludes more accurate assessment of the effects of blood transfusion on outcomes than we describe here. This is a shortcoming of our study that is unable to be controlled.

Based on the assessments listed in Table 4, we believe that the benefits of analyzing the relationship between transfusion of small amounts of PRBCs and surgical outcomes using the ACS-NSQIP database far outweigh potential weaknesses. In fact, it is likely that the only practical way to analyze this relationship is by using a large clinical database such as that of the ACS-NSQIP. We provide strong evidence to support further controlled trials assessing the relationship between transfusion of minimal, possibly discretionary amounts of PRBCs and surgical outcomes. Special attention should be devoted to the occurrence of surgical infections in future studies of this type.

CONCLUSIONS

Our results suggest a strong association between intraoperative transfusion of relatively small amounts of blood (1 unit of PRBCs) and adverse surgical outcomes in non-cardiac operations, especially adverse infectious complications. The clear implication is that limiting intraoperative blood loss and blood transfusion may improve outcomes in certain patients. Intraoperative transfusion of 1 unit of PRBCs should be undertaken with caution based on this study.

Accepted for Publication: August 8, 2011.
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Author Contributions: Drs Ferraris and Davenport had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. Study concept and design: Ferraris, Saha, and Zwischenberger. Acquisition of data: Davenport. Analysis and interpretation of data: Ferraris, Austin, and Zwischenberger. Drafting of the manuscript: Ferraris and Zwischenberger. Critical revision of the manuscript for important intellectual content: Ferraris, Davenport, Saha, and Austin. Statistical analysis: Ferraris, Davenport, and Austin. Administrative, technical, and material support: Zwischenberger. Study supervision: Ferraris.

Financial Disclosure: None reported.

REFERENCES


Minimal Transfusions

First Do No Harm

Erraris et al have shed light on an important yet infrequently discussed problem. They reviewed patients who were not hypotensive or bleeding to death and received only small amounts of PRBCs in the operating room. Ferraris and colleagues showed that transfusion of even minimal amounts of blood products increases morbidity, wound problems, pulmonary complications, postoperative renal dysfunction, systemic sepsis, composite morbidity, and postoperative length of stay. These are important outcomes that clinicians discuss every day.

Why did these noncardiac patients receive transfusions of 1 to 2 units of PRBCs? Of course, the ACS-NSQIP database does not have the reason recorded. However, we know the answer. We simply use (or allow the use of) blood products much too freely in hemodynamically stable patients. Usually we allow treatment for an isolated laboratory value rather than the entire patient, something we routinely tell our residents and students not to do.

This approach should stop. Hébert et al showed us that low hemoglobin levels are okay, Kiraly et al demonstrated that older blood decreases peripheral tissue oxygenation, Tsai et al revealed that older blood has a decreased 2,3-diphosphoglycerate level, and Malone et al reported that each additional unit of PRBCs increases mortality. Most of what we were taught about blood products 10 years ago was incorrect. Blajchman has reviewed the recent studies, and the data are clear. Unless your patient is actively bleeding to death, it is simply best not to transfuse any blood products. Of course, if the patient is bleeding rapidly and in shock, then PRBCs, plasma, and platelets are required. It is time for all surgeons (and the various surgical societies) to pay attention to this issue and follow the published guidelines. Surgeons routinely take patients to the operating room and cause various amounts of blood loss. From a physiological point of view, replacing operative blood loss with 1 to 2 units of PRBCs does not make sense. From a quality outcomes and preventable injury viewpoint, Ferraris and colleagues have shown that these minimal transfusions injure our patients.