Perioperative Blood Transfusion Is Predictive of Poststernotomy Surgical Site Infection: Marker for Morbidity or True Immunosuppressant?

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To analyze risk factors for the development of adult poststernotomy surgical site infections (SSIs), we performed a retrospective case-control study at a tertiary care hospital. Case patients with poststernotomy SSI between June 1999 and January 2001 were matched to control subjects without poststernotomy SSI according to date of procedure and age. Data were collected on known SSI risk factors. Of 711 procedures, we identified 38 cases with SSI and 114 matched controls. Univariate analysis revealed that receipt of transfused blood (odds ratio [OR], 3.19; 95% confidence interval [CI], 1.54–6.62), diabetes (OR, 2.90; 95% CI, 1.27–6.59), length of stay before hospitalization (OR, 1.19 per day; 95% CI, 1.02–1.37 per day), and American Society of Anesthesia score (OR, 2.19; 95% CI, 1.04–4.64) were significantly associated with SSI. Multivariate analysis revealed that transfusion (OR, 3.21; 95% CI, 1.41–7.31) and diabetes (OR, 3.65; 95% CI, 1.42–9.36) were predictors for SSI. The exact role of blood transfusion in the pathogenesis of SSI, whether as a direct immunosuppressant or a surrogate marker for morbidity, remains unresolved.

Surgical site infections (SSIs) have been associated with increased morbidity and mortality and excess health care costs [1]. Identification of factors that increase the risk for SSIs following surgery is a key step in the reduction of morbidity and mortality. In particular, the ascertainment of any modifiable risk factors would play an essential role in the future reduction of SSI risk.

Some previous investigations have noted an association between blood transfusion and postoperative infection [2–8], yet the controversial role of blood transfusion as a risk factor for such infections has received only modest attention among infectious diseases (ID) and infection control (IC) specialists. From mid-1999 through late 2000, we investigated median sternotomy SSIs in adult cardiothoracic patients at our hospital. In a retrospective case-control study, operative transfusion of blood was significantly predictive of SSI in a multivariate analysis. We present the results of our investigation primarily as a means to highlight the potential risk of blood transfusion for the development of SSIs and to encourage ID and IC practitioners to further investigate this potential risk factor.

PATIENTS AND METHODS

Study design. A matched case-control study was conducted at a 658-bed tertiary care center at Vanderbilt University (Nashville, TN). Eligible patients were adults >18 years of age who had undergone median sternotomy for coronary artery bypass grafting (CABG), valve
were conducted using Stata, version 7.0 (Stata). All analyses using conditional logistic regression. Multivariate forward stepwise conditional logistic regression analysis with a significance level of .05 for entry into the model was then performed to identify the significant predictors of sternal SSI. Multivariate forward stepwise conditional logistic regression analysis with a significance level of .05 for entry into the model was then performed to identify the significant predictors of sternal SSI. All analyses were conducted using Stata, version 7.0 (Stata).

**Case patient selection.** Cases were defined as eligible patients who received a diagnosis of sternal wound SSI using standardized definitions from the National Nosocomial Infection Surveillance (NNIS) system, a partnership between participating hospitals and the Centers for Disease Control and Prevention (CDC) [9]. Cases were identified through standard active surveillance by IC practitioners, as well as through active reporting from cardiothoracic case managers and laboratory reports of positive results of cultures of sternal wound specimens. SSIs were classified as either soft-tissue infections (superficial or deep infection) or mediastinitis [9].

**Control subject selection.** Controls were chosen among eligible patients with no evidence of SSI by standard surveillance and chart review. Controls were matched to cases by date of procedure and age (± 5 years), with a 1:3 ratio of cases to controls.

**Data collection.** A single IC practitioner and a trained assistant abstracted data from the charts of all cases and controls. Chart abstractions by the assistants were reviewed by the IC practitioner for accuracy. Risk factor data included patient demographic information (age, weight, and sex), comorbid illnesses or risk factors (diabetes mellitus, chronic obstructive pulmonary disease, American Society of Anesthesiology [ASA] score [10], and tobacco use), procedural characteristics (CABG or non-CABG; recurrent procedure; preoperative length of stay; specific surgical personnel; total number of operating room personnel; use of internal mammary artery, radial artery, or saphenous vein; number of bypass grafts; duration of extracorporeal bypass; duration of surgery; interval between patient entry into the operating room and the first incision; and the suture type used), preoperative skin preparatory information (type of skin preparatory agent and individual who performed skin preparation), antibiotic administration (type of antibiotic given before, during, and after the operation, and number of total doses administered perioperatively), and units of blood transfused during the procedure. Initiation of antibiotic prophylaxis was classified as appropriate if administration occurred ≤30 min prior to the initial incision [11].

**Statistical analysis.** Baseline characteristics between the 2 groups were compared using Student’s t test and the Wilcoxon rank sum test for continuous variables and χ² analysis and Fisher’s exact test for categorical variables. Univariate relationships between predictor variables and sternal SSI were analyzed using conditional logistic regression. Multivariate forward stepwise conditional logistic regression analysis with a significance level of .05 for entry into the model was then performed to identify the significant predictors of sternal SSI. All analyses were conducted using Stata, version 7.0 (Stata).

**RESULTS**

During the study period, 711 median sternotomy procedures were performed on adults, among whom 39 cases with sternal SSI (5.5%) and 114 matched controls (16%) were identified. Medical records for 1 case could not be located, resulting in exclusion. Of the 38 cases with sternal SSI, soft-tissue infections (superficial or deep) were diagnosed in 18 (47%), and mediastinitis was found in 20 (53%). Gram-positive organisms alone were found in 20 cases (52%) (Staphylococcus aureus in 8, Staphylococcus epidermidis in 3, enterococcal species in 1, and mixed gram-positive bacteria in 8), a gram-negative organism (Enterobacter aerogenes) was the sole pathogen isolated from 1 case, and mixed bacteria were isolated from 2 cases (5%). Culture results were negative for 6 cases (18%), and samples were not obtained for culture for 9 cases (24%).

Univariate analysis identified several variables significantly associated with adult sternal wound SSI: history of diabetes mellitus, ASA score, preoperative length of stay, and receipt of transfused blood (table 1). In a multivariate analysis using forward stepwise conditional logistic regression, blood transfusion (OR, 3.21; 95% CI, 1.41–7.31) and a history of diabetes (OR, 3.65; 95% CI, 1.42–9.36) were significant predictors of an increased SSI risk.

**DISCUSSION**

Our investigation found that receipt of transfused blood, along with a history of diabetes mellitus, was predictive of the development of SSI following median sternotomy in adults. The association of diabetes and SSI was expected, because numerous studies have identified an increased risk of wound infections in diabetic patients [11]. The finding that receipt of transfused blood may be associated with an increased SSI risk in cardiothoracic patients was unexpected but not altogether surprising, because multiple studies have shown a relationship between perioperative blood replacement and postoperative infection risk. The association between SSI and blood transfusion has not, however, received attention similar to that of other, more established SSI risk factors, because the role of blood transfusion in the pathogenesis of postoperative infections is controversial and has been debated for >20 years.

At the heart of the debate lies a central question: does transfusion lead to direct immunosuppression (i.e., to transfusion-associated immunomodulation [TRIM] [8]) that increases one’s risk for SSI, or does the receipt of blood products merely identify individuals with greater underlying comorbidity and, therefore, greater inherent risk for infection? This debate, however, has been largely confined to the surgical and transfusion medicine communities, with less attention devoted to this subject in the ID and IC literature.

Many observational studies and multiple randomized con-
trolled trials have described the potential association between transfusion and an increased risk of postoperative SSI [2, 5, 8, 12, 13]. This association has been noted with a variety of surgical procedures (colorectal, general abdominal, orthopedic, trauma, head and neck, and cardiothoracic surgery [6, 7, 12, 14–18]). Donated WBCs have been implicated as a source of transfusion-induced immunosuppression, and several clinical trials have compared the receipt of standard whole blood–or Buffy coat (BC)–depleted products with the receipt of WBC-depleted products. BC-depleted blood, although containing ~70% fewer WBCs than whole blood, still has a higher WBC count than WBC-depleted blood [19, 20]. Other trials have compared the receipt of autologous and allogeneic blood products, postulating that the effects of nonnative WBCs found in allogeneic blood will not occur after transfusion of native autologous WBCs. Results of these randomized clinical trials have failed, however, to provide a consensus answer to the association between transfusion and postoperative infection (table 2). In addition, many investigations have used nonstandardized and subjective definitions of infection outcomes [6, 7, 21]; have failed to take into account many, if not all, known risk factors for postoperative infection; and have utilized only univariate analyses [3, 4, 22].

With a growing yet discrepant body of literature on the sub-

Table 1. Baseline characteristics of case patients with poststernotomy surgical site infection and control subjects that were determined to be significantly different by univariate analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n = 38)</th>
<th>Controls (n = 114)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of diabetes, % of patients</td>
<td>47.4</td>
<td>25.4</td>
<td>2.90 (1.27–6.59)</td>
</tr>
<tr>
<td>Duration of hospitalization before operation, days</td>
<td>2.6 ± 3.7</td>
<td>1.5 ± 2.2</td>
<td>1.19 (1.02–1.37)</td>
</tr>
<tr>
<td>ASA score</td>
<td>3.68 ± 0.5</td>
<td>3.48 ± 0.5</td>
<td>2.19 (1.04–4.64)</td>
</tr>
<tr>
<td>Blood transfusion, units&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.74 ± 2.1</td>
<td>0.76 ± 1.2</td>
<td>3.19 (1.54–6.62)</td>
</tr>
</tbody>
</table>

<sup>Note</sup>. Data are mean ± SD, unless otherwise indicated. ASA, American Society of Anesthesiology.

<sup>a</sup> ORs calculated for blood transfusion as a binary variable (presence or absence of transfusion).

Table 2. Comparison of randomized clinical trials investigating the association between postoperative infection (PI) and perioperative blood transfusion (BT).

<table>
<thead>
<tr>
<th>Study</th>
<th>Initial no. of subjects</th>
<th>Surgical procedure</th>
<th>Blood products compared</th>
<th>NNIS system definitions for PI outcomes</th>
<th>Multivariate analysis of PI outcomes</th>
<th>Association between BT and PI detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>[3]&lt;sup&gt;a&lt;/sup&gt;</td>
<td>215</td>
<td>Elective colorectal</td>
<td>Whole vs. WBC depleted</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>[23]&lt;sup&gt;b&lt;/sup&gt;</td>
<td>475</td>
<td>Elective colorectal</td>
<td>Allogeneic vs. autologous</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>[14]</td>
<td>120</td>
<td>Elective curative colorectal cancer resection</td>
<td>Allogeneic vs. autologous</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>[19]</td>
<td>871</td>
<td>Elective colorectal adenocarcinoma resection</td>
<td>BC depleted vs. WBC depleted</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>[4]</td>
<td>60</td>
<td>Elective colorectal</td>
<td>Whole vs. WBC depleted</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>[20]</td>
<td>589</td>
<td>Elective colorectal</td>
<td>BC depleted vs. WBC depleted</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>[24]</td>
<td>697</td>
<td>Elective colorectal adenocarcinoma resection</td>
<td>BC depleted vs. WBC depleted</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>[21]</td>
<td>231</td>
<td>Unilateral total knee replacement</td>
<td>Allogeneic vs. autologous salvaged blood</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>[25]</td>
<td>50</td>
<td>Aortic aneurysm repair</td>
<td>Allogeneic vs. autologous salvaged blood</td>
<td>No</td>
<td>No&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td>[22]</td>
<td>914</td>
<td>Cardiothoracic (CABG and/or valve surgery)</td>
<td>BC depleted vs. WBC depleted</td>
<td>Yes</td>
<td>No</td>
<td>No&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>[26]</td>
<td>279</td>
<td>Colorectal</td>
<td>WBC/BC depleted vs. BC depleted vs. no transfusion</td>
<td>No</td>
<td>No</td>
<td>No&lt;sup&gt;e&lt;/sup&gt;, Yes&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>[27]</td>
<td>145</td>
<td>Aortic</td>
<td>Allogeneic vs. autologous</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

<sup>Note</sup>. BC, buffy coat; CABG, coronary artery bypass grafting; NNIS, National Nosocomial Infection Surveillance.

<sup>a</sup> Randomization occurred after decision was made to transfuse.

<sup>b</sup> Used mortality as the primary outcome; rates of infectious complications only were compared between the 2 groups.

<sup>c</sup> Infection outcome was defined as the development of systemic inflammatory response syndrome or sepsis.

<sup>d</sup> On the basis of results of intention-to-treat analysis.

<sup>e</sup> Between the 2 transfusion groups.

<sup>f</sup> Between the transfusion and nontransfusion groups.
ject, the association between blood transfusion and SSI remains unresolved. The occurrence of TRIM, seen particularly in recipients of allogeneic transfusions of WBC-containing blood products, has been supported by animal and human studies. Transfusion-related decreases in cell-mediated immune function, macrophage inhibition, and a reduction of CD4 helper lymphocyte levels have been demonstrated using various mouse models [4, 5]. Although limited, human studies also have shown significant decreases in natural killer cell activity, lymphocyte proliferation due to phytohemagglutinin, and the CD4:CD8 cell ratio, as well as significant increases in soluble IL-2 receptor and IL-6 levels following transfusion with whole blood, compared with such findings in subjects who received WBC-depleted blood or who did not receive a transfusion [3, 4]. These investigations support the biological plausibility of transfusion acting as an immunosuppressant.

There were some limitations to our investigation. Because of the retrospective nature of the study, several known risk factors for infection could not be studied, such as past tobacco or concurrent corticosteroid use or perioperative glucose levels. We were also unable to analyze risk with regard to certain aspects of the surgical procedure because of the relatively small numbers in each subgroup (i.e., valve replacement and CABG vs. CABG alone) and incomplete documentation (i.e., method of hair removal). Another potential limitation involves the large number of risk factors entered into the univariate statistical model. With 25 variables in the model, statistical chance alone dictates that 1 or 2 factors may be significant. The association between transfusion and SSI, and, in particular, transfusion’s potential role as an immunosuppressant, is biologically plausible, and the association between transfusion and SSI remained significant after multivariate analysis. Therefore, it is unlikely that this association was simply a product of chance alone. Finally, although data were not available on the type of blood transfused (e.g., allogeneic vs. autologous) or the specific WBC status of the units transfused in the study cohort, since 1998, all allogeneic and most autologous units of transfused blood at our institution were WBC depleted. Thus, it is highly likely that all transfusions received in our study were leukocyte depleted.

In the latest CDC guidelines for the prevention of SSIs, perioperative transfusion is briefly mentioned as a proposed SSI risk factor [11]. Although physicians generally weigh the risks and benefits of blood transfusion prior to administration of blood products, if blood replacement therapy were to be documented as a unique risk factor for infection, this finding might lead to further prudence and more-widespread use of blood-sparing techniques. In addition, universal reduction of leukocytes in all units of donated blood in the United States has now been proposed to eliminate the potential immunosuppressive effects of transfusion, a decision that has been met with controversy [8]. Critics argue that more-definitive answers with regard to the role of transfusion and TRIM in posttransfusion morbidity are needed before embarking on this expensive process. A larger study involving standardized NNIS outcome definitions, appropriate multivariate techniques, and all known risk factors for postoperative infection is now needed to further investigate the role of transfusion in postoperative infection.

Acknowledgments

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References