The Association Between Perioperative Allogeneic Transfusion Volume and Postoperative Infection in Patients Following Lumbar Spine Surgery

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Background: Perioperative allogeneic red blood cell transfusion is a risk factor for surgical site infection. The purpose of this study was to determine if the volume of perioperative allogeneic red blood cell transfusion influences the risk of surgical site infection following lumbar spine procedures.

Methods: A retrospective matched case control study was performed by reviewing all patients who had undergone lumbar spine surgery at our institution from 2005 to 2009. Surgical site infections (spinal or iliac crest) were identified, all within thirty days of the procedure. Controls were matched to the infection cohort according to age, sex, body mass index, diabetic status, smoking status, Charlson Comorbidity Index, length of surgery, and procedure. A conditional logistic regression was performed to examine the association between transfusion volume and surgical site infection. The results were summarized by an odds ratio.

Results: A total of 1799 lumbar procedures were identified with an infection rate of 3.1% (fifty-six cases). On the basis of the numbers, there was no significant difference in the matched variables between the infection cohort and the matched controls. The volume of transfusion was significantly associated with surgical site infection (odds ratio, 4.00 [95% confidence interval, 1.96 to 8.15]) after adjusting for both unmatched variables of preoperative hemoglobin level and volume of intraoperative blood loss.

Conclusions: In this retrospective matched case control study, the association between surgical site infection following lumbar spine surgery and volume of perioperative allogeneic red blood cell transfusion was supported.

Level of Evidence: Prognostic Level III. See Instructions for Authors for a complete description of levels of evidence.

Infections following spinal surgical procedures impart an increased risk of postoperative patient morbidity and mortality. Surgical site infection is the most common nosocomial infection in the early postoperative period[1]. More importantly, 77% of acute mortality in patients with surgical site infection is directly related to the infection[2]. The consequences of postoperative infection include loss of instrumentation fixation, pseudarthrosis, osteomyelitis, chronic pain, sepsis, and death[3-6]. In addition, the economic implications of infection following spinal surgery cannot be overstated. Patients who develop surgical site infection usually require longer postoperative hospitalization, are more likely to be managed in intensive care units, and have higher hospital readmission rates[7].

The incidence of surgical site infection following spinal procedures is influenced by a multitude of intrinsic and extrinsic factors. Patient-specific factors identified as increasing the risk for surgical site infection include advanced age[6,8,9], corticosteroid use[10,11], smoking[6,12,13], alcohol abuse[6], and diabetes[6,10,13,14]. Olsen et al. performed a large retrospective case control

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study in which diabetes was the greatest independent risk factor for spinal surgical site infection[15]. Schwarzkopf et al. found body mass index (BMI) to significantly influence the risk of surgical site infection following thoracic and lumbar spine surgery[16]. Intraoperative risk factors identified include the type of surgical approach, the procedure performed, revision procedures, and the length of the surgery[6,14]. A point of contention in the literature and among surgeons is the relationship between allogeneic perioperative blood product transfusion and morbidity. The rationale for aggressive perioperative red blood cell transfusion following spine surgery has been established[17]. Additionally, postoperative anemia has been correlated with longer hospital admission and higher readmission rates in patients following open reduction and internal fixation of hip fractures[18], although this has been questioned recently[19].

In the United States, 14 million units of blood are transfused annually and transfused blood is generally considered to be safe[20]. However, allogeneic transfusion does have some risks. The association between the development of surgical site infection and transfusion has been reported in the literature[21-24]. The immunomodulatory effects imparted by allogeneic transfusion are not completely understood. Allogeneic transfusion has been linked not only to an increased risk of nosocomial infection, but also to cancer recurrence and autoimmune diseases[25-27]. Although allogeneic red blood cell transfusion has been identified as a risk factor for the development of surgical site infection following spinal surgery[16], we are unaware of any studies that have evaluated if the volume of transfusion given influences infection risk. The purpose of this study was to determine if there is an association between the volume of perioperative red blood cell transfusion and the risk of surgical site infection following lumbar spine procedures.

Materials and Methods

Following institutional review board approval, all lumbar spinal surgical procedures performed at the University of Pittsburgh Medical Center from 2005 to 2009 by one senior fellowship-trained spine surgeon (J.K.) were retrospectively reviewed. The surgical procedures included laminectomy, instrumented and non-instrumented fusion, and anterior and posterior interbody fusions. Additional information collected for each procedure included if it was a primary or revision procedure, if allogeneic or autogenous bone graft (iliac crest) was used, and if bone morphogenetic protein 2 (BMP-2) was used. All included patients had a subfascial medium postoperative blood salvage system (Hemovac System; Zimmer, Warsaw, Indiana) placed prior to closure.

Infections were recorded in each group and defined as surgical site infections (spinal or iliac crest) that occurred within thirty days of the procedure as in accordance with the Centers for Disease Control and Prevention definition[2]. All diagnosed surgical site infections were treated with operative irrigation and debridement and intravenous antibiotics.

The volume of allogeneic red blood cell transfusion for each procedure was obtained from our central blood bank database. All patients who underwent transfusion received blood intraoperatively or in the immediate postoperative period, defined as within twenty-four hours after surgery. Indication for perioperative transfusion was determined by the attending surgeon and anesthesiologist. Factors that influenced transfusion included large-volume blood loss, hypotension, and oliguria. Intraoperative autotransfusion was used in all patients. Intraoperative blood loss was estimated at the conclusion of each procedure and was recorded for all patients included in the study.

Potential risk factors for surgical site infection were identified and were recorded by medical record review. The Charlson Comorbidity Index score was obtained on each patient to summarize preexisting comorbid illness[28]. The medical record was searched for the presence of the comorbidities listed in the Appendix, and the comorbidity score was a summation of the points associated with each condition. This comorbidity score has been previously validated as a predictor of mortality in patients with a wide range of disease processes (stroke, end-stage renal disease, pneumonia, cancer) and after certain treatments such as coronary artery bypass surgery[29-34]. Patients who had an incomplete medical record in which a comorbidity score could not be generated were excluded from the study.

The analysis was performed as a matched case-control study. One to five control subjects were matched to each case subject by age, sex, BMI, smoking status, diabetes status, Charlson Comorbidity Index, length of surgery, revisions, iliac crest bone graft, and the use of allograft. These variables were chosen to eliminate them as potential confounders. Subject characteristics and risk data were compared between case and control subjects with use of generalized estimating equations for categorical and continuous variables. The impact of volume of transfusion on the occurrence of surgical infection was examined by conditional logistic regression through the PHREG procedure (SAS, version 9.3; SAS Institute, Cary, North Carolina), with each case and matched controls forming a separate stratum. The volume of transfusion was treated as a continuous variable and surgical infection was treated as a nominal variable (yes or no). To examine the impact of non-matched variables in the association, we further adjusted for possible confounders, specifically the preoperative hemoglobin level and the volume of intraoperative blood. Confounding was assessed by the impact of the potential confounder on the parameter estimate for the main effect (i.e., volume of transfusion). If a removal of a possible confounding variable caused a change of 10% or more in the value of the parameter estimate, that variable was considered to be a confounder and was included in the final model. Pairwise interactions were assessed where relevant. The results were summarized by the odds ratio (OR) and its 95% confidence interval (95% CI). The odds ratio represents the average increase in odds associated with a one-unit increase in the exposure. All analyses were performed with the alpha level set to 0.05.

Source of Funding

The statistical analysis was performed through the Clinical and Translational Science Institute (CTSI) and was funded by the National Institutes of Health (Grant Numbers UL1 RR024153 and UL1TR000005).

Results

A total of 1799 lumbar spine surgical procedures had an infection rate of 3.1% (fifty-six cases). A total of ninety-one lumbar controls were subsequently identified. For the matched data, thirty-one cases had one control, nineteen cases had two controls, four cases had three controls, and two cases had five controls. Of the fifty-six infection cases, thirty-nine involved only the midline surgical incision and seventeen involved the iliac crest.

The average age of all subjects included in this study was sixty-one years (range, twenty-three to eighty-three years). This average and variation were consistent across both infection and control groups. A wide range of procedures were included in this study; however, laminectomy with instrumented fusion was the most frequently performed, accounting for 87.5% (forty-nine of fifty-six) of the infection cases and 89% (eighty-one of ninety-one) of the control cases ($p = 0.91$).

The length of surgery was, on average, five minutes longer in the infection cohort (272.7 minutes) compared with controls (267.6 minutes) ($p = 0.45$). The length of surgery was

TABLE I Subject Characteristics for Infection Cases and Their Matched Controls Following Lumbar Surgery

Variables	Infection Cases (N = 56)	Matched Controls (N = 91)	P Value
Matched variables			
Age* *(yr)*	61.76 ± 12.43 (26 to 83)	60.51 ± 14.87 (23 to 83)	0.84
Sex† *(male)*	22 (39.29%)	46 (50.55%)	0.10
BMI* *(kg/m^2)*	34.00 ± 5.13 (24 to 49)	33.73 ± 4.25 (27 to 49)	0.87
Smokers†	12 (21.43%)	16 (17.58%)	0.42
Diabetics†	17 (30.36%)	26 (28.57%)	0.84
Charlson Comorbidity Index* *(points)*	3.46 ± 1.43 (1 to 8)	3.40 ± 1.17 (2 to 7)	0.74
Length of surgery* *(min)*	272.68 ± 65.55 (176 to 457)	267.60 ± 55.70 (143 to 420)	0.45
Revision procedure†	36 (64.29%)	58 (63.74%)	0.89
Iliac crest bone graft†	50 (89.29%)	77 (84.62%)	0.34
BMP-2 and allograft†	19 (33.93%)	34 (37.36%)	0.60
Non-matched variables*			
Preoperative hemoglobin *(g/dL)*	13.98 ± 1.62 (10.20 to 16.80)	14.52 ± 1.20 (12.10 to 16.8)	0.01
Volume of intraoperative blood loss *(cm^3)*	1512.23 ± 477.49 (550 to 2875)	1352.86 ± 369.86 (600 to 2300)	0.01

*The values are given as the mean and the standard deviation, with the range in parentheses. †The values are given as the number of patients in each group, with the percentages in parentheses.

also analyzed separately for primary and revision procedures for the infected and control groups. Revision procedures for both the infection (296 minutes) and control lumbar (287.9 minutes) subgroups required significantly more time ($p = 0.001$) than primary procedures in the same subgroup; the infection subgroup required 230.9 minutes and the control subgroup required 225 minutes.

Autogenous iliac crest bone graft was harvested from the posterior superior iliac spine through a separate oblique incision. Iliac crest bone graft was incorporated in the fusion construct in a similar number of lumbar infected cases (89.3% [fifty of fifty-six]) and control cases (84.6% [seventy-seven of ninety-one]). There was no significant difference based on the numbers in the percentage of cases that used allograft cancellous bone chips or BMP-2 between infection or control cohorts ($p = 0.6$). Revision procedures accounted for 64.3% (thirty-six of fifty-six) of the lumbar infection cases and 63.7% (fifty-eight of ninety-one) of the lumbar control cases ($p = 0.89$). There was no significant difference in the matched variables between infection cases and controls (the p value range was 0.10 to 0.89). There was a significant difference in preoperative hemoglobin level and volume of intraoperative blood loss between cases and controls ($p = 0.01$). Matched and non-matched variables analyzed between the infection and control groups are summarized in Table I.

Overall, there was not a significant difference in the number of patients who received allogeneic transfusion between the infection or control cohorts ($p = 0.37$). However, of the patients who underwent transfusion, those who developed surgical site infection received nearly one and a half more units of blood than did matched controls. The transfusion data are summarized in Table II.

The volume of transfusion was significantly associated with surgical infection (OR, 2.87 [95% CI, 1.63 to 5.06]). The

TABLE II Perioperative Transfusion Data for Infection Cases and Matched Controls

Perioperative Transfusion Data	Infection Cases (N = 56)	Matched Controls (N = 91)	P Value
No. of patients undergoing blood transfusion*	43 (76.8%)	66 (72.5%)	0.37
Transfusion volume† *(units)*	2.89 ± 2.38 (1 to 7)	1.40 ± 1.19 (1 to 4)	<0.001

*The values are given as the number of patients, with the percentage in parentheses. †The values are given as the mean and the standard deviation, with the range in parentheses.

odds ratio for the association between transfusion volume and surgical site infection after controlling for preoperative hemoglobin level was 3.41 (95% CI, 1.82 to 6.39). Similarly, the odds ratio after adjusting by volume of intraoperative blood loss was 3.38 (95% CI, 1.75 to 6.55). In addition, the volume of transfusion was significantly associated with surgical site infection (OR, 4.00 [95% CI, 1.96 to 8.15]) after adjusting for both unmatched variables (preoperative hemoglobin level and volume of intraoperative blood loss). The association between transfusion volume and surgical site infection remained significant in all models. These models were reassessed along with pairwise interactions; however, no significant interactions were found.

Discussion

Surgical site infection following lumbar spine surgery prolongs hospitalization for a median of two weeks, increasing health-care costs by over 300% per patient[35]. The association between perioperative allogeneic transfusion and surgical site infection has been described[16,22,23,36,37]; however, this relationship has not been clearly defined. Determining the contribution that transfusion has to the development of surgical site infection is inherently challenging because of the numerous confounding factors often present, which also influences risk. Despite modern screening, the transmission of virulent agents such as hepatitis, human immunodeficiency virus (HIV), Epstein-Barr virus, and others exists with allogeneic transfusion[36-38]. Allogeneic transfusions expose hosts to foreign antigens such as human leukocyte antigen dendritic presenting cells[39]. Blood transfusion can result in immune activation or tolerance. Several clinical syndromes associated with immune activation following allogeneic transfusion have been described, including transfusion reactions, transfusion-associated graft-versus-host disease, transfusion-related lung injury, alloimmunization, and the development of autoimmune diseases[40]. Immune tolerance or suppression following transfusion is demonstrated by the absence of an immune reaction, increased incidence of cancer recurrence in patients who receive chronic transfusions, microchimerism, and increased predisposition to infection[26]. The immune tolerance that can be imparted by allogeneic transfusion is supported by the enhanced survival of cardiac, renal, and hepatic allografts in patients who receive allogeneic blood compared with those who do not[41-45]. Similarly, transfusion of allogeneic blood has been associated with a significantly higher rate of surgical site infection following various different procedures[46-48]. The association between allogeneic blood transfusion and surgical site infection has also been made following spinal surgery[15]. Proposed mechanisms include defective antigen presentation, decreased natural killer cell function, and a reduction in delayed hypersensitivity and histamine release[49,50]. Additionally, current storage methods for allogeneic blood may be suboptimal, resulting in structural and functional degradation of the red blood cells. Blood stored for more than fourteen days has a decreased ability to deform and unload oxygen while in circulation[51]. These deformed cells are more adhesive to endothelial cells, which can cause capillary sludging and obstruction. This can facilitate poor peripheral perfusion and can limit immune response[52,53]. It is also postulated that these structural changes result in the accumulation of proinflammatory cytokines, which, upon entry in the host, also facilitate an aberrant immune response. Koch et al. specifically evaluated this issue and found that patients who received blood stored for at least two weeks following cardiac surgery had significantly higher postoperative complications and one-year mortality compared with those who received blood stored for shorter periods of time[54].

Although the association between blood transfusion and postoperative infection has been described in the literature, it is unclear what, if any, volume of transfusion contributes to that risk. Restrictive transfusion practices have decreased morbidity and mortality in chronically ill patients[55,56]. However, restrictive transfusion practices are not particularly beneficial in patients who undergo spine surgery. Pull ter Gunne et al. retrospectively reviewed 300 consecutive patients who underwent spinal surgery with at least 2 L of intraoperative blood loss and found that patients with postoperative hemoglobin levels of ≤8 g/dL had a six times higher risk of surgical site infection compared with those with a hemoglobin level of at least 10 g/dL. They concluded that restrictive transfusion practices may not be beneficial for patients undergoing spine surgery[17].

The purpose of this study was to specifically determine if the volume of allogeneic red blood cell transfusion influences the risk of surgical site infection following lumbar spine surgery. To our knowledge, no other study has specifically evaluated this topic. Controls were matched with use of several known intrinsic and extrinsic risk factors for surgical site infection and then were randomly selected. Patients who developed postoperative infection following spine surgery received significantly more allogeneic red blood cell volume than those who did not (OR, 2.87 [95% CI, 1.63 to 5.06]). The odds of having a surgical site infection are 2.87 for a one-unit increase in the volume of transfusion. There were two non-matched variables between the infection and control groups that must be taken into account. Preoperative hemoglobin level is an indicator for increased allogeneic red blood cell transfusion following spine surgery[57,58]. Patients in the infection group had a significantly lower preoperative hemoglobin level (13.98 g/dL) than patients in the control group (14.52 g/dL) ($p = 0.01$). Additionally, intraoperative blood loss was, on average, 159.4 mL greater for the infection cohort compared with controls ($p = 0.01$). Both of these non-matched variables are potential explanations why the infection cohort received significantly more allogeneic red blood cell transfusion than matched controls. We are aware of no such association having been made in the literature between either of these non-matched variables and the risk for infection. The volume of transfusion was significantly associated with surgical site infection (OR, 4.00 [95% CI, 1.96 to 8.15]) after adjusting for both unmatched variables of

preoperative hemoglobin level and the volume of intraoperative blood. The association between transfusion volume and surgical site infection remained significant in all models.

This study was limited because of its retrospective nature, and thus, from these data, we cannot support or refute restrictive transfusion practices following spine surgery. Specific limitations that should be highlighted include the lack of a specific transfusion algorithm and data on the age of the transfused allogeneic red blood cells.

In conclusion, these data support the premise that allogeneic red blood cell transfusion volume may influence the risk of surgical site infection following lumbar spine surgery, implying that there may be a dose-dependent effect. A more complete understanding of the immunomodulatory effects that allogeneic transfusion has on the host is required. Prospective studies are required to determine if there is a critical volume of allogeneic transfusion that shifts the risk-benefit ratio, and if that volume is influenced by the presence of other surgical site infection risk factors or patients' comorbid illness. The development of surgical site infection following spinal surgery is clearly a multifactoral issue.

Appendix

eA A table showing the Charlson Comorbidity Index scoring system is available with the online version of this article as a data supplement at jbjs.org. ■

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