Infectious complications in transfused patients after radical cystectomy

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LIU J-J, MULLANE P, KATES M, GANDHI N, SCHOENBERG MP, DRAKE C, HAHN NM, FRANKS, BIVALACQUA TJ. Infectious complications in transfused patients after radical cystectomy. *Can J Urol* 2016;23(4):8342-8347.

Introduction: *Infectious complications are common after radical cystectomy (RC), and allogeneic blood transfusions may increase infection risk by an immunosuppressive effect. While it has been suggested that perioperative blood transfusion (PBT) may be associated with adverse oncologic outcomes after RC, no large analyses have assessed whether PBT increases the risk of perioperative infection after RC.*

Materials and methods: *We used the Nationwide Inpatient Sample (1998 to 2011) to study the rate of PBT during RC for bladder cancer and identify infectious complications. We compared rates of infectious complications in patients who did and did not receive PBT and developed a multivariable model to assess the independent risk of infectious complication associated with PBT controlling for age, year of surgery, obesity, chronic kidney disease, comorbidity score, and type of urinary diversion.*

Results: *We identified 126,454 RCs performed during the study period. A total of 34,203 (27%) received a PBT. The use of PBT increased over the study period, from 18.4% in 1998 to 31.6% in 2011 ($p < 0.0001$). Patients who received a PBT had an increased risk of perioperative infectious complications [36.7% versus 27.7%, unadjusted OR (95% CI) = 1.51 (1.43-1.60), $p < 0.0001$]. After adjusting for potential confounders, PBT remained an independent predictor of infectious complications [adjusted OR (95% CI) = 1.46 (1.38-1.55), $p < 0.0001$].*

Conclusions: *This analysis provides strong observational evidence that PBT is associated with an increased risk of perioperative infectious complications, which may be secondary to transfusion-related immunomodulation. Urologists should aggressively pursue blood conservation strategies and adhere to evidence-based restrictive transfusion thresholds, particularly given the rising rate of PBT.*

Key Words: infectious complication, radical cystectomy, blood transfusion

Introduction

Transfusion medicine has evolved over the past four decades as the understanding of the immunologic effects of allogeneic blood transfusion (ABT) has improved. In the 1980s, scientists focused on the development of improved screening measures for transmission of infectious diseases, such as HIV. In the 2000s, many non-infectious risks of ABT were recognized, such as transfusion related acute lung injury (TRALI). Most recently, ABT in the perioperative setting (perioperative blood transfusion, PBT) has been associated with increased risk of cancer recurrence in some malignancies.[1,2] The concept of transfusion related immunomodulation (TRIM) encompasses

Accepted for publication May 2016

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the immunologic dysregulation that occurs with ABT that can result in susceptibility to microbial infection, downregulation of host defenses against cancer cells, and alloimmunization against transfused antigens.[3] As the adverse effects of transfusion have become increasingly recognized, a more parsimonious approach to transfusion has been advocated, with more restrictive hemoglobin thresholds for ABT.[4]

The association between PBT and negative outcomes is well recognized in surgical patients, including an increased risk for infectious complications.[3,5-9] Studies examining PBT with allogeneic blood products have largely included patients undergoing cardiac or colorectal surgery.[5-7,10] In urologic surgery transfusion requirements have dramatically decreased, owing in large part to the widespread usage of minimally invasive approaches. Radical cystectomy (RC) is unique compared to other oncologic procedures in urology in that PBT is fairly prevalent, ranging from 20% to 60%, likely due to a combination of factors, including a slower adoption of robotics for RC, an elderly population with significant medical comorbidities, and increasing usage of neoadjuvant chemotherapy, which predisposes to preoperative anemia.[11-13]

We used an established, nationally representative administrative database to examine trends in transfusions and infectious complications in patients undergoing RC for urothelial carcinoma from 1998 to 2011, in order to test the hypothesis that receipt of PBT was independently associated with an increased rate of infectious complications.

Materials and methods

Creation of dataset

Administrative records were extracted from discharge datasets for the years 1998-2011 from the Nationwide Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP). The NIS is the largest publicly available, all-payer database for inpatient care in the United States consisting of an annual 20% stratified sample of community and academic hospitals. The recent update of the NIS includes data from approximately 1,000 hospitals in over 45 states representing approximately 96% of the U.S. population. The NIS also utilizes a weighting methodology based on hospital stratification to allow for creation of national estimates.

HCUP-supplied Clinical Classifications Software (CCS) ICD-9-CM was used to generate diagnostic, comorbidity, and procedural classification codes. A dataset was created for patients with a diagnosis of urothelial carcinoma of the bladder (188.x) and a code for radical cystectomy (57.7). Urinary diversion type was classified as intestinal (ileal or colon) conduit (57.87) or continent diversion (neobladder or continent catheterizable stoma, 56.51). Patients who received blood products (whole blood or packed red blood cells) during their hospitalization were identified using ICD-9 codes 99.03 and 99.04. Comorbidities were identified by ICD9 coding for diabetes, chronic kidney disease, obesity, and smoking status, and the van Walraven score was calculated from other available variables within the dataset. The van Walraven score was chosen because it is a validated comorbidity index for usage in administrative datasets that is highly predictive of post-hospitalization complications, readmissions and mortality.[14] Infectious complications were categorized as superficial or deep wound infection (998.5), urinary tract infection (499, 590.x, 595.x), pneumonia (997.3, 480-487.0), intra- or retroperitoneal abscess (567.x), and sepsis (998, 038.x, 785.50, 785.59).

Statistical analysis

Because the stratified sampling frame of the NIS requires the use of advanced techniques (facilitated by PROC SURVEYMEANS in SAS) to estimate variance, continuous variables are presented as mean ± standard error. Multi-group comparisons were carried out using a one-way analysis of variance (ANOVA) for continuous variables and Pearson's chi-squared test for categorical variables. Trends over time were examined using a Mann-Kendall test for trend[15] (a nonparametric test to determine the presence and direction of a trend over time). A Cox proportional hazards model was constructed including age, van Walraven score, year of surgery, receipt of PBT, pre-existing renal insufficiency, obesity and urinary diversion type based on the outcome of any infectious complication. A predetermined alpha of 0.05 was used as the threshold of statistical significance. Analyses were performed using SAS (SAS 9.3, SAS Institute, Cary, NC, USA).

Results

We identified a total of 126,454 weighted admissions for RC in patients with bladder cancer during the study period. There was also an increase in the number of RCs performed per year over the study period from 8,377 in 1998 to 10,759 in 2011, p for trend < 0.05. 34,203 (27%) patients received a PBT of either whole blood or packed RBCs. Patient demographics are in Table 1. The proportion of patients receiving PBT increased significantly over the study period, from 18% in 1998 to 32% in 2011 (p, < 0.0001, Figure 1).

TABLE 1. **Receipt of perioperative blood transfusion (PBT) during radical cystectomy**

	Received PBT n = 34203 (27.0%)	**No PBT n = 92251 (73.0%)**	**p value**
Age (median ± SD)	70 ± 0.2	68 ± 0.2	< 0.0001
Race			< 0.0001
White	24136 (70.6%)	62968 (68.3%)	
Black	3090 (9.0%)	1752 (1.9%)	
Hispanic	1120 (3.3%)	2378 (2.6%)	
Asian/Pacific Islander	460 (1.3%)	1007 (1.1%)	
Native American	73 (0.2%)	140 (0.2%)	
Other/missing	5324 (15.6%)	24006 (26.0%)	
van Walraven score (median ± SD)	6.9 ± 0.1	5.5 ± 0.1	< 0.0001
Pre-existing renal insufficiency	2533 (7.4%)	3448 (3.7%)	< 0.0001
Obesity	1643 (4.8%)	3991 (4.3%)	0.0003
Urinary diversion type			< 0.0001
Intestinal conduit	25777 (75.4%)	58422 (63.3%)	
Neobladder or other continent diversion	2035 (5.9%)	6237 (6.8%)	
Other/unknown	6391 (18.7%)	27592 (29.9%)	

Recipients of PBT had increased rates of infectious complications (37% versus 28%, p < 0.0001, Table 2). Patient who received PBT were slightly older than those who did not (p < 0.0001). African-American patients received more PBT (9% of transfused group versus 1.9% of non-transfused group, p < 0.0001). Transfused patients also had higher comorbidity indices, and were more likely to have renal insufficiency or be obese (p < 0.05 for all). Continent diversions were less common in the transfused group (p < 0.0001). Specifically organ system infections were significantly more common in the transfused group, particularly wound infections (4.6% versus 2.9%), UTI (19.9% versus 15.7%) and sepsis (19.2% versus 12.3%). Overall complication rates (defined as any medical or surgical complication) increased over time from 56% in 1998 to 66% in 2011 (p = 0.007). Inpatient mortality did not increase during the study period (~1.5%). There was a small increase in comorbid conditions, in the form of an increasing van Walraven score, for patients over the study period (p = 0.0007). On multivariable analysis, age, van Walraven score, receipt of PBT, pre-existing renal insufficiency, and obesity were all associated with infectious complications, Table 3. Type of urinary diversion (continent versus non-continent) was not an independent predictor of infectious complications.

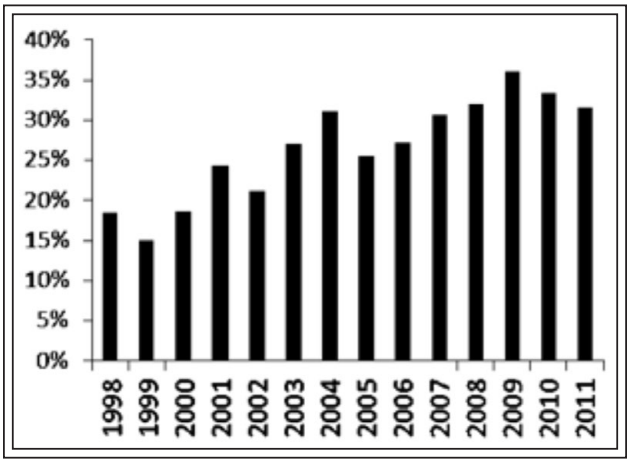

Figure 1. Proportion of patients undergoing radical cystectomy who received a perioperative blood transfusion.

Discussion

The principal finding of this study is that receipt of PBT is independently associated with increased risk of infectious complications after RC for bladder cancer in a nationally representative dataset. Receipt of blood transfusion increases the risk of serious

TABLE 2. **Rates of infectious complications**

	Received PBT n = 34203 (27.0%)	**No PBT n = 92251 (73.0%)**	**p value**
Infectious complication (any)	12559 (36.7%)	25648 (27.8%)	< 0.0001
Wound infection	1587 (4.6%)	2691 (2.9%)	< 0.0001
Urinary tract infection	6802 (19.9%)	14509 (15.7%)	< 0.0001
Pneumonia	1806 (5.3%)	4168 (4.5%)	< 0.0001
Sepsis	6556 (19.2%)	11376 (12.3%)	< 0.0001
Intra or retroperitoneal abscess	239 (0.7%)	324 (0.4%)	< 0.0001

PBT = perioperative blood transfusion

TABLE 3. **Factors associated with infectious complications**

	Odds ratio (95% confidence interval)	**p value**
Age	1.010 (1.007-1.013)	< 0.0001
Elixhauser score	1.039 (1.034-1.043)	< 0.0001
Year of surgery	0.967 (0.96-0.973)	< 0.0001
Receipt of PBT	1.461 (1.376-1.552)	< 0.0001
Pre-existing renal insufficiency	1.266 (1.123-1.427)	0.0001
Urinary diversion type	1.006 (0.945-1.072)	0.85
Obesity	1.281 (1.121-1.463)	0.0003

PBT = perioperative blood transfusion

infections in all hospitalized patients[13] and increased rates of infection after PBT are well documented in the trauma, cardiac and colorectal surgery literature.[2,16,17] Colorectal surgery patients who receive PBT have longer hospital stays and also an increased incidence of postoperative infections.[18] Critically ill patients in an ICU setting who receive ABT are more likely to develop nosocomial infections and have longer hospital stays, even after controlling for severity of illness.[19] Although infections represent the most common perioperative complication following RC,[20] there are no previous studies to determine any association between PBT and postoperative infections in this cohort of patients. Much of the current focus in the transfusion literature is on a possible association of PBT with adverse oncologic outcomes, however, the impact of PBT on postoperative infectious morbidity after RC is clinically important given the high rate of complications after RC, especially compared to other urologic oncology procedures.

The biological mechanism behind the deleterious effects of ABT is referred to as transfusion-related immunomodulation (TRIM). Immune-modulated responses following ABT can lead to acute lung injury, multiple organ failure, graft-versus host-disease, and exacerbation of autoimmune disorders.[3] Conversely, attenuation of the immune response following PBT can result in postoperative and nosocomial infections and cancer recurrence.[13,21] One study that examined general surgical patients (including those undergoing oncologic procedures) demonstrated that even after controlling for comorbidities and other factors predisposing patients to PBT, even low volume transfusions (1 or 2 U PRBC) were associated with increased rates of postoperative infectious complications.[21] In our own institutional dataset of patients who received neoadjuvant chemotherapy prior to RC, we found that patients receiving PBT were more likely to have infectious complications as well.[22]

The second major finding of the study is that the proportion of patients receiving PBT is increasing over time, despite the publication of multiple randomized trials supporting restrictive transfusion strategies. The current guidelines from the AABB (formerly the American Association of Blood Banks) recommend a hemoglobin trigger of 7 g/dL to 8 g/dL for hospitalized patients, and the literature has been expanding over the past decade on the benefits of adopting restrictive transfusion strategies, even in patients with existing cardiovascular disease.[4] Despite these recommendations, there exists a wide variation in practice, and a general overuse of transfusion both within and between institutions.[23-26] Possible explanations as to why PBT is increasing include a lack of understanding or compliance with transfusion guidelines, increasing comorbid conditions in the surgical population, as well as the increasing usage of neoadjuvant chemotherapy, which predisposes to preoperative anemia.[27] Our findings highlight that as a group, bladder cancer patients are increasingly being transfused after RC, and that there are clinical implications from the transfusion of blood products in this patient population.

As with all administrative data, undercoding is a limitation, as well as the inability to capture complications that occur after hospital discharge (or on readmission), a common occurrence after RC. NIS sampling frame and data variables do change slightly from year to year, and trend analyses using NIS data must consider this limitation. We sought to mitigate this effect by ensuring that ICD-9 code definitions for RC did not change during the study period (1998-2011) and by designing the study period such that it did not cross the greatest revision in the NIS data structure, which occurred in 1998.

We were not able to quantify other important perioperative factors that could play an important role in potential consequences of PBT such as preoperative hemoglobin, duration of surgery, and number and timing of units transfused. Certainly patients with more advanced disease could have more blood loss during surgery due to more locally advanced cancers, however, we did not have oncologic variables. We also could not account for receipt of neoadjuvant chemotherapy or preoperative hemoglobin levels prior to RC, which could have a role in the increasing usage of PBT over the study period. Although it would be ideal to know all of these variables to control for them in our analysis, utilizing a dataset such as the NIS sacrifices some of the granularity that can be obtained from institutional datasets that have smaller sample sizes and over-represent practice patterns of tertiary care centers for a nationwide dataset that samples all inpatient hospitalizations and allows for comparisons of practice patterns and outcomes over time. While the NIS contains limited data on disease specific variables for each inpatient encounter, its size and sampling frame facilitate the analysis of comparatively rare clinical events at a national level. The decision to transfuse is multi-factorial, and regardless of the study population (whether using a single institution vs large national dataset), it would be difficult to control for the objective and subjective factors that contribute to the decision to transfuse blood products during the perioperative period.

The surgical community has recognized the importance of reducing PBT across all disciplines, and various strategies have been employed to reduce the rate of PBT. Preoperative iron supplementation in anemic patients and intraoperative infusion of anti-fibrinolytics such as tranexamic acid have been shows to reduce the need for blood transfusions in major surgical procedures.[28,29] Manipulation of cardiopulmonary factors such as maintaining low CVP, pharmacologic intervention with pressors, and preoperative hemodilution have all been employed to reduce the rate of PBT in other major surgical operations, however, there is a dearth of information for these techniques in RC.[30-32]

How the adoption of robotic assisted techniques will affect both rates of PBT as well as associated complications is difficult to assess in this study since the ICD code for robotic assistance did not exist until late 2008. The most recent data estimate that 13% of RC are performed robotically nationwide.[33] Recent randomized trials comparing open versus robotic approaches to radical cystectomy suggest that there may be less blood loss with the robotic technique.[34,35] Thus, the adoption of robotics could affect rates of PBT and the subsequent consequences, however, this will depend on how prevalent the robotic approach becomes, the degree of reduction in blood loss and whether this reduction translates into decreased rates of PBT. Future studies utilizing the NIS will be able to elucidate the effect of robotic techniques on transfusion rates.

Conclusions

Usage of PBT is increasing over time in RC for bladder cancer, despite national recommendations for restrictive transfusion strategies. In a multivariable model, receipt of PBT was the strongest independent predictor of occurrence of an infectious complication, followed by obesity and pre-existing renal insufficiency. As a group, urologic oncologists need to be aware of the possible adverse effects and work with our colleagues in perioperative services to adhere to national guidelines and adopt restrictive transfusion protocols in this high risk group of patients. □

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